

Approach to Internal Medicine

A Resource Book for Clinical
Practice

David Hui · Alexander A. Leung ·
Christopher Ma *Editors*

Fifth Edition

 Springer

Approach to Internal Medicine

Approach to Internal Medicine

A Resource Book for Clinical Practice

Fifth Edition

Edited by

David Hui • Alexander A. Leung • Christopher Ma

Assisted by

Anwar Saifal • Caitlyn Collins

Editors

David Hui
The University of Texas MD
Anderson Cancer Center
Houston, TX
USA

Alexander A. Leung
University of Calgary
Calgary, AB
Canada

Christopher Ma
University of Calgary
Calgary, AB
Canada

ISBN 978-3-030-72979-0 ISBN 978-3-030-72980-6 (eBook)

<https://doi.org/10.1007/978-3-030-72980-6>

© The Editor(s) and The Author(s), under exclusive license to Springer Nature Switzerland AG 2022

This work is subject to copyright. All rights are solely and exclusively licensed by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.

The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

The publisher, the authors and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To Ella, Rupert, Nancy, Benjamin

David Hui

To May and all my loved ones

Christopher Ma

To Mary and all my family

Alexander A. Leung

To Saireena and all my family

Anwar Saifal

To Jordan and all my loved ones

Caitlyn Collins

Preface

“He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all.”

Sir William Osler

In this age of the internet and mobile devices, when every bit of medical information is literally at our fingertips, why do we still need a handbook? Clinicians are now, more so than ever, faced with an overwhelming amount of data, and the need for a clinical resource that is reliable, accurate, clear, and concise is of paramount importance. To take advantage of the ever growing literature, clinicians need to have a fundamental understanding of the basics, a conceptual framework to organize all the data, and a principled approach to medical decision making. This is how *Approach to Internal Medicine* can be most helpful.

Approach to Internal Medicine strives to provide practicing clinicians and trainees with a practical, evidence-based, and concise resource for everyday clinical use, bedside teaching and examination preparation. Now in its fifth edition, our editorial team has substantially updated its content, which consists of over 250 internal medicine topics under 17 subspecialties. In each topic, the sections on differential diagnoses, investigations, and treatments are designed for the rapid retrieval of high-yield clinical information. Unique to *Approach to Internal Medicine*, we have included multiple comparison tables aimed at highlighting the distinguishing features between various clinical entities, and numerous clinical pearls and mnemonics (marked by ★).

Good patient care requires dedication and teamwork. This also holds true for the mammoth task of updating the current edition. We are very fortunate to have recruited a new editor (Dr. Christopher Ma) and two new assistant editors (Dr. Saifal Anwar and Dr. Caitlyn Collins), who bring with them their wealth of knowledge and new ideas. We are also indebted to our section editors and contributors for their meticulous review of each subspecialty, providing expert input on the most up-to-date information. We are grateful to all previous contributors and users of this handbook for their feedback over the past years. We also would like to thank the editorial and production teams at Springer, particularly Katherine Kreilkamp and Margaret Moore for their expert guidance and support throughout this project. Finally, we are obliged to our families for their understanding and support during the countless nights and weekends updating this edition.

While every effort has been made to ensure the accuracy of information in this handbook, the author, editors, and publisher are not responsible for omissions, errors, or any consequences that result from application of the information contained herein. Verification of the information in this manual remains the professional responsibility of the practitioner. Readers are strongly urged to consult other

appropriate clinical resources prior to applying information in this manual for direct patient care. This is particularly important since patterns of practice and clinical evidence evolve constantly. We welcome any constructive feedback to help make this manual a more accurate, practical, comprehensive, and user-friendly resource.

Contact us at:

medicine.aim@gmail.com

David Hui, MD, MSc, FAAHPM

The University of Texas MD Anderson Cancer Center
Houston, TX, USA

Christopher Ma, MD, MPH, FRCPC

University of Calgary
Calgary, AB, Canada

Alexander A. Leung, MD, MPH, FRCPC, MRCP(UK), FACP

University of Calgary
Calgary, AB, Canada

Saifal Anwar, MD, FRCPC

University of Alberta
Edmonton, AB, Canada

Caitlyn Collins, MD, FRCPC

University of Alberta
Edmonton, AB, Canada

Disclaimer

Approach to Internal Medicine is meant to be a practical field guide. Dosages of medications are provided for quick reference only. Readers should consult other resources before applying information in this manual for direct patient care. The author, editors, and publisher of *Approach to Internal Medicine* cannot be held responsible for any harm, direct or indirect, caused as a result of application of information contained within this manual.

Contents

1 Pulmonary Medicine	1
Ashley-Mae E. Gillson	
2 Cardiology	29
Jacques Rizkallah	
3 Nephrology	83
Adam Bass	
4 Critical Care	107
Wendy I. Sligl	
5 Gastroenterology	127
Christopher Ma	
6 Hematology	159
Michael H. Kroll	
7 Oncology	205
Hilary Y. Ma and Tejal Patel	
8 Infectious Diseases	247
Stephanie W. Smith and Keely Hammond	
9 Rheumatology	293
Britney Jones and Steven J. Katz	
10 Neurology	319
Theodore Mobach	
11 Endocrinology	365
Nadia Moledina and Alexander A. Leung	
12 Dermatology	397
Susan Y. Chon	
13 Geriatrics	417
Diana Rucker	

14 Palliative Care 431
David Hui

15 Nutrition 449
Maitreyi Raman

16 Obstetric Medicine 459
Kara A. Nerenberg

17 General Internal Medicine 477
Janeve Desy and Shannon M. Ruzycki

Appendix A 499

Appendix B 501

Index 509

Contributors

Adam Bass, MSc, MD, FRCPC Division of Nephrology, Department of Medicine, University of Calgary, Calgary, AB, Canada

Susan Y. Chon, MD, FAAD Division of Internal Medicine, Department of Dermatology, The University of Texas MD, Anderson Cancer Center, Houston, TX, USA

Janeve Desy, MD, MEHP, FRCPC, RDMS Division of General Internal Medicine, Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

Ashley-Mae E. Gillson, HBSc, MD, FRCPC Division of Pulmonary Medicine, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Keely Hammond, MD, FRCPC Department of Medicine, University of Alberta, Edmonton, AB, Canada

David Hui, MD, MSc, FAAHPM Department of Palliative Care and Rehabilitation Medicine, Department of General Oncology, Division of Cancer Medicine, The University of Texas MD, Anderson Cancer Center, Houston, TX, USA

Britney Jones, MD, FRCPC Division of Rheumatology, Department of Medicine, University of Calgary, Calgary, AB, Canada

Steven J. Katz, MD, FRCPC Division of Rheumatology, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Michael H. Kroll, MD, FACP Department of Benign Hematology, The University of Texas MD, Anderson Cancer Center, Houston, TX, USA

Alexander A. Leung, MD, MPH, FRCPC, MRCP(UK), FACP Division of Endocrinology & Metabolism, Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, AB, Canada

Christopher Ma, MD, MPH, FRCPC Division of Gastroenterology & Hepatology, Department of Medicine, University of Calgary, Calgary, AB, Canada

Hilary Y. Ma, MD Department of General Oncology, The University of Texas MD, Anderson Cancer Center, Houston, TX, USA

Theodore Mobach, BSc, FRCPC(Neurology), CSCN(EMG) Department of Clinical Neurosciences, University of Calgary, Calgary, AB, Canada

Nadia Moledina, MD, FRCPC Division of Endocrinology & Metabolism, Department of Medicine, University of Calgary, Calgary, AB, Canada

Kara A. Nerenberg, MD, MSc, FRCPC Division of General Internal Medicine, Departments of Medicine, Obstetrics & Gynecology, and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada

Tejal Patel, MD Department of General Oncology, The University of Texas MD, Anderson Cancer Center, Houston, TX, USA

Maitreyi Raman, MD, MSc, FRCPC Division of Gastroenterology & Hepatology, Department of Medicine, University of Calgary, Calgary, AB, Canada

Jacques Rizkallah, MD, FRCPC Department of Cardiac Sciences, University of Calgary, Calgary, AB, Canada

Diana Rucker, MSc, MD, FRCPC Division of Geriatrics, Department of Medicine, University of Alberta, Edmonton, AB, Canada

Shannon M. Ruzycski, MD, MPH, FRCPC Division of General Internal Medicine, Department of Medicine, University of Calgary, Calgary, AB, Canada

Wendy I. Sligl, MD, MSc, FRCPC Department of Critical Care Medicine, University of Alberta, Edmonton, AB, Canada

Stephanie W. Smith, MD, MSc, FRCPC Division of Infectious Diseases, Department of Medicine, University of Alberta, Edmonton, AB, Canada



Asthma

2020 Global Initiative for Asthma Guidelines

FitzGerald et al. *Can J Respir Crit Care Sleep Med* 2017;1(4)Lougheed et al. *Can Respir J* 2012;19(2)

DIFFERENTIAL DIAGNOSIS OF WHEEZING

EXTRATHORACIC AIRWAY OBSTRUCTION

- **OROPHARYNX**—enlarged tonsils, retropharyngeal abscess, obesity, post-nasal drip
- **LARYNX**—laryngeal edema, laryngostenosis, laryngocele, epiglottitis, anaphylaxis, severe laryngopharyngeal reflux, laryngospasm
- **VOCAL CORDS**—vocal cord dysfunction, paralysis, hematoma, tumor, cricoarytenoid arthritis

INTRATHORACIC AIRWAY OBSTRUCTION

- **TRACHEAL OBSTRUCTION**—tracheal/subglottic stenosis, tracheomalacia, tracheobronchitis (herpetic, fungal), malignancy, benign tumor, aspiration, foreign body
- **TRACHEAL COMPRESSION**—goiter, right-sided aortic arch
- **LOWER AIRWAY OBSTRUCTION**—asthma, COPD, bronchiolitis, bronchiectasis, carcinoid tumor, aspiration, malignancy
- **PARENCHYMA**—pulmonary edema
- **VASCULAR**—pulmonary embolism

PATHOPHYSIOLOGY

DEFINITION OF ASTHMA—heterogeneous disease, characterized by chronic airway inflammation with variable expiratory airflow limitation, which may later become persistent

CLINICAL PHENOTYPES OF ASTHMA

- **ALLERGIC ASTHMA**—most recognized; often starts in childhood and associated with a past or family history of allergic disease such as eczema, allergic rhinitis, or food/drug allergy; induced sputum eosinophils often increased; responds well to inhaled corticosteroid (ICS) treatment

PATHOPHYSIOLOGY (CONT'D)

- **NON-ALLERGIC ASTHMA**—asthma not associated with allergy. Sputum analysis may be neutrophilic, eosinophilic, or paucigranulocytic; lower short-term response rate to ICS
- **ADULT-ONSET ASTHMA**—often non-allergic, more frequently in women; often requires higher doses of ICS or is relatively refractory to corticosteroid treatment. Occupational asthma must be ruled out
- **ASTHMA WITH PERSISTENT AIRFLOW LIMITATION**—patients with longstanding asthma develop incompletely reversible airflow limitation thought to be due to airway wall remodeling
- **ASTHMA WITH OBESITY**—prominent respiratory symptoms and little eosinophilic airway inflammation

EXACERBATORS OF ASTHMA

- **INFECTIONS**—viral, bacterial, fungal
- **OUTDOORS**—respirable particulates, ozone, sulfur dioxide, cold air, humidity, smoking
- **INDOORS**—smoke, dust mites, air conditioners, humidity, perfumes, scents, mold, animal dander
- **NON-ADHERENCE**
- **INCORRECT INHALER TECHNIQUE**
- **MAJOR PSYCHOLOGICAL OR SOCIOECONOMIC PROBLEMS**

RISK FACTORS FOR ASTHMA

EXACERBATIONS—>1 exacerbation in previous year, socioeconomic status, poor adherence, incorrect inhaler technique, low lung function, smoking, eosinophilia

CLINICAL FEATURES

HISTORY—history of asthma and any life-threatening exacerbations, number of ER visits/hospital admissions in the last 6 months (or ever),

CLINICAL FEATURES (CONT'D)

any ICU admissions, previous prednisone use, triggers for attacks, usual peak expiratory flow rate, change in peak flow rates, wheezing, cough, dyspnea, decreased function, exercise limitation, nocturnal symptoms, absenteeism from work/school, postnasal drip, recurrent sinusitis, GERD, past medical history, medication history, psychosocial issues, occupational and work environment, home environment (pets, heating source, filter changes, mold)

PHYSICAL—HR ↑, RR ↑, pulsus paradoxus, O₂ requirement, moderate-severe dyspnea, barrel chest, cyanosis, stridor, chest hyperresonance, decreased breath sounds, wheezing, forced expiratory time

TYPES OF WHEEZING—inspiratory wheeze and expiratory wheeze are classically associated with extrathoracic and intrathoracic airway obstruction, respectively. However, they are neither sensitive nor specific and cannot help to narrow differential diagnosis

INVESTIGATIONS**BASIC**

- **LABS**—CBC (including eosinophils), lytes, urea, Cr, troponin/CK
- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S, nasopharyngeal swab for viral studies
- **IMAGING**—CXR

SPECIAL

- **ABG**—if acute respiratory distress
- **PEAK FLOW METER**—need to compare bedside reading to patient's baseline
- **SPIROMETRY/PFT** (non-acute setting)—↑ FEV₁ >12% and an absolute ↑ by 200 mL post-bronchodilator suggests asthma
- **BRONCHIAL PROVOCATION TESTING** (i.e. methacholine challenge, non-acute setting)—if diagnosis of asthma not confirmed by spirometry alone. A decrease of FEV₁ >20% after methacholine challenge suggests asthma. Sens 95%
- **ALLERGY TESTING** (non-acute setting)—skin prick testing has high sensitivity, allergen serology IgE testing
- **SPUTUM EOSINOPHIL COUNTS** (non-acute setting)—performed in specialized centres for monitoring of asthma control in patients with moderate to severe asthma
- **FRACTIONAL CONCENTRATION OF EXHALED NITRIC OXIDE (FeNO)**—not currently recommended for general asthma population; further studies required to determine specific patients who would benefit and frequency of testing

ACUTE MANAGEMENT

ABC—O₂ to keep sat >92%, IV

BRONCHODILATORS—*salbutamol* 100 µg MDI 2 puffs q6h ATC + q1h PRN and *ipratropium* 20 µg MDI 2 puffs q6h scheduled (frequency stated is only a guide, may increase or decrease on a case by case basis); consider asthma protocol if present in Emergency Department

STERIOD—*prednisone* 0.5–1 mg/kg PO daily × 7–14 days (may be shorter depending on response) or *methylprednisolone* 0.4–0.8 mg/kg IV daily (until conversion to prednisone)

OTHERS—if refractory case and life-threatening, consider IV epinephrine, IV salbutamol, theophylline, inhaled anesthetics, MgSO₄

RESPIRATORY SUPPORT—non-invasive ventilation, intubation and mechanical ventilation

LONG-TERM MANAGEMENT

EDUCATION—**smoking cessation** (see p. 490). **Asthma action plan. Puffer technique** education and review; consider medication adherence and cost to patient

ENVIRONMENTAL CONTROL—**avoidance** of outdoor/indoor allergens, irritants, and infections; home environment cleanliness (e.g. steam cleaning)

VACCINATIONS—influenza vaccine annually and pneumococcal vaccine every 5 years

MANAGE COMORBIDITIES—obesity, GERD, allergies, rhinitis/sinusitis/nasal polyps, anxiety/depression

ASTHMA MEDICATIONS

- **STEP 1** (infrequent asthma symptoms <2 per month and no risk factors for exacerbations)—low dose ICS-formoterol as needed
- **STEP 2** (asthma symptoms or need for reliever ≥2x per month)—daily low dose ICS or as needed low dose ICS-formoterol; also consider daily leukotriene receptor antagonist (LTRA), which is most effective in asthma complicated with sinus disease and exercise-induced asthma, or low dose scheduled ICS plus SABA as needed (*salbutamol* 100 µg MDI 2 puffs PRN)
- **STEP 3** (asthma symptoms most days)—low dose ICS-LABA, consider increasing to medium dose ICS
- **STEP 4** (asthma symptoms most days and low lung function)—medium dose ICS-LABA, consider increasing to high dose ICS, add-on tiotropium or LTRA
- **STEP 5** (severe asthma symptoms or need for reliever most days and low lung function)—high dose ICS-LABA, consider low doses oral corticosteroids

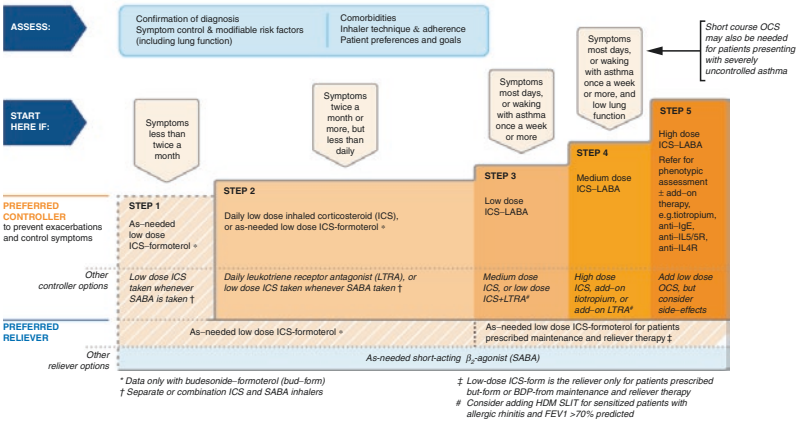
LONG-TERM MANAGEMENT (CONT'D)

- **PHENOTYPE ASSESSMENT**—referral
- **ADD-ON THERAPY**—anti-IgE (i.e. omalizumab for refractory allergic asthma), anti-IL5/5R (i.e. SC mepolizumab or benralizumab with severe eosinophilic asthma), anti-IL4R (i.e. SC dupilumab for severe type 2 asthma, or requiring oral corticosteroids)
- **AZITHROMYCIN**—consider *azithromycin* 500 mg PO 3 ×/week (consider ototoxicity

LONG-TERM MANAGEMENT (CONT'D)

- and cardiac arrhythmia; requires ECG to check for long QTc, sputum for atypical mycobacteria; treatment for at least 6 months to determine efficacy)
- **BRONCHIAL THERMOPLASTY**—severe asthma, currently should only be performed as a part of clinical study; further evidence on effectiveness and safety needed

SUGGESTED INITIAL CONTROLLER TREATMENT IN ADULTS AND ADOLESCENTS WITH A DIAGNOSIS OF ASTHMA



HDM: house dust mite; ICS: inhaled corticosteroid; LABA: long-acting beta2-agonist; LTRA: leukotriene receptor antagonist; OCS: oral corticosteroids; SABA: short-acting beta2-agonist; SLIT: sublingual immunotherapy

© 2020 Global Initiative for Asthma, reprinted with permission. Available from www.ginasthma.org

TREATMENT ISSUES

ASTHMA CONTROL CRITERIA

Characteristic	Frequency or value
Daytime symptoms	<4 days/week
Night-time symptoms	<1 night/week
Physical activity	Normal
Exacerbations	Mild, infrequent
Absence from work or school due to asthma	None
Need for a SABA	<4 doses/week
FEV1 or PEF	≥90% personal best
PEF diurnal variation ^a	<10–15%
Sputum eosinophils	<2–3%

^aDiurnal variation is calculated as the difference between the highest and lowest PEF divided by the highest PEF multiplied by 100 for morning and night (determined over a 2 week period)

TREATMENT ISSUES (CONT'D)

ASSESSING ASTHMA SEVERITY

- **MILD**—well controlled with step 1 or 2 treatment (i.e. PRN ICS-formoterol alone)
- **MODERATE**—well controlled with step 3 treatment (i.e. low dose ICS-LABA)
- **SEVERE**—requires step 4 or 5 treatment (i.e. high dose ICS-LABA to prevent it from becoming uncontrolled) or asthma that remains uncontrolled

COMMON INHALED MEDICATIONS

- **SHORT-ACTING β-AGONISTS (SABA)**—*salbutamol* MDI 100 µg 1–2 puffs PRN or 2.5 mg NEB PRN, *terbutaline* 500 µg INH PRN
- **SHORT-ACTING MUSCARINIC ANTAGONISTS (SAMA)**—*ipratropium* MDI 20 µg 2 puffs QID or 500 µg NEB QID
- **LONG-ACTING β-AGONISTS (LABA)**—*formoterol* 6–24 µg INH BID, *salmeterol* diskus 50 µg 1 puff BID

TREATMENT ISSUES (CONT'D)

- **LONG-ACTING MUSCARINIC ANTAGONISTS (LAMA)**—*tiotropium* 18 µg INH daily
- **INHALED CORTICOSTEROIDS**—*beclomethasone* 125–250 µg INH BID, *budesonide* turbuhaler 200–400 µg INH BID or 0.5–1 mg NEB BID, *fluticasone* 125–250 µg INH BID, *ciclesonide* MDI 100–400 µg INH daily (only indicated for asthma at this time, not COPD), *mometasone twisthaler* 100–400 µg INH BID

ADMISSION CRITERIA

	FEV1 (L)	PEF (L/min)	PaO ₂	Action
Very severe	–	–	<90% with O ₂	Admit
Severe	<1.6 (<40%)	<200 (<40%)	<90%	Admit
Moderate	1.6–2.1	200–300	>90%	Admit?
Mild	>2.1 (>60%)	>300 (>60%)	>90%	Send home

DISCHARGE CRITERIA—consider discharging patient if peak flow >70% of usual (or predicted) value for at least 1 h after bronchodilator

SPECIFIC ENTITIES**EXERCISE-INDUCED ASTHMA**

- **PATHOPHYSIOLOGY**—mild asthma with symptoms only during exercise due to bronchoconstriction as a result of cooling of airways associated with heat and water loss
- **DIAGNOSIS**—spirometry. Exercise or methacholine challenge may help in diagnosis
- **TREATMENTS**—prophylaxis with *salbutamol* 2 puffs MDI, given 5–10 min before exercise. Consider leukotriene antagonists or inhaled glucocorticoids if frequent use of prophylaxis

OCCUPATIONAL ASTHMA AND WORK-EXACERBATED ASTHMA

- **PATHOPHYSIOLOGY**—may be induced or aggravated by exposure to allergens or other sensitizing agents at work, or sometimes from a single, massive exposure; estimated 5–20% of new adult-onset asthma cases can be attributed to an occupational exposure

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—PEF monitoring at and away from work
- **MANAGEMENT**—refer to Occupational Medicine specialist, use strategies to limit exposure to allergen/sensitizing agent; consider changing occupations; treat asthma as per guidelines

TRIAD ASTHMA (Samter syndrome)—triad of asthma, aspirin/NSAIDs sensitivity, and nasal polyps. Cyclooxygenase inhibition → ↓ prostaglandin E₂ → ↑ leukotriene synthesis → asthma symptoms. Management includes ASA/NSAIDs avoidance and leukotriene antagonists (montelukast)

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

- **PATHOPHYSIOLOGY**—associated with asthma and cystic fibrosis. Due to colonization of the airways by *Aspergillus fumigatus*, leading to an intense, immediate hypersensitivity-type reaction in the airways
- **CLINICAL FEATURES**—history of asthma or cystic fibrosis (CF), recurrent episodes of fever, dyspnea, and productive cough (brownish sputum). Peripheral blood eosinophilia. CXR findings of patchy infiltrates and central bronchiectasis, CT chest findings of central bronchiectasis, “finger-in-glove” appearance (i.e. mucus-filled dilated bronchi)
- **DIAGNOSIS**—one predisposing condition (asthma or CF); obligatory criteria (positive *Aspergillus* extract skin test, detectable serum IgE level, elevated total serum IgE concentration); other criteria (≥2 must be present: serum antibodies to *A. fumigatus* or elevated *A. fumigatus*-specific IgG levels, radiographic pulmonary opacities consistent with ABPA, elevated eosinophil in glucocorticoid-naïve patients)
- **TREATMENTS**—systemic glucocorticoids (i.e. *prednisone* 0.5 mg/kg PO daily or equivalent × 14 days), followed by tapering over 3–4 months; consult Infectious Diseases service; consider antifungal therapy with itraconazole or voriconazole as part of initial therapy for acute ABPA, with the goal of reduction in the long-term glucocorticoid dose

Patterson et al. Clin Infect Dis 2016;63(4)

Acute Dyspnea 2015 ACCP/CTS Guideline Prevention of Acute Exacerbations of COPD

DIFFERENTIAL DIAGNOSIS

RESPIRATORY

- **AIRWAY**—COPD exacerbation, asthma exacerbation, acute bronchitis, infectious exacerbation of bronchiectasis, foreign body obstruction
- **PARENCHYMA**—pneumonia, cryptogenic organizing pneumonia (COP), ARDS, acute exacerbation of interstitial lung disease
- **VASCULAR**—pulmonary embolism, pulmonary hypertension
- **PLEURAL**—pneumothorax, pleural effusion

CARDIAC

- **MYOCARDIAL**—HF exacerbation, myocardial infarction
- **VALVULAR**—aortic stenosis, acute aortic regurgitation, mitral stenosis, endocarditis
- **PERICARDIAL**—pericardial effusion, tamponade

SYSTEMIC—sepsis, metabolic acidosis, anemia, cachexia

OTHERS—neuromuscular, psychogenic, anxiety

PATHOPHYSIOLOGY

PRECIPITANTS OF COPD EXACERBATION—infections, lifestyle/environmental (10% [cigarette smoke, dust, pollutants, cold air]), non-adherence to medications, pulmonary embolism, pulmonary edema, pneumothorax, progression of COPD

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THE CLINICAL EXAMINATION PREDICT AIRFLOW LIMITATION?

	LR+	LR-
History		
Smoking >40 pack-years	12	0.63
Smoking ever	1.8	0.16
Sputum >1/4 cup	4	0.84
Chronic bronchitis symptoms	3	0.78
Wheezing	3.8	0.66
Any exertional dyspnea	2.2	0.83
Coughing	1.8	0.69
Any dyspnea	1.2	0.55

CLINICAL FEATURES (CONT'D)

	LR+	LR-
Physical		
Barrel chest	10	0.90
Decreased cardiac dullness	10	0.88
Match test	7.1	0.43
Rhonchi	5.9	0.95
Hyperresonance	4.8	0.73
FEV1 >9 s	4.8	-
FEV1 6-9 s	2.7	-
FEV1 <6 s	0.45	-
Subxiphoid cardiac apical impulse	4.6	0.94
Wheezing	4.4	0.88
Maximum laryngeal height ≤ 4 cm	4.2	0.70
Pulsus paradoxus (>15 mmHg)	3.7	0.62
Decreased breath sounds	2.6	0.66
Accessory muscle use	-	0.70
Clinical Judgement		
Overall Clinical Prediction of Moderate-Severe Disease	5.6	-
Overall Clinical Prediction of Mild Disease	2.3	-

APPROACH—“No single item or combination of items from the clinical examination rules out airflow limitation.” The best findings associated with increased likelihood of airflow limitation are objective wheezing, FEV1 >9 s, positive match test, barrel chest, hyperresonance, and subxiphoid cardiac impulse. “Three findings predict the likelihood of airflow limitation in men: years of cigarette smoking, subjective wheezing and either objective wheezing or peak expiratory flow rate.”

Holleman et al. JAMA 1995;273(4)

UPDATE—multivariate ‘Rule In’ Obstructive Disease Model (history of obstructive airways disease, smoking >40 pack-years, age ≥45, and laryngeal height ≤4 cm) has posterior odds of disease of 220. Multivariate ‘Rule Out’ Obstructive Disease Model (smoking <30 years, no wheezing symptoms, and no auscultated wheezing) has posterior odds of disease of 0.02

Simel et al. The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, troponin/CK, Ca, Mg, PO₄
- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S/fungal, nasopharyngeal swab for viral studies
- **IMAGING**—CXR
- **ECG**—left atrial enlargement, atrial fibrillation, sinus tachycardia
- **SPIROMETRY/PFT**—FEV1/FVC <0.7, may be partially reversible. Severity based on FEV1
- **ABG**—if acute respiratory distress

SPECIAL

- **BNP**—if suspect HF
- **D-DIMER, CT CHEST**—if suspect PE
- **ECHOCARDIOGRAM**

DIAGNOSTIC & PROGNOSTIC ISSUES

DIAGNOSIS OF COPD—should be considered in patients at risk of developing disease; smoking history is most important risk factor; increased risk in patients with past history of asthma or severe childhood respiratory disease, exposed to passive smoke or biomass fuel; spirometry is essential for diagnosis (fixed post-bronchodilator FEV1/FVC ratio <0.70 or less than the lower limit of normal)

GOLD CLASSIFICATION FOR COPD—all have FEV1/FVC <0.7. Severity of airflow limitation based on post-bronchodilator FEV1

- **STAGE 1** (mild)—FEV1 ≥ 80% predicted
- **STAGE 2** (moderate)—FEV1 50–79% predicted
- **STAGE 3** (severe)—FEV1 30–49% predicted
- **STAGE 4** (very severe)—FEV1 <30% predicted

MODIFIED MEDICAL RESEARCH COUNCIL (mMRC) DYSPNEA SCALE

- **0**—no breathlessness except on strenuous exercise
- **1**—short of breath when hurrying or walking up a slight hill
- **2**—walks slower than people of same age on level because of breathlessness or has to stop when walking at own pace
- **3**—stops for breath after walking 100m or after a few minutes
- **4**—too dyspneic to leave house; breathless when dressing

COPD ASSESSMENT TEST—a validated patient-reported outcome that consists of 8 items (cough, phlegm, chest tightness, shortness of breath on exertion, activity level, confidence to leave home, sleep, energy), each rated using a 6-point numeric rating scale from 0 to 5, with a higher total score indicating greater symptom burden

GOLD ABCD GRADING—assessment for initiation of COPD therapy

DIAGNOSTIC & PROGNOSTIC ISSUES (CONT'D)

Exacerbations/ Hospitalizations	Assess symptoms	
	mMRC 0–1; CAT <10	mMRC ≥2; CAT ≥10
0–1 exacerbations without hospitalization	Gold A	Gold B
≥2 exacerbations or ≥1 hospitalization	Gold C	Gold D

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 Report

PROGNOSIS OF PATIENTS WITH ACUTE EXACERBATION OF COPD—in-hospital mortality 5–10%

BODE INDEX

- **BMI**—0 points = >21, 1 point = ≤21
- **OBSTRUCTION** (post-bronchodilator FEV1)—0 points = ≥65% predicted, 1 point = 50–64%, 2 points = 36–49%, 3 points = ≤35%
- **DISTANCE WALKED IN 6 MIN**—0 points = ≥350 m, 1 point = 250–349 m, 2 points = 150–249 m, 3 points = ≤149 m
- **EXERCISE MMRC DYSPNEA SCALE**—0 points = 0–1, 1 point = 2, 2 points = 3, 3 points = 4
- **SCORING**—total BODE score calculated as sum of all points. Relative risk for death (any cause) is increased by 34% per one-point increase in BODE score. Relative risk for death (from respiratory failure, pneumonia, or pulmonary embolism) is increased by 62% per one-point increase in BODE score

Celli et al. *NEJM* 2004;350:(10)

ACUTE MANAGEMENT

ABC—O₂ to keep sat >90%, or 88–92% if CO₂ retainer, IV

BRONCHODILATORS—*salbutamol* 100 µg MDI 2 puffs q4h ATC + q1h PRN and *ipratropium* 20 µg MDI 2 puffs q4h ATC

STEROIDS—*prednisone* 40–60 mg PO daily × 5–14 days (tapering dose not always necessary) or *methylprednisolone* 60–125 mg IV q6–12 h (inpatient)

ANTIBIOTICS—give if any two of the following criteria are met: ↑ sputum purulence, ↑ dyspnea or ↑ sputum volume. Other considerations include the need for non-invasive mechanical ventilation and “at risk” for poor outcomes (substantial comorbidities, severe COPD, frequent exacerbations >3/year, recent antibiotics within 3 months); choices depend on clinical circumstance (*levofloxacin* 500 mg PO daily × 5–7 days [or 750 mg PO daily × 5

ACUTE MANAGEMENT (CONT'D)

days if no renal disease], *doxycycline* 100 mg PO BID × 5–7 days, *amoxicillin* 500 mg PO BID × 5–7 days, *cefuroxime* 250–500 mg PO BID × 5–7 days, *ceftriaxone* 1g IV × 5–7 days, or *azithromycin* 500 mg PO × 1 day then 250 mg PO daily × 4 days)

RESPIRATORY SUPPORT—non-invasive ventilation, intubation and mechanical ventilation

OTHERS—DVT prophylaxis (*unfractionated heparin* 5000 U SC q8–12 h, *enoxaparin* 40 mg SC q24h, *dalteparin* 5000 U SC q24h, *tinzaparin* 75 IU/kg SC q24h), physiotherapy

LONG-TERM MANAGEMENT

EDUCATION—**smoking cessation** (see p. 490). Disease-specific self-management program. **Inhaler technique** education and review

VACCINATIONS—influenza vaccine annually and pneumococcal vaccine booster every 5 years

REHABILITATION—**education** and **exercise training** (increases quality of life and exercise tolerance); **pulmonary rehabilitation** associated with ↓ risk of recurrent exacerbation in patients with moderate to very severe COPD and recent AECOPD (<4 weeks)

LONG-TERM MANAGEMENT (CONT'D)

LONG-TERM OXYGEN THERAPY—if chronic hypoxemia

INITIAL PHARMACOLOGIC THERAPY—based on symptoms and risk of exacerbations

- **GOLD A (MINIMAL SYMPTOMS, LOW RISK OF EXACERBATION)**—short-acting bronchodilator with SABA (short-acting beta agonist) and/or SAMA (short-acting muscarinic antagonist)
- **GOLD B (MORE SYMPTOMS, LOW RISK OF EXACERBATION)**—regular treatment with long-acting bronchodilator (LAMA or LABA) plus SABA for symptom relief as needed
- **GOLD C (MINIMAL SYMPTOMS, HIGH RISK OF EXACERBATION)**—regular treatment with LAMA plus SABA for symptom relief as needed
- **GOLD D (MORE SYMPTOMS, HIGH RISK OF EXACERBATION)**—regular treatment with LAMA or combination LABA and LAMA if severe breathlessness (CAT >20); if features of asthma/COPD overlap syndrome, ICS/LABA combination may be preferred; plus SABA for symptom relief as needed

SUBSEQUENT PHARMACOLOGIC THERAPY

Current therapy	If persistent dyspnea or high COPD impact (i.e. mMRC ≥2 or CAT ≥10) with no exacerbations	If ≥1 exacerbations in past year ± persistent dyspnea or high COPD impact
SABA or SABA-SAMA PRN	Add LAMA or LABA	Add LAMA
LAMA or LABA monotherapy	Change to LAMA/LABA	LAMA/LABA if peripheral eosinophils normal LABA/ICS if LAMA contraindicated and 1 exacerbation in past year with peripheral eosinophils >300/μL or ≥2 exacerbations/1 hospitalization in past year with peripheral eosinophils ≥100/μL
LABA/ICS	LAMA/LABA/ICS or LAMA/LABA if no response to ICS or adverse effects from ICS	LAMA/LABA/ICS if prior indication for ICS LAMA/LABA if lack of response to ICS or adverse effects from ICS
LAMA/LABA	Trial of different LAMA/LABA or alternate delivery system Consider low dose theophylline, repeat pulmonary rehabilitation	LAMA/LABA/ICS or Continue LAMA/LABA and add phosphodiesterase-4 inhibitor (roflumilast 500 μg PO daily) ^a or azithromycin ^b
LAMA/LABA/ICS	Continue LAMA/LABA/ICS Consider low dose theophylline (400 mg PO daily × 3 days, then 400–600 mg PO daily, therapeutic level 10–20 μg/mL), repeat pulmonary rehabilitation Consider stopping ICS if lack of response or adverse effect to ICS	Add roflumilast ^a or azithromycin ^b Stop ICS if lack of response or adverse effect

^aroflumilast for patients with FEV₁ <50% predicted and at least 1 hospitalization in past year

^bazithromycin preventive therapy is more effective in patients who are not current smokers; consider development of resistant organisms such as non-Tuberculous mycobacterium

LONG-TERM MANAGEMENT (CONT'D)

INVASIVE INTERVENTIONS—if symptoms still persistent and/or decline in function, consider lung volume reduction procedures (surgery, endobronchial valves), lung transplantation

TREATMENT ISSUES

COMMON INHALED MEDICATIONS (DPI=dry powder inhaler; SMI=soft mist inhaler)

- **LAMA**—*tiotropium* DPI 18 mcg daily or SMI 2 inhalations of 2.5 mcg once daily, *glycopyrronium* DPI 50 mcg capsule once daily, *umeclidinium* DPI 62.5 mcg inhalation daily, *aclidinium* DPI 400 mcg BID
- **LABA**—*formoterol* DPI 12–24 mcg BID, *indacaterol* DPI 75 mcg daily, *salmeterol* DPI 50 mcg BID
- **LAMA/LABA COMBINATIONS**—*glycopyrrolate* 50 mcg/*indacaterol* 110 mcg 1 INH daily, *tiotropium* 2.5 mcg/*olodaterol* 2.5 mcg 2 INH daily, *umeclidinium* 62.5 mcg/*vilanterol* 25 mcg 1 INH daily
- **LAMA/LABA/ICS**—*fluticasone furoate* 100 mcg/*umeclidinium* 62.5 mcg/*vilanterol* 25 mcg 1 INH daily

FACTORS FOR IMPENDING INTUBATION—cardiac or respiratory failure, hemodynamic instability, markedly elevated respiratory rate (>35/min), fatigue and labored respiration, use of accessory muscles, worsening hypercapnia, acidosis (especially lactic), stridor (impending upper airway obstruction), agonal breathing (impending respiratory arrest)

LIFE-PROLONGING MEASURES FOR COPD—smoking cessation, supplemental O₂, lung transplant

INDICATIONS FOR SUPPLEMENTAL HOME O₂—ABG done at room air. PaO₂ <55 mmHg alone or PaO₂ <60 mmHg in the presence of bilateral ankle edema, cor pulmonale, or hematocrit >56%

SPECIFIC ENTITIES **α 1-ANTITRYPSIN DEFICIENCY**

- **PATHOPHYSIOLOGY**—production of an abnormal protease inhibitor (homozygous ZZ) with impaired transport out of the liver. Serum level is only 10–15% of normal → increased protease activity leads to emphysema and cirrhosis (10%)
- **DIAGNOSIS**— α 1-antitrypsin levels; targeted testing should be considered in patients with COPD diagnosed before 65 years of age or with a smoking history of <20 pack years
- **TREATMENTS**—similar to COPD, α 1-antitrypsin replacement

SPECIFIC ENTITIES (CONT'D)**ASTHMA AND COPD OVERLAP SYNDROME (ACOS)**

- **DIAGNOSIS**—patients with clinical features of both asthma and COPD. Airflow limitation not fully reversible, FEV₁/FVC ratio <0.7 or <LLN and bronchodilator increase in FEV₁ >12% and 400 mL; history of atopy or allergies; exposure to risk factors (i.e. >10 pack year smoking or equivalent, indoor/outdoor air pollutant exposure)
- **TREATMENTS**—similar to COPD and asthma

BRONCHIOLITIS OBLITERANS

- **PATHOPHYSIOLOGY**—severe inflammation of bronchioles → airflow obstruction. Very different from bronchiolitis obliterans organizing pneumonia (BOOP)/cryptogenic organizing pneumonia (COP), a parenchymal lung disorder
- **CAUSES**—infection (viral, *Mycoplasma*), inflammatory (ulcerative colitis, rheumatoid arthritis), transplant (bone marrow, lung), toxic fumes, idiopathic
- **TREATMENTS**—bronchiolitis obliterans (with an organizing intraluminal exudate and proliferative granulation tissue polyp) is usually steroid responsive. Constrictive bronchiolitis (late, fibrotic, concentric) is not responsive to glucocorticoids

BRONCHIECTASIS

- **PATHOPHYSIOLOGY**—airway obstruction, destruction, altered immunity → ↑ cellular and mediator inflammatory response → ↑ elastase, sputum production → recurrent infections → vicious cycle → permanent dilatation of bronchi. Major types of bronchiectasis include
 - **CYLINDRICAL OR TUBULAR BRONCHIECTASIS**—dilated airways alone, sometimes represents residual effect of pneumonia and may resolve
 - **VARICOSE BRONCHIECTASIS**—focal constrictive areas along the dilated airways
 - **SACULAR OR CYSTIC BRONCHIECTASIS**—most severe form. Progressive dilatation of the airways, resulting in large cysts or saccules
- **CAUSES**
 - **FOCAL**—broncholith, post-infectious, tumor, extrinsic lymph node compression, post-lobar resection, recurrent aspiration
 - **DIFFUSE**
 - **POST-INFECTIOUS**—bacterial (*Pseudomonas*, *Haemophilus*), mycobacterium, fungal, viral (adenovirus, measles, influenza, HIV)

SPECIFIC ENTITIES (CONT'D)

- **IMMUNODEFICIENCY**—cancer, chemotherapy, hypogammaglobulinemia, immunosuppression, sequelae of toxic inhalation or aspiration of foreign body
- **INTERSTITIAL LUNG DISEASE**—traction bronchiectasis
- **INFLAMMATORY**—RA, SLE, Sjögren syndrome, relapsing polycondritis, IBD
- **INHERITED**— α 1-antitrypsin deficiency, cystic fibrosis, primary ciliary dyskinesia (Kartagener syndrome, Young syndrome), tracheobronchomegaly (Mounier-Kuhn syndrome), cartilage deficiency (Williams-Campbell syndrome), Marfan syndrome

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—high-resolution CT chest (signet ring sign), PFT (obstruction \pm reversibility)
- **TREATMENTS**—exercises, chest physiotherapy, and bronchodilators similar to COPD; however, if reversible, inhaled corticosteroids should be given early. Ensure adequate systemic hydration. Effective treatment of exacerbations

Related Topics

Cryptogenic Organizing Pneumonia (p. 21)
 Pulmonary Function Tests (p. 25)
 Smoking (p. 490)

PneumoniaMetlay et al. *AJRCCM* 2019;200(7)**TYPES OF PNEUMONIA****COMMUNITY-ACQUIRED PNEUMONIA**

- **BACTERIAL**—*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus*, *Moraxella*
- **ATYPICAL**—*Mycoplasma*, *Chlamydia*, *Legionella*, TB, community-acquired MRSA
- **VIRAL**—influenza, parainfluenza, metapneumovirus, RSV, adenovirus, SARS-CoV-2
- **FUNGAL**—blastomycosis, cryptococcus, histoplasmosis

ASPIRATION PNEUMONIA

- **POLYBACTERIAL INCLUDING ANAEROBES**—*Bacteroides*, *Peptostreptococcus*, *Fusobacterium* species and other Gram-positive bacilli
- **CHEMICAL PNEUMONITIS**

PNEUMONIA IN THE IMMUNOCOMPROMISED (see p. 277)

NOSOCOMIAL PNEUMONIA—begins in non-intubated patient within 48 hours of admission

- **POLYBACTERIAL**—*S. aureus*, MRSA, *Pseudomonas aeruginosa*, Enterobacteriaceae (*Klebsiella*, *Escherichia coli*, *Serratia*), *Haemophilus*, *Acinetobacter*
- **VIRAL**—influenza

VENTILATOR-ASSOCIATED PNEUMONIA—begins >48 hours after the patient is intubated (see p. 107)

HEALTHCARE ASSOCIATED PNEUMONIA—pneumonia that (A) occurs within 90 days of hospitalization of 2 days or more, a stay at nursing home, or a visit to an oral puncture care facility, hospital-based clinic or hemodialysis facility; or (B) occurs within 3 days of receiving antibiotics, chemotherapy, or any type of wound care

PATHOPHYSIOLOGY**COMPLICATIONS OF PNEUMONIA**

- **PULMONARY**—ARDS, lung abscess \pm cavitory formation, parapneumonic effusion/empyema, pleuritis \pm hemorrhage
- **EXTRAPULMONARY**—purulent pericarditis, hyponatremia (from SIADH), sepsis

CLINICAL FEATURES**RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE COMMUNITY-ACQUIRED PNEUMONIA?**

	LR+	LR-
History		
Cough	1.8	0.31
Sputum	1.3	0.55
Dyspnea	1.4	0.67
Fever	1.7–2.1	0.59–0.71
Asthma	0.1	3.8
Dementia	3.4	0.94
Immunosuppression	2.2	0.85
Physical		
RR >25	1.5–3.4	0.78–0.82
Dullness to percussion	2.2–4.3	0.79–0.93
Decreased breath sounds	2.3–2.5	0.64–0.78
Crackles	1.6–2.7	0.62–0.87
Bronchial breath sounds	3.5	0.9
Egophony	2.0–8.6	0.76–0.96

CLINICAL FEATURES (CONT'D)

PREDICTION RULE—Diehr model (rhinorrhea = -2 points, sore throat = -1 point, night sweats = +1 point, myalgias = +1 point, sputum all day = +1 point, RR >25 = +2 points, temp $\geq 37.8^\circ\text{C}$ [$\geq 100^\circ\text{F}$] = +2 points. If score ≥ 3 , LR+ 14; if ≥ 1 , LR+ 5.0; if < -1 LR+ 0.22)

APPROACH—individual or combinations of symptoms and signs have inadequate test characteristics to rule in or rule out the diagnosis of pneumonia. “Decision rules that use the presence or absence of several symptoms and signs to modify the probability of pneumonia are available, the simplest of which requires the absence of any vital sign abnormalities to exclude the diagnosis.” If diagnostic certainty is required in the management of a patient with suspected pneumonia, then chest radiography (gold standard) should be performed

Metlay et al. JAMA 1997;278(17)
Simel et al. The Rational Clinical Examination. McGraw-Hill, 2009

SURFACE LUNG MARKINGS

- **INFERIOR MARGIN OF THE LUNGS**—level of 6th rib at the mid-clavicular line, level of 8th rib at the mid-axillary line, and level of 10th rib at the mid-scapular line
- **OBLIQUE (MAJOR) FISSURES**—draw a line diagonally from T3 vertebral body posteriorly to the 6th rib anteriorly
- **HORIZONTAL (MINOR) FISSURE**—draw a horizontal line at the level of right anterior 4th rib

Related Topics

Hypoxemia (p. 110)
 Parapneumonic Effusion and Empyema (p. 14)
 Ventilator-Associated Pneumonia (p. 107)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, troponin/CK, C-reactive protein, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S/fungal, urine C&S
- **IMAGING**—CXR \pm CT chest
- **ABG**—if respiratory distress, and for PSI if deciding on possible hospitalization

SPECIAL

- **BRONCHOSCOPY**
- **NASOPHARYNGEAL SWAB**—if suspect viral infection, check for influenza A/B, parainfluenza, SARS-CoV-2, human metapneumovirus, RSV, adenovirus

INVESTIGATIONS (CONT'D)

- **MYCOPLASMA IgM**
- **URINE FOR LEGIONELLA ANTIGEN**

DIAGNOSTIC AND PROGNOSTIC ISSUES**PNEUMONIA SEVERITY OF ILLNESS (PSI) SCORE**

- **SCORING**—age, female (-10), nursing home (+10), cancer (+30), liver disease (+20), heart failure (+10), CVA (+10), renal failure (+10), altered mental status (+20), RR >30 (+20), SBP <90 mmHg (+20), temp $>40^\circ\text{C}$ [$>104^\circ\text{F}$] (+15), HR >125 (+10), pH <7.35 (+30), BUN >10.7 mmol/L [>30 mg/dL] +20, Na <130 mmol/L (+20), glucose >13.9 mmol/L [>250 mg/dL] +10, hematocrit <30% (+10), P_aO_2 <60 mmHg or O_2 saturation <90% on room air (+10), pleural effusion (+10)
- **UTILITY**—originally developed as a prognostic tool. Consider admission if PSI score >90. Clinical judgment more important than PSI in determining admission

INFECTIOUS DISEASES SOCIETY OF AMERICA (IDSA)/AMERICAN THORACIC SOCIETY (ATS) SEVERITY CRITERIA FOR ICU ADMISSION

- **MAJOR CRITERIA**—septic shock requiring vasopressor support, respiratory failure requiring mechanical ventilation
- **MINOR CRITERIA**—altered mental status, hypotension requiring aggressive fluid resuscitation, temperature $<36^\circ\text{C}$, respiratory rate ≥ 30 , $\text{PaO}_2/\text{FiO}_2 \leq 250$, blood urea ≥ 7 mmol/L (20 mg/dL), leukocyte count ≤ 4000 cells/ μL , platelets $<100,000/\mu\text{L}$, multilobar infiltrates
- **UTILITY**—severe community-acquired pneumonia is defined as meeting 1 major criteria or ≥ 3 minor criteria

MANAGEMENT

ACUTE—ABC, O_2 , IV, consider **salbutamol** 100 μg MDI 2 puffs q6h + q1h PRN

ANTIBIOTICS

- **COMMUNITY-ACQUIRED PNEUMONIA**—see treatment issues for an approach to selecting the appropriate regimen (remember to adjust for renal function)
 - **TETRACYCLINE**—doxycycline 100 mg PO BID $\times 5$ days
 - **MACROLIDES**—azithromycin 500 mg PO $\times 3$ days; clarithromycin 500 mg PO BID $\times 5$ days

MANAGEMENT (CONT'D)

- **FLUOROQUINOLONES**—levofloxacin 750 mg PO daily × 5 days, moxifloxacin 400 mg PO daily × 5 days; avoid if exposed to fluoroquinolone within last 3–6 months
- **β-LACTAMS**—amoxicillin 1 g PO TID, amoxicillin-clavulanate 2 g PO BID, cefuroxime 750 mg IV q8h or 500 mg PO BID, cefotaxime 1 g IV q8h, ceftriaxone 1–2 g IV q24h, usually × 5 days
- **ANAEROBIC COVERAGE**—if suspect aspiration, add clindamycin 150–450 mg PO q6h or 600–900 mg IV q8h or metronidazole 500 mg PO/IV BID–TID
- **NOSOCOMIAL PNEUMONIA**—see treatment issues for an approach to selecting the appropriate regimen
 - **ANTI-PSEUDOMONAL**—ceftazidime, cefepime, meropenem, ciprofloxacin, aminoglycosides, piperacillin-tazobactam (do not use same class of agent when double covering for *Pseudomonas*)
 - **FURTHER GRAM-NEGATIVE COVERAGE**—ciprofloxacin 500 mg PO BID, gentamicin 6 mg/kg IV q24h, tobramycin 6 mg/kg IV q24h (follow levels to adjust dosing)
 - **ANAEROBIC COVERAGE**—if suspect aspiration, replace gentamicin with clindamycin 150–450 mg PO q6h or 600–900 mg IV q8h or add metronidazole 500 mg PO BID
 - **ANTIBIOTIC COURSE**—7–8 days for most, 14–21 days for *Pseudomonas*, *S. aureus*, *Stenotrophomonas*, *Acinetobacter*
- **ASPIRATION PNEUMONIA**—clindamycin 600 mg IV BID, switch to 300 mg PO QID when stable. May add cefotaxime or ceftriaxone for Gram-positive and Gram-negative coverage
- **TUBERCULOSIS PNEUMONIA**—see p. 267
- **PNEUMOCYSTIS JIROVECI PNEUMONIA**—see p. 278

NON-PHARMACOLOGIC TREATMENTS

- **VACCINATIONS**—influenza vaccine annually and pneumococcal vaccine booster every 5 years
- **CHEST PHYSIOTHERAPY**

TREATMENT ISSUES

IMPORTANT NOTE—avoid using the same antibiotic class if given within 3 months. Consider vancomycin or linezolid if MRSA suspected; emergence of community-acquired MRSA associated with serious necrotizing infections

OUTPATIENT ANTIBIOTICS CHOICE

- **PREVIOUSLY HEALTHY**—macrolide (azithromycin, clarithromycin, or doxycycline). Other antibiotic choices include fluoroquinolone, macrolide plus amoxicillin ± clavulanate

TREATMENT ISSUES (CONT'D)

- **COMORBIDITIES** (COPD, diabetes, renal failure, HF, malignancy)—macrolide or fluoroquinolone
- **SUSPECTED ASPIRATION WITH INFECTION**—amoxicillin-clavulanate or clindamycin
- **INFLUENZA WITH BACTERIAL SUPERINFECTION**—β-lactam or fluoroquinolone

INPATIENT ANTIBIOTIC CHOICE—second-third-generation β-lactam plus macrolide or respiratory fluoroquinolone

ICU ANTIBIOTICS CHOICE

- **PSEUDOMONAS UNLIKELY**—macrolide plus β-lactam or fluoroquinolone plus β-lactam
- **PSEUDOMONAS UNLIKELY BUT β-LACTAM ALLERGY**—fluoroquinolone with or without clindamycin
- **PSEUDOMONAS LIKELY**—double coverage with agents that are effective against *Pseudomonas* (different classes)
- **PSEUDOMONAS LIKELY BUT β-LACTAM ALLERGY**—aztreonam plus levofloxacin or aztreonam plus moxifloxacin, with or without aminoglycoside

NURSING HOME ANTIBIOTICS CHOICE

- **TREATMENT IN NURSING HOME**—fluoroquinolone or macrolide plus amoxicillin-clavulanate

DISCHARGE DECISION—clinical stabilization usually takes 2–3 days. When symptoms have significantly improved, vital signs normalized, and patient has defervesced, patients at low risk may be safely discharged on the day of switching to oral therapy without adverse consequences. Time to radiographic resolution is variable, with up to 5 months for pneumococcal pneumonia associated with bacteremia

SPECIFIC ENTITIES

CAUSES OF NON-RESOLVING PNEUMONIA—**non-infectious** (malignancy especially bronchoalveolar carcinoma or lymphoma, cryptogenic organizing pneumonia, hemorrhage), **non-bacterial** (viral, fungal), **immunocompromised** host, **antibiotic resistance**, **pneumonia complications** (abscess, empyema, ARDS)

CAUSES OF RECURRENT PNEUMONIA

- **IMMUNOCOMPROMISED** ★ **SADDIST** ★—Suppressants (steroids, chemotherapy, transplant medications, alcohol), **AIDS**, **Diabetes**, **Decreased nutrition**, **Immunoglobulin** (hypogammaglobulinemia), **Solid organ failure** (renal, liver, splenectomy), **Tumors**
- **PULMONARY**—bronchiectasis, COPD, cystic fibrosis, abnormal anatomy
- **GI**—aspiration

SPECIFIC ENTITIES (CONT'D)**LUNG ABSCESS**

- **CAUSES**—**anaerobes** (*Peptostreptococcus*, *Prevotella*, *Bacteroides*, *Fusobacterium*), **Gram-positive** (*Streptococcus milleri*, microaerophilic streptococcus, *S. aureus*), **Gram-negative** (*Klebsiella*, *Haemophilus*, *Legionella*). Nocardia and actinomycosis can rarely cause lung abscess

Pulmonary EmbolismKearon. *Chest* 2012;141(2 Suppl)Kearon. *Chest* 2016;149(2)**PATHOPHYSIOLOGY**

VIRCHOW TRIAD—risk factors for venous thromboembolism

- **ENDOTHELIAL OR VESSEL WALL INJURY**—fracture of pelvis, femur, or tibia
- **HYPERCOAGULABILITY**—obesity, pregnancy, estrogen, smoking, **cancer** (high suspicion of occult malignancy in patients who develop pulmonary embolism while on anticoagulation), **autoimmune disorders** (antiphospholipid antibody syndrome, lupus anticoagulant, IBD), **genetics** (history of DVT/PE, factor V Leiden, antithrombin III deficiency, protein C/S deficiency, prothrombin G20210A mutation, hyperhomocysteinemia)
- **STASIS**—surgery requiring >30 min of anesthesia, prolonged immobilization, CVA, HF

CLINICAL FEATURES

HISTORY—dyspnea (sudden onset), pleuritic chest pain, cough, hemoptysis, pre/syncope, unilateral leg swelling/pain, past medical history (previous DVT/PE, active cancer, immobilization or surgery in last 4 weeks, miscarriages), medications (birth control pill, anticoagulation)

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), respiratory examination (pulmonary hypertension if chronic PE), cardiac examination (right heart strain), leg swelling

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE PULMONARY EMBOLISM?

PREDICTION RULES—Wells criteria, PISA-PED, Geneva rule

APPROACH—combining the pretest probability with results of D-dimer testing reduces the need for further investigations in patients with low (<15%) to moderate (15–35%) clinical pretest probability. A patient with low to moderate clinical

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—antibiotics with anaerobic coverage until radiographic improvement and stabilization (usually several weeks to months, can be completed with oral antibiotics once patient is stable). No need for percutaneous drainage. If complicated abscess, consider thoracic surgery consult for consideration of VATS/lung resection

CLINICAL FEATURES (CONT'D)

cal probability of PE with a normal D-dimer has a LR of 0 (95% CI 0–0.06) for PE. When there is a discrepancy between clinical gestalt and clinical prediction rule, consider placing the patient into the higher pretest probability group

Chunilal et al. JAMA 2003;290(21)

Simel et al. The Rational Clinical Examination. McGraw-Hill, 2009

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, PTT, INR, troponin/CK × 3, D-dimer (if low probability for PE or outpatient), βhCG in women of reproductive age
- **IMAGING**—CXR, duplex US of legs, V/Q scan, CT chest (PE protocol)
- **ECG**—may see normal sinus rhythm (most common), sinus tachycardia (most common abnormality), atrial fibrillation, right ventricular strain (T wave inversion in anterior precordial leads), non-specific ST-T wave changes, right axis deviation, right bundle branch block and/or S₁Q₃T₃ (tall S wave in lead I, Q wave and inverted T wave in lead III)
- **ABG**—if respiratory distress

SPECIAL

- **ECHOCARDIOGRAM**—to check for right heart strain (dilated RV and elevated RVSP). Particularly important if hemodynamic changes
- **PULMONARY ANGIOGRAM**—gold standard (usually not needed)
- **THROMBOPHILIA WORKUP**—factor V Leiden, prothrombin G20210A, anticardiolipin antibody, lupus anticoagulant, protein C, protein S, antithrombin III, fibrinogen; consider homocysteine level and workup for paroxysmal nocturnal hemoglobinuria and

INVESTIGATIONS (CONT'D)

antiphospholipid syndrome in cases of combined arterial–venous thrombosis. Routine testing for hypercoagulable disorders is **not** warranted

DIAGNOSTIC ISSUES

CXR FINDINGS IN PULMONARY EMBOLISM—normal, atelectasis, unilateral small pleural effusion, enlarged central pulmonary artery, elevated hemidiaphragm, Westermark sign (abrupt truncation of pulmonary vessel), Hampton hump (wedge infarct)

D-DIMER (sens 85–96%, spec 45–68%, LR+ 1.7–2.7, LR– 0.09–0.22)—a normal D-dimer can rule out PE if low clinical suspicion

V/Q SCAN (sens high, spec high)—result often not definitive (intermediate probability) because of other intraparenchymal abnormalities

CT PE PROTOCOL (sens 57–100%, spec 78–100%)—can be very helpful as it provides clues to other potential diagnoses/pathologies as well

LEG VEIN DOPPLER (sens 50%, spec moderate)—serial dopplers may be used for diagnosis of DVT if CT or V/Q scan failed to demonstrate PE but clinical suspicion still high

WELLS CRITERIA FOR PULMONARY EMBOLISM

- **SCORING**—signs/symptoms of DVT (+3), alternative diagnosis less likely (+3), HR >100 (+1.5), immobilization or surgery in last 4 weeks (+1.5), previous DVT/PE (+1.5), hemoptysis (+1), active cancer (+1)
- **LOW SUSPICION** (sum 0–1, <10% chance)—D-dimer → if positive, CT or V/Q scan
- **INTERMEDIATE SUSPICION** (sum 2–6, 30% chance)—D-dimer → CT or V/Q scan → if negative but suspicious, leg doppler → if negative but still suspicious, pulmonary angiogram
- **HIGH SUSPICION** (sum >6, >70% chance)—CT or V/Q scan → if negative but suspicious, leg Doppler → if negative but still suspicious, pulmonary angiogram
- **MODIFIED WELLS SCORE**—PE likely (score >4); PE unlikely (≤4)

Related Topics

Anticoagulation Therapies (p. 179)

DVT (p. 177)

Hypercoagulable States (p. 174)

Pulmonary Embolism in Pregnancy (p. 464)

MANAGEMENT

ACUTE—ABC, O₂ to keep sat >94%, IV

THROMBOLYTICS—controversial as increased risk of intracranial bleed and multiple contraindications (see below). Consider only if hemodynamically unstable, right ventricular strain or life-threatening massive pulmonary embolism. Must be done in ICU. TPA 100 mg IV over 2 h, or streptokinase 250,000 IU over 30 min, the 100,000 IU/h over 12–24 h or 1.5 million IU over 2 h. Unfractionated heparin may be used concurrently

ANTICOAGULATION—if moderate to high risk of developing PE, consider initiating anticoagulation while waiting for investigations. **Heparin** (unfractionated heparin 5,000 U IV bolus, then 1,000 U/h and adjust to 1.5–2.5 × normal PTT; use UFH if considering thrombolysis), **LMWH** (enoxaparin 1 mg/kg SC BID or 1.5 mg/kg SC daily, tinzaparin 175 U/kg SC daily), or **fondaparinux** 5 mg SC daily (<50 kg), 7.5 mg SC daily (50–100 kg), or 10 mg SC daily (>100 kg). If using vitamin K antagonist, start **warfarin** 5 mg PO daily within 48 h and continue heparin/LMWH/fondaparinux for at least 5 days and until INR is between 2 and 3 for at least 48 h. **Factor Xa inhibitors** (e.g. rivaroxaban, apixaban) are the only direct oral anticoagulants that have been studied and approved as monotherapy (not requiring pre-treatment with heparin). **Direct thrombin inhibitors** (e.g. dabigatran) require a short course of LMWH for 5 days prior to transitioning to oral therapy (see Approach to Anticoagulation Therapies p. 179)

SURGICAL—embolectomy. Consider if thrombolysis failed or contraindicated or if hemodynamically unstable

IVC FILTER—if anticoagulation contraindicated

TREATMENT ISSUES**CONTRAINDICATIONS TO THROMBOLYTIC THERAPY**

- **ABSOLUTE CONTRAINDICATIONS**—history of hemorrhagic stroke or stroke of unknown origin, ischemic stroke in previous 3 months, malignant intracranial neoplasm, suspected aortic dissection, active bleeding, major trauma in previous 2 months, intracranial surgery or head injury within 3 weeks
- **RELATIVE CONTRAINDICATIONS**—TIA within 6 months, oral anticoagulation, pregnancy or within 1 week postpartum, non-compressible puncture sites, traumatic/prolonged (>10 min) CPR, uncontrolled hypertension (SBP >185 mmHg, DBP >110 mmHg), recent bleeding

TREATMENT ISSUES (CONT'D)

($<2-4$ weeks), current use of anticoagulants, advanced liver disease, infective endocarditis, active peptic ulcer, thrombocytopenia

ANTICOAGULATION DURATION

- **FIRST PULMONARY EMBOLISM WITH REVERSIBLE OR TIME-LIMITED RISK FACTOR**—anticoagulation for at least 3 months
- **UNPROVOKED PE**—at least 3 months of treatment. If no obvious risk factors for bleeding, consider indefinite anticoagulation
- **PE AND MALIGNANCY**—direct oral anticoagulants (DOACs) and SC LMWH are generally preferred over warfarin. Treatment should be continued until eradication of cancer as long as there are no significant contraindications to anticoagulation
- **PE AND RENAL DISEASE** (CrCl <30 mL/min)—treatment with warfarin
- **PE AND LIVER DISEASE**—SC LMWH; warfarin difficult to control and INR may not reflect antithrombotic effect
- **PE AND PREGNANCY OR PREGNANCY RISK**—SC LMWH is preferred for outpatient treatment. Total duration of therapy should be 3–6 months until 6 weeks post-partum unless patient has risk factors for hypercoagulable state

Pleural Effusion**DIFFERENTIAL DIAGNOSIS**

EXUDATIVE—malignancy, infection, connective tissue disease, hypothyroidism, pulmonary embolism, hemothorax, pancreatitis, chylothorax, trapped lung

TRANSUDATIVE—HF, hypoalbuminemia (GI losing enteropathy, cirrhosis, nephrotic syndrome, malnutrition), SVC obstruction, hepatic hydrothorax, urinothorax, atelectasis, trapped lung, peritoneal dialysis, hypothyroidism, pulmonary embolism

NOTE—pulmonary embolism, malignancy, hypothyroidism, trapped lung, SVC obstruction, and sarcoidosis are usually exudative, but can occasionally be transudative. HF following diuresis may become “pseudo-exudative”

CLINICAL FEATURES

HISTORY—dyspnea, cough, hemoptysis, chest pain, weight loss, fever, trauma, occupational exposures, past medical history (pneumonia, liver disease, kidney disease, thyroid disease, cancer, HF, thromboembolic disease, connective tissue disease, smoking), medications

SPECIFIC ENTITIES**FAT EMBOLISM**

- **PATHOPHYSIOLOGY**—embolism of fat globules to lungs, brain, and other organs \rightarrow metabolized to fatty acids leading to inflammatory response. Commonly caused by closed fractures of long bones, but may also occur with pelvic fractures, orthopedic procedures, bone marrow harvest, bone tumor lysis, osteomyelitis, liposuction, fatty liver, pancreatitis and sickle cell disease
- **CLINICAL FEATURES**—triad of dyspnea, neurological abnormalities (confusion), and petechial rash (head and neck, chest, axilla). May also have fever, thrombocytopenia and DIC
- **DIAGNOSIS**—clinical diagnosis (rash is pathognomonic). Investigations may include CXR, V/Q scan, CT chest and MRI head
- **TREATMENTS**—supportive care as most patients will fully recover. Mortality is 10%. Primary prophylaxis includes early mobilization. Consider trial of systemic steroids

CLINICAL FEATURES (CONT'D)

PHYSICAL—vitals, cyanosis, clubbing, tracheal deviation away from side of effusion (if no collapse or trapped lung), peripheral lymphadenopathy, Horner syndrome, respiratory examination (decreased breath sounds and tactile fremitus, stony dullness to percussion), cardiac examination, leg swelling (HF or DVT); chest US is the most sensitive and specific test and should be done at point-of-care

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN EXUDATIVE PLEURAL EFFUSION?

	Sens	Spc	LR+	LR-
Pleural cholesterol >55 mg/dL	85–94%	95–99%	7.1–250	0.07–0.16
Pleural LDH >200 U/L	70%	98%	18	0.32
Pleural: serum cholesterol ratio >0.3	93%	94%	14	0.08

CLINICAL FEATURES (CONT'D)

	Sens	Spc	LR+	LR-
Pleural: serum LDH ratio >0.6	88%	91%	9.2	0.14
Pleural: serum protein ratio >0.5	90%	90%	7.0	0.12
Combined ≥ 1 of the Light criteria	97%	85%	5.2	0.04
Pleural protein >3 g/dL	88%	86%	5.1	0.14
Pleural LDH >2/3 upper limit of normal	88–89%	93–100%	1.7–13	0.23–0.26
Serum: pleural albumin gradient <1.2 mg/dL	86–95%	42–100%	1.5–36	0.06–0.32

APPROACH—pleural effusions meeting none of the Light criteria are most likely transudative. However, if the effusion meets the Light criteria or if the effusion has a pleural cholesterol >55 mg/dL, pleural LDH >200 U/L, or ratio of pleural cholesterol to serum cholesterol >0.3, the effusion is likely exudative

Wilcox et al. *JAMA* 2014;311(23)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, LDH, total protein, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—bedside US necessary to examine pleural effusion for size, presence of loculations, CXR (PA, lateral), consider CT chest
- **THORACENTESIS**—send pleural fluid for cell count and differential, Gram stain, C&S, AFB and fungal cultures, LDH, total protein, pH, and cytology. Under special circumstances, also consider amylase, glucose, cholesterol, adenosine deaminase (for TB), albumin

SPECIAL

- **BIOPSY**—closed pleural biopsy (useful in diffuse pleural disease such as tuberculosis), medical thoracoscopy, surgical biopsy (video-assisted thoracic surgery); referral to Pulmonary Medicine or Thoracic Surgery necessary

DIAGNOSTIC ISSUES

OVERALL APPROACH—generally, if the effusion is >1/4 of hemithorax, enough fluid is present for diagnostic thoracentesis. US-guided thoracentesis is standard of care. If only a small amount of fluid is present (<10 mm [<0.4 in.]) and/or HF suspected, start with diuresis or continue to monitor with bedside ultrasound. If no improvement, perform thoracentesis to distinguish between transudative and exudative causes

THE LIGHT CRITERIA FOR EXUDATIVE EFFUSION—any one of the following criteria would suggest exudative effusion: fluid/serum total protein ratio >0.5, fluid/serum LDH ratio >0.6, fluid LDH >2/3 upper limit of normal serum level

PLEURAL FLUID ANALYSIS

- **FLUID ACIDOSIS** (pH <7.2)—complicated parapneumonic, TB, malignancy, rheumatoid arthritis, SLE, hemothorax, esophageal rupture, paragonimiasis
- **LOW FLUID GLUCOSE** (<3.3 mmol/L [<60 mg/dL])—parapneumonic, TB, malignancy, rheumatoid arthritis, eosinophilic granulomatosis with polyangiitis, hemothorax, paragonimiasis
- **FLUID EOSINOPHILIA** (>10%)—paragonimiasis, malignancy, eosinophilic granulomatosis with polyangiitis, asbestos, drug reaction, pulmonary embolism, hemothorax, pneumothorax, idiopathic (20%)
- **CYTOLOGY FOR MALIGNANCY**—yield for diagnosis with single attempt is 60%, two attempts is 85%, three attempts is 90–95%; obtain as much fluid as possible to increase diagnostic yield
- **FLUID FOR AFB**—obtain as much fluid as possible and ask laboratory to centrifuge collection and to culture sediment to increase diagnostic yield; if high positive predictive value for TB, consider referral to Pulmonary Medicine for closed pleural biopsy

MANAGEMENT

SYMPTOM CONTROL— O_2 , **diuresis** (furosemide), **drainage** (thoracentesis, pigtail catheter, indwelling pleural catheter, chest tube), **pleurodesis** (talc slurry or poudrage), **surgery** (talc slurry, pleuroperitoneal shunt, pleural abrasion, pleurectomy)

TREAT UNDERLYING CAUSE**SPECIFIC ENTITIES****PARAPNEUMONIC EFFUSION**

- **UNCOMPLICATED**—exudative effusion that resolves with resolution of pneumonia. Generally disappears with antibiotics alone

SPECIFIC ENTITIES (CONT'D)

- **COMPLICATED**—persistent bacterial invasion and fluid collection. Characterized by pleural fluid acidosis but sterile fluid. Pleural loculation may occur as fibrin gets deposited from inflammation. Treated the same as empyema
- **EMPHYEMA**—presence of bacteria in Gram stain or pus in drainage (culture not necessary). pH often <7.2. For unoculated fluid, chest tube/small-bore catheter drainage usually adequate. Consider referral to Pulmonary/Thoracic Surgery early. Regardless of degree of loculations, consider use of thrombolytics TPA 10 mg with DNase 5mg instillation into chest tube BID × 3 days. If patient still unwell after several days of antibiotic treatment, consider referral to Thoracic Surgery for consideration of VATS/decortication

Rahman NM et al. *N Engl J Med* 2011; 365:518–526

SPECIFIC ENTITIES (CONT'D)

TRAPPED LUNG—stable chronic effusion, especially with history of pneumonia, pneumothorax, thoracic surgery or hemothorax. Diagnosis is established by measuring negative change in intrapleural pressure during thoracentesis. Depending on chronicity, treat by lung re-expansion. Thoracotomy with decortication sometimes required in infectious cases

HEPATOHYDROTHORAX—suspect if cirrhosis and portal hypertension, even in the absence of ascites. Pleural effusion results from passage of peritoneal fluid into pleura because of negative intrathoracic pressures and diaphragmatic defects. Do not insert chest tube. Treat with diuresis, salt restriction, and consider liver transplantation/TIPS procedure

Chronic Cough

Gibson et al. *Chest* 2016;149(1)

DIFFERENTIAL DIAGNOSIS

NON-PULMONARY—GERD, reflux-cough syndrome, ACE inhibitors, occult congestive heart failure

PULMONARY

- **AIRWAY**—post-nasal drip/upper airway cough syndrome, asthma, chronic bronchitis, non-asthmatic eosinophilic bronchitis, bronchiectasis, neoplasm, foreign body, post-viral
- **PARENCHYMA**—occult infection, occult aspiration, interstitial lung disease, lung abscess
- **VASCULAR**—early pulmonary hypertension

PATHOPHYSIOLOGY

DEFINITION OF CHRONIC COUGH—>3 weeks; unexplained chronic cough is defined as cough persisting >8 weeks

COMPLICATIONS OF CHRONIC COUGH—exhaustion, insomnia, anxiety, headaches, dizziness, hoarseness, musculoskeletal pain, urinary incontinence, abdominal hernias

COUGH REFLEX

- **AFFERENT**—chemical or mechanical stimuli → cough receptors in the epithelium of the upper and lower respiratory tracts, pericardium, esophagus, diaphragm, and stomach → afferent nerves (vagus, glossopharyngeal, trigeminal, and phrenic) → cough center in the medulla
- **EFFERENT**—cough center with cortical input → efferent signals travel down the vagus, phrenic, and spinal motor nerves → expiratory muscles → cough

INVESTIGATIONS**BASIC**

- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S
- **INDUCED SPUTUM ANALYSIS FOR EOSINOPHIL COUNT**
- **IMAGING**—CXR (order inspiratory and expiratory views if foreign body aspiration or endobronchial lesion suspected); consider CT chest if indicated
- **SPIROMETRY/PFT**

SPECIAL

- **SINUS IMAGING**
- **BRONCHOPROVOCATION TESTING (i.e. METHACHOLINE CHALLENGE)**
- **ESOPHAGEAL PH MONITORING**

MANAGEMENT

TREAT UNDERLYING CAUSE—switch to ARB if ACE inhibitor suspected as cause of chronic cough; smoking cessation if chronic bronchitis

SYMPTOM CONTROL

- **PHARMACOLOGIC MEASURES**—*benzonatate* 100 mg PO q8h PRN, *codeine* 7.5–60 mg PO BID, *dihydrocodeine* 5–10 mg PO TID, *hydrocodone* 5 mg PO BID, *morphine* 7.5–15 mg PO BID, *dextromethorphan* 10–30 mg PO q6h, *sodium cromoglycate* 10 mg NEB QID, *levodropropizine* 75 mg PO TID, *guaifenesin* 200–400 mg PO q4h or 600 mg PO BID, *gabapentin* 100–300 mg PO TID
- **NON-PHARMACOLOGIC MEASURES**—consider endobronchial therapy for cancer airway lesions, high intrathoracic vagotomy in refractory severe cases

SPECIFIC ENTITIES**POST-NASAL DRIP/UPPER AIRWAY COUGH SYNDROME**

- **PATHOPHYSIOLOGY**—secretions in the upper airway stimulate cough receptors within the pharyngeal or laryngeal mucosa
- **CAUSES**—allergic, perennial non-allergic rhinitis, vasomotor rhinitis, acute nasopharyngitis, sinusitis
- **DIAGNOSIS**—non-specific findings; consider sinus imaging

Hemoptysis**DIFFERENTIAL DIAGNOSIS**

NON-CARDIOPULMONARY—epistaxis, upper GI bleed, coagulopathy

CARDIAC—HF, mitral stenosis

PULMONARY

- **AIRWAY**—bronchitis (acute, chronic), bronchiectasis, malignancy, foreign body, trauma
- **PARENCHYMA**
 - **MALIGNANCY**—lung cancer, metastasis
 - **INFECTIONS**—necrotizing pneumonia (*Staphylococcus*, *Pseudomonas*), abscess, septic emboli, TB, fungal
 - **ALVEOLAR HEMORRHAGE**—granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, anti-glomerular basement membrane disease, pulmonary capillaritis, connective tissue disease
- **VASCULAR**—pulmonary embolism, pulmonary hypertension, AVM, iatrogenic

PATHOPHYSIOLOGY

MASSIVE HEMOPTYSIS—100–600 mL blood in 24h. Patients may die of asphyxiation (rather than exsanguination)

CLINICAL FEATURES

HISTORY—characterize hemoptysis (amount, frequency, previous history), cough (productive), dyspnea, chest pain, epistaxis, hematemesis, weight loss, fever, night sweats, exposure, travel, joint inflammation, rash, visual changes, past medical history (smoking, lung cancer, TB, thromboembolic disease, cardiac disease), medications (warfarin, ASA, NSAIDs, natural supplements)

PHYSICAL—vitals, weight loss, clubbing, cyanosis, lymphadenopathy, Horner syndrome, respiratory and cardiac examination, leg swelling (HF or DVT), joint examination, skin examination

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—reduce irritant exposure, antihistamine-decongestant combinations (*diphenhydramine* 25–50 mg PO q4–6 h PRN, pseudoephedrine, *ipratropium nasal spray* 0.03% 2 sprays/nostril BID–TID, nasal corticosteroids, nasal saline rinses BID), surgical correction for anatomical abnormalities

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, INR, PTT, urinalysis, type and screen, crossmatch
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/C&S/AFB/fungal/cytology
- **IMAGING**—CXR, CT chest (warranted in most patients unless obvious explanation)
- **BRONCHOSCOPY**—warranted in most patients unless obvious explanation

SPECIAL

- **ETIOLOGY WORKUP**—ANA, p-ANCA (myeloperoxidase MPO antibodies), c-ANCA (anti-proteinase-3 PR3 antibodies), anti-GBM antibody, rheumatologic screen (extractable nuclear antigens)
- **ABG**—if respiratory distress

MANAGEMENT

ACUTE—ABC, **O₂, IV, intubation** to protect airway if significant hemoptysis (consider selective intubation down unaffected side, double lumen tube if anesthesia expertise available), position patient in lateral decubitus position with affected lung on bottom to preserve non-affected lung. Urgent interventional **bronchoscopy** (cold saline, topical epinephrine, tranexamic acid instillation, cautery, airway blocker, double lumen endotracheal tube). Discuss with interventional radiology for consideration of **angiographic bronchial artery embolization** (<5% risk of spinal cord ischemia due to the inadvertent embolization of a spinal artery), **lung resection**

TREAT UNDERLYING CAUSE—patients on anticoagulation should be reversed. Consider *tranexamic acid* 500 mg/5 mL inhaled × 5 days for non-massive hemoptysis. **Correct coagulopathy** (*vitamin K* 10 mg SC/IV × 1 dose or FFP); **antibiotics**; **radiation** for tumors; **diuresis** for HF; **immunosuppression** for vasculitis

MANAGEMENT (CONT'D)

SYMPTOM CONTROL—cough suppressants, sedatives, stool softeners, transfusions

SPECIFIC ENTITIES**ANTI-GLOMERULAR BASEMENT MEMBRANE DISEASE (GOODPASTURE DISEASE)**

- **PATHOPHYSIOLOGY**—anti-glomerular basement membrane antibodies → attack pulmonary and renal basement membrane

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—hemoptysis and hematuria, with respiratory and renal failure if severe
- **DIAGNOSIS**—lung/kidney biopsy
- **TREATMENTS**—steroids, cyclophosphamide, plasmapheresis

Solitary Pulmonary NoduleMcWilliams et al. *NEJM* 2013;369(10)**DIFFERENTIAL DIAGNOSIS**

MALIGNANT—bronchogenic, carcinoid, metastatic cancer

BENIGN—healed infectious granuloma, benign tumors (hamartoma), AVM, rheumatoid nodule, granulomatosis with polyangiitis (GPA), hydatid cyst, rounded atelectasis, intra-pulmonary lymph nodes, pseudotumor

PATHOPHYSIOLOGY

DEFINITION—≤3 cm well-defined lesion, completely surrounded by lung parenchyma

CLINICAL FEATURES

HISTORY—most patients are asymptomatic unless lesion is central; dyspnea, cough, hemoptysis, wheezing, chest pain, weight loss, fever, night sweats, rheumatologic screen, past travel history, occupational exposures, medical history (smoking, lung cancer or other malignancies, TB, infections, rheumatoid arthritis), medications

PHYSICAL—vitals, weight loss, clubbing, cyanosis, Horner syndrome, SVC syndrome, lymphadenopathy, respiratory examination, abdominal examination (hepatomegaly), bony tenderness

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, LDH, AST, ALT, ALP, bilirubin, INR, PTT
- **IMAGING**—old films (2 years earlier for comparison), CXR, CT chest

SPECIAL

- **ABG**
- **SCREENING FOR INFLAMMATORY DISORDERS**—ESR, CRP, ANA, ANCA
- **BIOPSY**—bronchoscopy or CT guided
- **PET/CT SCAN**—if moderate to high suspicion of lung cancer

DIAGNOSTIC ISSUES**FINDINGS SUGGESTIVE OF MALIGNANCY****★ ABCD ★**

- **AGE >50**
- **BORDER**—irregular, nodular cavity with thick wall, or spiculated, corona radiata
- **CALCIFICATION**—eccentric or noncalcified
- **DIAMETER DEFINITION OF PULMONARY MASS >3 CM DIAMETER [>1.2 IN]**. If <3 cm, 20–50% malignant. If ≥3 cm, 50% malignant

TIMING—if malignant, usually able to detect an increase in size of SPN between 30 days and 2 years. Unlikely to be malignant if significant change in <30 days or no change in 2 years

CALCIFICATION CLUES

- **MALIGNANCY**—eccentric calcification or noncalcified
- **TUBERCULOSIS OR HISTOPLASMOSIS**—central/complete calcification
- **BENIGN HAMARTOMA**—classic appearance but only present <10% of the time

BROCK UNIVERSITY CANCER PREDICTION EQUATION

- **VARIABLES**—age, sex, family history of lung cancer, emphysema, nodule size, nodule type (non-solid or ground-glass, partially solid, solid), upper lung involvement, nodule count, spiculation
- **OUTPUT**—probability of cancer within 2–4 years

MANAGEMENT

TREAT UNDERLYING CAUSE—if **low probability (<5%)**, observation with serial CT scans. If **moderate probability**, consider tissue sampling by bronchoscopy. If **high probability**, consider referral to pulmonary/interventional pulmonary medicine or thoracic surgery for staging and diagnosis

TREATMENT ISSUES**FLEISCHNER GUIDELINES FOR FOLLOWUP****SOLID PULMONARY NODULES**

Nodule size	Low malignancy risk (<5%)	Moderate (5–65%) or high (>65%) malignancy risk
Solitary		
<6 mm	No routine follow-up	CT at 12 mo
6–8 mm	CT at 6–12 mo, then consider CT at 18–24 mo	CT at 6–12 mo, then CT at 18–24 mo
>8 mm	CT at 3 mo, then at 9 and 24 mo	PET/CT, biopsy or resection
Multiple (evaluation based on largest nodule)		
<6 mm	No routine follow-up	Optional CT at 12 mo
≥6 mm	CT at 3–6 mo, then consider CT at 18–24 mo	CT at 3–6 mo, then CT at 18–24 mo

NOTE—not applicable to patients <35 years, in lung cancer screening, with immunosuppression, known pulmonary disease, or symptoms of active primary cancer; CT chest performed without contrast as contiguous 1 mm sections using low dose; nodules unchanged >2 years are considered benign

SUB-SOLID PULMONARY NODULES

Nodule size	Recommendations
-------------	-----------------

Solitary pure ground-glass

<6 mm	No routine follow-up If high risk, consider CT at 2 and 4 y
≥6 mm	CT at 6–12 mo; if unchanged, CT q2 years until 5 y Growing nodules should undergo resection

Solitary part-solid

<6 mm	No routine follow-up
≥6 mm	CT at 3–6 mo; if unchanged and solid component remains < 6 mm, annual CT chest for 5 y Nodules with solid component >8 mm or growing should undergo resection

Multiple

<6 mm	CT at 3–6 months; if stable, no routine follow-up If high risk, consider CT at 2 and 4 y
-------	---

TREATMENT ISSUES (CONT'D)

Nodule size	Recommendations
≥6 mm	CT at 3–6 mo; if stable, subsequent evaluation is based on most suspicious nodule

SPECIFIC ENTITIES**PANCOAST TUMOR**

- PATHOPHYSIOLOGY**—superior sulcus tumors (mostly squamous cell carcinoma) invading and compressing the paravertebral sympathetic chain and brachial plexus
- CLINICAL FEATURES**—shoulder and arm pain (C8, T1, T2 distribution), **Horner syndrome** (upper lid ptosis, lower lid inverse ptosis, miosis, anhidrosis, enophthalmos, loss of ciliary-spinal reflex), and neurological symptoms in the arm (intrinsic muscles weakness and atrophy, pain and paresthesia of 4th and 5th digit). Other associated findings include clubbing, lymphadenopathy, phrenic or recurrent laryngeal nerve palsy, and superior vena cava syndrome
- DIAGNOSIS**—CXR, CT chest, percutaneous core biopsy
- TREATMENTS**—concurrent chemoradiotherapy

THORACIC OUTLET OBSTRUCTION

- PATHOPHYSIOLOGY**—obstruction of the neurovascular bundle supplying the arm at the superior aperture of the thorax. Common structures affected include the brachial plexus (C8/T1 > C5/C6/C7, 95%), subclavian vein (4%), and subclavian artery (1%)
- CAUSES**—**anatomic** (cervical ribs, congenital bands, subclavicular artery aneurysm), **repetitive hyperabduction/trauma** (hyperextension injury, painters, musicians), **neoplasm** (supraclavicular lymphadenopathy)
- CLINICAL FEATURES**—triad of numbness, swelling and weakness of the affected upper limb, particularly when carrying heavy objects. Brittle finger nails, Raynaud phenomenon, thenar wasting and weakness, sensory loss, decreased radial and brachial pulses, pallor of limb with elevation, upper limb atrophy, drooping shoulders, supraclavicular and infraclavicular lymphadenopathy. Specific maneuvers include **Roos test** (repeatedly clench and unclench fists with arms abducted and externally rotated), **modified Adson maneuver** (Valsalva maneuver with the neck fully extended, affected arm elevated,

SPECIFIC ENTITIES (CONT'D)

and the chin turned away from the involved side), **costoclavicular maneuver** (shoulders thrust backward and downward), **hyperabduction maneuver** (raise hands above head with elbows flexed and extending out laterally from the body), and **Tinel maneuver** (light percussion of brachial plexus in supraclavicular fossa reproduces symptoms)

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—cervical spine films, CXR, MRI
- **TREATMENTS**—conservative (keep arms down at night, avoiding hyperabduction), surgery

Related Topics

Lung Cancer (p. 205)

SVC Syndrome (p. 244)

Pulmonary HypertensionHirani et al. *Can J Cardiol* 2020;36(7)**WHO CLASSIFICATION OF PULMONARY HYPERTENSION****GROUP I. PULMONARY ARTERIAL HYPERTENSION**

- **IDIOPATHIC**—primary
- **FAMILIAL DISORDERS**
- **DRUG AND TOXIN INDUCED**
- **PAH ASSOCIATED WITH SPECIFIC DISORDERS**—connective tissue disease, HIV, portal hypertension, congenital heart disease, schistosomiasis
- **PAH LONG TERM RESPONDERS TO CALCIUM CHANNEL BLOCKERS**
- **PAH WITH SIGNIFICANT VENOUS OR CAPILLARY INVOLVEMENT**—pulmonary veno-occlusive disease, pulmonary–capillary hemangiomatosis
- **PERSISTENT PULMONARY HYPERTENSION OF NEWBORN**

GROUP II. PULMONARY VENOUS HYPERTENSION DUE TO LEFT HEART DISEASE—heart disease with preserved LVEF, heart disease with reduced LVEF, valvular heart disease, cardiovascular conditions leading to postcapillary PH

GROUP III. PULMONARY HYPERTENSION DUE TO LUNG DISEASE AND/OR HYPOXEMIA—obstructive lung disease, restrictive lung disease, mixed restrictive/obstructive disease, including obstructive sleep apnea and obesity hypoventilation syndrome, developmental lung disease

GROUP IV. PULMONARY HYPERTENSION DUE TO PULMONARY ARTERY OBSTRUCTIONS—chronic thromboembolic, other pulmonary artery obstructions (i.e. tumor, parasites, foreign material)

GROUP V. PULMONARY HYPERTENSION WITH UNCLEAR AND/OR MULTIFACTORIAL MECHANISMS—hematological (pulmonary Langerhans cell histiocytosis, lymphangiomatosis), systemic and metabolic disorders (sarcoidosis),

WHO CLASSIFICATION OF PULMONARY HYPERTENSION (CONT'D)

complex congenital heart disease, others (compression of pulmonary vessels by tumor, fibrosing mediastinitis)

PATHOPHYSIOLOGY

DEFINITION OF PULMONARY HYPERTENSION—mean pulmonary arterial pressure (PAP) >25 mmHg at rest or mean PAP >30 mmHg with exercise measured with right heart catheterization

CLINICAL FEATURES

HISTORY—unexplained dyspnea on exertion, cough, chest pain, hemoptysis, dizziness, syncope, hoarseness, past medical history (cardiac and respiratory diseases, thromboembolic diseases, HIV, cirrhosis, autoimmune and rheumatologic disorders), medications (amphetamine, diet pill such as dexfenfluramine)

PHYSICAL—vitals (tachypnea, tachycardia, atrial fibrillation, hypoxemia), peripheral cyanosis, small pulse volume, elevated JVP (prominent a wave or absent if atrial fibrillation, large v wave), right ventricular heave, loud or palpable P2, right-sided S4, tricuspid regurgitation murmur, Graham-Steell murmur (high-pitched, decrescendo diastolic rumble over LUSB), crackles, congestive liver, ascites, ankle edema

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, albumin, ANA, RF, anti-CCP, anti-Scl-70, anticentromere antibody, ESR, HIV serology, TSH
- **IMAGING**—CXR, CT chest, V/Q scan or CT chest PE protocol, echocardiogram

INVESTIGATIONS (CONT'D)

- **ECG**
- **OVERNIGHT POLYSOMNOGRAPHY**—if suspect OSA
- **ABG**
- **PFT**

SPECIAL

- **RIGHT HEART CATHETERIZATION WITH VASOREACTIVITY TESTING**

MANAGEMENT

SYMPTOM CONTROL—diuretics, O₂, anticoagulation, calcium channel blockers if positive vasoreactivity test (in high doses), endothelin receptor antagonists (bosentan,

MANAGEMENT (CONT'D)

ambrisentan), **phosphodiesterase type-5 inhibitors** (sildenafil), prostacyclin analogues (epoprostenol, iloprost, selexipag), soluble guanylate cyclase stimulators (riociguat)

TREAT UNDERLYING CAUSE**ATRIAL SEPTOSTOMY****LUNG TRANSPLANT****REFERRAL TO A SPECIALIZED PULMONARY HYPERTENSION CLINIC****SPECIFIC ENTITIES**

EISENMENGER SYNDROME—left-to-right shunt leading to pulmonary hypertension and eventually right-to-left shunt

Interstitial Lung DiseaseRaghu et al. *AJRCCM* 2018;198(5)**DIFFERENTIAL DIAGNOSIS**

PRIMARY (idiopathic)—usual interstitial pneumonia (UIP), respiratory bronchiolitis-associated interstitial lung disease (RBILD), desquamate interstitial pneumonia (DIP), acute interstitial pneumonia (AIP), non-specific interstitial pneumonia (NSIP), lymphoid interstitial pneumonia (LIP), cryptogenic organizing pneumonia (COP)

SECONDARY ★DICE★

- **DRUGS**—chemotherapy (bleomycin), sulfa, penicillin, sulfonyleurea, gold, penicillamine, phenytoin, amiodarone, nitrofurantoin
- **INFILTRATIVE**—lymphangitic carcinomatosis, sarcoidosis
- **INFECTIONS**—TB, histoplasmosis, coccidioidomycosis
- **INFLAMMATORY**—rheumatoid arthritis, SLE, scleroderma, ankylosing spondylitis, myositis
- **CONGESTIVE HEART FAILURE**
- **ENVIRONMENT**—**organic dust** (hypersensitivity pneumonitis), **inorganic dust** (asbestos, silica, beryllium, coal worker's pneumoconiosis)
- **EOSINOPHILIA-ASSOCIATED PULMONARY INFILTRATES**—allergic bronchopulmonary aspergillosis (ABPA), parasitic, drugs
- **ETC**—pulmonary histiocytosis X, idiopathic pulmonary hemosiderosis, lymphangioleiomyomatosis, radiation

CLINICAL FEATURES

HISTORY—dyspnea (duration, progression), cough, hemoptysis, wheezes, chest pain, impaired exercise tolerance, occupational history (details of all previous jobs, exposure to gases or chemicals

CLINICAL FEATURES (CONT'D)

particularly important), environmental exposure (home setting, air-conditioning, pets, hobbies), rash, joint swelling, past medical history (smoking), medications, family history

PHYSICAL—vitals (tachypnea, hypoxemia), cyanosis, clubbing (idiopathic pulmonary fibrosis, asbestosis, rheumatoid lung, fibrosing NSIP), decreased chest expansion, crackles (fine), wheezes, cor pulmonale. Note that sarcoidosis and silicosis may have a normal lung examination

Related Topics

- Allergic Bronchopulmonary Aspergillosis (p. 4)
- Restrictive Lung Disease (p. 26)
- Rheumatoid Arthritis (p. 297)
- Sarcoidosis (p. 483)
- Tuberculosis (p. 267)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, ANA, RF, anti-CCP antibody, anti-Scl-70, anticentromere antibody, anti-Jo-1 antibody
- **IMAGING**—CXR, CT chest (high resolution), echocardiogram (if suspect pulmonary hypertension)

• **ABG**• **PFT****SPECIAL**

- **BIOPSY**—bronchoscopy (transbronchial biopsy), referral to thoracic surgery for VATS lung biopsy

DIAGNOSTIC ISSUES**CHARACTERISTIC CXR PATTERNS FOR INTERSTITIAL LUNG DISEASE**

- **UPPER LOBE PREDOMINANCE**—sarcoidosis, hypersensitivity pneumonitis, pneumoconiosis, silicosis, histiocytosis X, PJP, ankylosing spondylitis, ABPA, TB
- **LOWER LOBE PREDOMINANCE**—idiopathic pulmonary fibrosis, asbestosis, rheumatoid arthritis, scleroderma, drugs
- **BILATERAL HILAR/MEDIASTINAL ADENOPATHY WITH INTERSTITIAL INFILTRATES**—sarcoidosis, berylliosis, lymphangitic carcinomatosis, TB, fungal, lymphoma
- **EGGSHELL CALCIFICATION OF HILAR/MEDIASTINAL LYMPH NODES**—silicosis (other pneumoconiosis), TB, fungal
- **CALCIFIED PLEURAL PLAQUES**—asbestos
- **PLEURAL EFFUSIONS WITH INTERSTITIAL INFILTRATES**—HF, lymphangitic carcinomatosis, rheumatoid arthritis, SLE

MANAGEMENT

TREAT UNDERLYING CAUSE—**sarcoidosis** (if stage \geq II or symptomatic, consider glucocorticoids for several months with tapering dose)
LUNG TRANSPLANT

SPECIFIC ENTITIES**IDIOPATHIC PULMONARY FIBROSIS (IPF)**

- **PATHOPHYSIOLOGY**—unknown. Fibrotic rather than inflammatory process; associated with histopathological and/or radiological pattern of usual interstitial pneumonia (UIP)
- **DIAGNOSIS**—high resolution CT chest may show patterns of UIP (honeycombing, interlobular septal thickening, traction bronchiectasis, peripheral, sub-pleural, lack of ground glass pattern), probable UIP, indeterminate for UIP or alternate diagnosis; bronchoscopy (to rule out other causes, mostly infectious); consider open lung biopsy if CT is not consistent with above
- **TREATMENTS**—multidisciplinary discussion for diagnosis and treatment. Referral for lung

SPECIFIC ENTITIES (CONT'D)

transplantation should be done early; consider palliative care involvement, pulmonary rehabilitation, vaccinations, supplemental oxygen; consider pirfenidone or nintedanib for mild to moderate disease. Systemic steroids ineffective

HYPERSENSITIVITY PNEUMONITIS

- **PATHOPHYSIOLOGY**—inhaled organic antigens \rightarrow immune response \rightarrow acute, subacute, or chronic granulomatous pneumonia
 - **DIAGNOSIS**—**major criteria** (compatible symptoms, antigen exposure, imaging findings, lavage lymphocytosis, histologic findings [poorly formed granulomas], re-exposure triggers symptoms); **minor criteria** (bilateral crackles, \downarrow DLCO, hypoxemia). Combination of major and minor criteria will help raise suspicion of hypersensitivity pneumonitis. Serology may be helpful
 - **TREATMENTS**—cessation of exposure, steroids
- ORGANIZING PNEUMONIA (OP)**—previously known as bronchiolitis obliterans organizing pneumonia (BOOP)

- **CAUSES**—**idiopathic** (80%, also known as cryptogenic organizing pneumonia [COP]), **post-infectious** (CMV, influenza, adenovirus, *Chlamydia*), **drugs** (amiodarone, bleomycin, gold, sulfasalazine, cephalosporin, cocaine), **connective tissue disease** (RA, SLE, scleroderma, Sjögren syndrome, dermatomyositis), **immunologic** (essential mixed cryoglobulinemia), **transplantation** (bone marrow, lung, kidney), **malignancy** (MDS, lymphoproliferative diseases, radiation)
- **CLINICAL FEATURES**—about 50% of cases preceded by viral-like respiratory infection. Symptoms include dyspnea on exertion, persistent non-productive cough, and weight loss
- **DIAGNOSIS**—characteristic findings on CXR and CT chest include bilateral, diffuse, ill-defined alveolar opacities distributed peripherally. PFT shows mainly restrictive lung disease pattern
- **TREATMENTS**—*prednisone* 1 mg/kg PO daily for several months with slow taper

Obstructive Sleep ApneaFleetham et al. *Can Respir J* 2011;18(1)**DIFFERENTIAL DIAGNOSIS OF SLEEP DISORDERS****HYPERSOMNOLENCE**

- **SLEEP DISRUPTION**—obstructive sleep apnea (OSA), periodic limb movement disorder
- **INADEQUATE SLEEP TIME**—medicine residents, shift workers

DIFFERENTIAL DIAGNOSIS OF SLEEP DISORDERS (CONT'D)

- **INCREASED SLEEP DRIVE**—narcolepsy, primary CNS hypersomnolence, head injury, severe depression, medications

DIFFERENTIAL DIAGNOSIS OF SLEEP DISORDERS (CONT'D)

INSOMNIA

- **ACUTE**—stress, travel through time zones, illness, medications (steroids), illicit drugs (stimulants)
- **CHRONIC**—conditioned, psychiatric disorders, poor sleep hygiene, medical disorders, pain, restless leg syndrome, circadian rhythm disorder

PARASOMNIA—sleep walking, sleep terrors, nocturnal seizures, rapid eye movement behavior disorder

PATHOPHYSIOLOGY

ABNORMAL PHARYNX ANATOMY—decreased upper airway muscle tone and reduced reflexes protecting pharynx from collapse, increased hypercapnic set point → airway collapse with hypoxemia and hypercapnia → partial collapse leads to snoring and hypopnea, full collapse leads to apnea → terminated with arousal → repeated arousals lead to hypersomnolence. Severe chronic hypoxemia leads to pulmonary hypertension

ASSOCIATIONS—obesity, hypothyroidism, acromegaly, amyloidosis, neuromuscular disease, vocal cord paralysis, nasopharyngeal carcinoma, Down syndrome (macroglossia)

COMPLICATIONS—hypertension, pulmonary hypertension, CAD, CVA, increased motor vehicle accidents

Related Topics

- CPAP (p. 113)
- Hypertension (p. 70)
- Pulmonary Hypertension (p. 20)

CLINICAL FEATURES

HISTORY—daytime sleepiness, habitual snoring, witnessed apneic episodes, poor sleep hygiene, morning headaches, fall asleep while driving, dyspnea, cough, exercise capacity, short-term memory loss, excessive caffeine intake, alcohol intake, past medical history (weight gain, thyroid disease, neurological disease), and medications. The Epworth Sleepiness Scale and STOP-Bang Questionnaire may be used as screening tools

PHYSICAL—vitals (hypertension, hypoxia). Obtain weight and height (BMI often >30 kg/m²). Asterixis and plethora secondary to hypercapnia. Check for low-hanging soft palate, large uvula,

CLINICAL FEATURES (CONT'D)

enlarged tonsils, retrognathia, micrognathia, ↑ neck circumference (>42 cm [>16.5 in.] for ♂, >39 cm [>15.4 in.] for ♀), and acanthosis nigricans. Perform respiratory and cardiac examination (hypertension and pulmonary hypertension, restrictive lung disease). Inspect for potential causes such as nasopharyngeal carcinoma, hypothyroidism (goiter), acromegaly (course facial structures), and amyloidosis (periorbital infiltrate, shoulder pad sign)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE OBSTRUCTIVE APNEA?

	LR+	LR-
Symptoms		
Nocturnal choking/gasping	3.3	0.57
Morning headache	1.5–3.8	0.73–0.93
Reported apnea	1.4	0.47
Excessive daytime sleepiness	1.3–1.4	0.80–0.81
Snoring	1.1–1.5	0.12–0.60
Signs		
Mallampati Class 3 or 4	1.6	0.60–0.68
Pharyngeal narrowing	1.4	0.63
Combination of Findings		
Overall clinical impression	1.7	0.67
STOP-Bang Questionnaire	1.4–1.8	0.20–0.23
Snoring Severity Scale ≥4 and BMI ≥26	1.6	0.07
Sleep Apnea Clinical Score (SACS) >15	5.2	–
Sleep Apnea Clinical Score (SACS) ≤5	0.25	–

APPROACH—obstructive sleep apnea is common (2–14% in community screened patients) and is associated with HTN, HF, diabetes and arrhythmia. Individual signs and symptoms lack diagnostic accuracy and are insufficient to rule in/rule out OSA. Snoring is non-specific but patients with a normal BMI who do not snore are unlikely to have OSA. Multi-item questionnaires (e.g. STOP-Bang Questionnaire) may identify patients at low risk of OSA. The Sleep Apnea Clinical Score requires further validation before use for screening in primary care

Myers et al. *JAMA* 2013;310(7)

INVESTIGATIONS

POLYSOMNOGRAPHY
ABG
PFT

MANAGEMENT

LIFESTYLE CHANGES—sleep hygiene (avoid daytime napping, avoid caffeine, reduce alcohol intake, exercise regularly but not immediately before sleep, maintain regular sleep schedule, ensure comfortable sleep environment without noises or bright light), restrict body position during sleep

TREAT UNDERLYING CAUSE—for patients with obstructive sleep apnea, recommend weight loss (diet, exercise, weight management program; consider referral for bariatric surgery if BMI >40 kg/m² or >35 kg/m² with serious comorbid disease), avoidance of alcohol/sedatives. CPAP is the gold standard for therapy. Other options include orthodontic devices to hold lower jaw forward and surgical procedures such as tracheostomy, tonsillectomy, nasal surgery, uvulopalatopharyngoplasty; however, therapies other than CPAP are not generalizable. Thus, every effort should be made to treat with CPAP

TREATMENT ISSUES

PATIENTS WITH OBSTRUCTIVE SLEEP APNEA AND HF—optimization of HF therapy first, then consider trial of CPAP therapy for 3 months if OSA still persists; CPAP can ↑ ventilation during sleep, ↓ hypoxemia, ↑ sleep quality, and ↑ cardiac function (↓ LV transmural pressure and improves cardiac output)

SPECIFIC ENTITIES**OBESITY HYPOVENTILATION SYNDROME (OHS)**—also known as Pickwickian syndrome.

Defined by hypoventilation (awake PaCO₂ >45 mmHg) in the absence of other causes of hypoventilation. OHS patients have sleep disordered breathing, and most have OSA. BMI is usually >35 kg/m². Treatment options include respiratory stimulants, ventilatory support (non-invasive ventilation), oxygen therapy, and weight loss

NARCOLEPSY—severe daytime hypersomnolence, cataplexy (loss of postural tone, usually with emotions), sleep paralysis (usually happens after sleep–wake transition), hypnagogic hallucinations (visual or auditory hallucinations during drowsiness)

RESTLESS LEG SYNDROME

- **PATHOPHYSIOLOGY**—associated with iron deficiency, hypoparathyroidism, uremic neuropathy, diabetic neuropathy, rheumatoid arthritis, and fibromyalgia
- **CLINICAL FEATURES**—desire to move extremities, associated with paresthesias, dysesthesias, and motor restlessness (floor pacing, leg rubbing). Symptoms tend to be worse at rest, particularly in the evenings and at night. Relieved by activity
- **TREATMENTS**—dopamine agonists (pergolide, pramipexole, or ropinirole), levodopa/carbidopa, gabapentin, clonazepam, and oxycodone if precipitated by pain. A trial of iron therapy is indicated in all patients even in the absence of overt iron deficiency

Respiratory Acidosis: Hypoventilation**DIFFERENTIAL DIAGNOSIS**

CNS (respiratory center depression)—brain stem injury (tumor, stroke), sleep apnea, obesity, medications (opioids)

RESPIRATORY

- **UPPER AIRWAY OBSTRUCTION**—epiglottitis, laryngospasm
- **LOWER AIRWAY OBSTRUCTION**—COPD, asthma, sleep apnea

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **DEAD SPACE VENTILATION**—infection, pleural effusion
- **NEUROMUSCULAR**—myasthenia gravis, Guillain-Barré syndrome, myopathy, ALS, hypophosphatemia, hypokalemia
- **CHEST WALL RESTRICTION**—kyphosis, scoliosis, ankylosing spondylitis

PHYSIOLOGIC COMPENSATION—secondary to metabolic alkalosis

PATHOPHYSIOLOGY

DEFINITION OF RESPIRATORY ACIDOSIS— $\text{PaCO}_2 > 40$ mmHg (or upper limit of normal), which is synonymous with hypoventilation

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, CK
- **IMAGING**—CXR
- **ABG**

MANAGEMENT

ACUTE—ABC, O_2 , IV, non-invasive ventilation, intubation

TREAT UNDERLYING CAUSE**Related Topics**

- Approach to ABG (p. 95)
- Metabolic Acidosis (p. 94)
- Metabolic Alkalosis (p. 97)

Respiratory Alkalosis: Hyperventilation**DIFFERENTIAL DIAGNOSIS**

CARDIOPULMONARY—hypoxia, pneumonia, early restrictive disease, mild HF, pulmonary embolism, mechanical ventilation

NON-CARDIOPULMONARY—fever, sepsis, CNS, anxiety, hyperthyroidism, drugs, pregnancy, liver failure

PHYSIOLOGIC COMPENSATION—secondary to metabolic acidosis

PATHOPHYSIOLOGY

DEFINITION OF RESPIRATORY ALKALOSIS— $\text{PaCO}_2 < 40$ mmHg (or lower limit of normal), which is synonymous with hyperventilation

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, TSH, urinalysis, βhCG in women of reproductive age
- **IMAGING**—CXR, CT chest
- **ABG**
- **SPECIAL**
 - **SEPTIC WORKUP**—blood C&S, urine C&S
 - **D-DIMER**—if suspect PE but low probability

MANAGEMENT

ACUTE—ABC, O_2 , IV, sedation (use with great caution as patients may experience respiratory decompensation)

TREAT UNDERLYING CAUSE**Hypoxemia**

See HYPOXEMIA (p. 110)

Ventilation Issues

See VENTILATION ISSUES (p. 113)

Approach to Pulmonary Function Tests**OVERALL APPROACH TO PFT INTERPRETATION**

STEP 1. ID AND DEMOGRAPHICS—name, date/time, age, height, weight, BMI, smoking history

STEP 2. ANALYZE FLOW VOLUME LOOP AND SPIROMETRY—identify obstructive or restrictive pattern

STEP 3. ANALYZE SPIROMETRY—identify obstructive defect, reversibility, and severity. Note that restrictive defect cannot be diagnosed without knowledge of lung volumes

OVERALL APPROACH TO PFT INTERPRETATION (CONT'D)

STEP 4. ANALYZE LUNG VOLUMES—identify restrictive defect, severity

STEP 5. ANALYZE DLCO AND DLCO ADJUSTED FOR ALVEOLAR VOLUME (VA)—a measure of gas exchange; if abnormal, suggests disease even if spirometry and lung volumes are normal

CLASSIFICATION OF PULMONARY DISEASES

OBSTRUCTIVE—asthma, COPD, bronchiectasis, cystic fibrosis, bronchiolitis obliterans

RESTRICTIVE

- **PARENCHYMAL**—sarcoidosis, idiopathic pulmonary fibrosis, pneumoconiosis, other interstitial lung diseases
- **EXTRAPARENCHYMAL**—neuromuscular (diaphragmatic paralysis, myasthenia gravis, Guillain-Barré syndrome, muscular dystrophies), chest wall (kyphoscoliosis, obesity, ankylosing spondylitis)

TERMINOLOGIES

DLCO—carbon monoxide diffusion capacity

FEF25–75%—forced expiratory flow during the middle of an FVC maneuver, represents flow of small airways

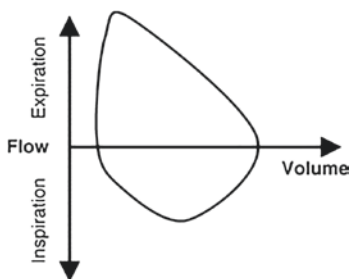
FEV1—forced expiratory volume during the first second of an FVC maneuver

FVC—forced vital capacity, maximum volume exhaled after maximum inhalation

MEP—maximum expiratory pressure

MIP—maximum inspiratory pressure

TLC—total lung capacity at maximal inhalation

FLOW–VOLUME LOOP PATTERNS**NORMAL**

OBSTRUCTIVE DISEASE—scooped appearance of expiratory curve seen in COPD. Variable extrathoracic obstruction (e.g. paralyzed vocal cords) appears as flattening of inspiratory curve. Variable intrathoracic obstruction (e.g. tracheal tumor) appears as flattening of expiratory curve. Flattening of the inspiratory curve (i.e. negative portion of the flow–volume loop) represents

FLOW–VOLUME LOOP PATTERNS (CONT'D)

extrathoracic obstruction; intrathoracic obstruction affects the expiratory curve (i.e. positive portion of the flow–volume loop)

RESTRICTIVE DISEASE—expiratory portion of curve appears relatively tall (preserved flow rates), but narrow (↓ lung volumes)

SPIROMETRY AND LUNG VOLUME PATTERNS

OBSTRUCTIVE DISEASE—↓ FEV1/FVC ratio (↓ FEV1 out of proportion to ↓ FVC); definitions vary but GOLD criteria define ↓ FEV1/FVC as <0.7 or less than lower limit of normal. If improvement >12% and 200 mL post-bronchodilator, consider diagnosis of asthma (reversibility). Note that mild obstructive (small airways) disease may have normal FEV1/FVC with ↓ FEF 25–75%

RESTRICTIVE DISEASE—↓ TLC, defined as <80% predicted (only applies to plethysmography); 70–79% = mild; 60–69% = moderate; <60% = severe. Note that patients may have both obstructive and restrictive disease

NOTE—general rule for the lower limit of normal for most PFT results is 80% of predicted (FEV1, FVC, DLCO, TLC) but less accurate for FEV1/FVC ratio and for patients of extremes of age

OVERALL APPROACH

	TLC	FEV1/ FVC	MIP	MEP
Obstructive	N/↑	↓	N	N
Restrictive				
Parenchymal	↓	N/↑	N	N
Extraparenchymal (inspiratory)	↓	N	N/↓	N
Extraparenchymal (inspiratory + expiratory)	↓	↓/N/↑	N/↓	N/↓

ANALYZING DLCO**REFERENCE VALUES FOR DLCO**

	% predicted
High	>140%
Normal	81–140%
Borderline low	76–80%
Mild decrease	61–75%
Moderate decrease	41–60%
Severe decrease	<40%

ANALYZING DLCO (CONT'D)

OBSTRUCTIVE DISEASE PRESENT—DLCO usually normal in asthma and chronic bronchitis but ↓ in emphysema

RESTRICTIVE DISEASE PRESENT—DLCO adjusted for alveolar volume usually ↓ in interstitial lung diseases and atelectasis and normal in neuromuscular diseases, chest wall abnormalities, and obesity

ANALYZING DLCO (CONT'D)

ISOLATED DLCO ABNORMALITY (WITHOUT OBVIOUS OBSTRUCTIVE OR RESTRICTIVE DISEASE)—↓ DLCO may result from anemia, ↑ carboxyhemoglobinemia, PE, and pulmonary hypertension; ↑ DLCO may result from pulmonary hemorrhage, obesity, left-to-right shunts, and polycythemia



Aortic Dissection

DIFFERENTIAL DIAGNOSIS

CARDIAC

- **MYOCARDIAL**—myocardial infarction, angina, myocarditis
- **VALVULAR**—aortic stenosis, aortic regurgitation
- **PERICARDIAL**—pericarditis
- **VASCULAR**—aortic dissection

RESPIRATORY

- **PARENCHYMAL**—pneumonia, cancer
- **PLEURAL**—pneumothorax, pneumomediastinum, pleural effusion, pleuritis
- **VASCULAR**—pulmonary embolism, pulmonary hypertension

GI—esophagitis, esophageal cancer, GERD, peptic ulcer disease, Boerhaave syndrome, cholecystitis, pancreatitis

OTHERS—musculoskeletal, shingles, anxiety

PATHOPHYSIOLOGY

ANATOMY—layers of aorta include intima, media, and adventitia. Majority of tears found in ascending aorta at right lateral wall where the greatest shear force is produced

AORTIC TEAR AND EXTENSION—aortic intimal tear leads to blood extravasation into aortic media creating a false lumen; this may produce a tearing, ripping sudden chest pain radiating to the back. Aortic regurgitation can occur if false lumen disrupts aortic leaflet producing a diastolic murmur. Pericardial tamponade may occur with dissection into the aortic root, leading to hypotension or syncope. Extension of a false lumen along the aorta may also occlude blood flow into any of the following vascular structures:

- **CORONARY**—acute myocardial infarction (usually RCA)
- **BRACHIOCEPHALIC, LEFT SUBCLAVIAN, DISTAL AORTA**—absent or asymmetric peripheral pulse, limb ischemia
- **RENAL**—anuria, renal failure

PATHOPHYSIOLOGY (CONT'D)

- **CAROTID**—syncope/hemiplegia/death
- **ANTERIOR SPINAL**—paraplegia/quadruplegia, anterior cord syndrome

CLASSIFICATION SYSTEMS

- **STANFORD**—**A**=any ascending aorta involvement, **B**=all others
- **DeBAKEY**—**I**=ascending and at least aortic arch, **II**=ascending only, **III**=originates in descending and extends proximally or distally

RISK FACTORS

- **COMMON**—hypertension, age, male
- **VASCULITIS**—Takayasu arteritis, giant cell arteritis, rheumatoid arthritis, Behçet syndrome, syphilitic aortitis
- **COLLAGEN DISORDERS**—Marfan syndrome, Ehlers-Danlos syndrome, Loeys-Dietz, cystic medial necrosis
- **VALVULAR**—bicuspid aortic valve, aortic coarctation, Turner syndrome, aortic valve replacement
- **OTHERS**—cocaine, trauma, pregnancy, iatrogenic (e.g. cardiac catheterization)

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION

SERIES: DOES THIS PATIENT HAVE AN ACUTE THORACIC AORTIC DISSECTION?

	LR+	LR-
History		
Hypertension	1.6	0.5
Sudden chest pain	1.6	0.3
Tearing or ripping pain	1.2–10.8	0.4–0.99
Physical		
Pulse deficit	5.7	0.7
Focal neurological deficit	6.6–33	0.71–0.87
Diastolic murmur	1.4	0.9

CLINICAL FEATURES (CONT'D)

	LR+	LR-
CXR/ECG		
Enlarged aorta or wide mediastinum	2.0	0.3
L VH on ECG	0.2–3.2	0.84–1.2

APPROACH—presence of tearing, ripping, or migrating pain may suggest dissection. Pulse deficit or focal neurological deficits greatly increase likelihood of dissection. Absence of pain of sudden onset decreases likelihood of dissection. Normal aorta and mediastinum on CXR help to exclude diagnosis

Klompas JAMA 2002;287(17)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, troponin/CK×3, glucose, AST, ALT, ALP, bilirubin, albumin, lipase, INR/PTT
- **IMAGING**—CXR, echocardiogram (TEE), CT chest or MRI chest

ECG**SPECIAL**

- **AORTOGRAPHY**

DIAGNOSTIC AND PROGNOSTIC ISSUES

CXR FINDINGS—wide mediastinum (>6 cm [2.4 in.]), indistinct aortic knuckle, pleural cap, difference in diameter between ascending and descending aorta, blurring of aortic margin secondary to local extravasation of blood, pleural

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

effusion or massive hemothorax, displaced calcification (separation of the intimal aortic calcification from the edge of the aortic shadow >1 cm [0.4 in.])

PROGNOSIS

- **TYPE A**—with surgery, 1-month survival 75–80%, 10-year survival 55%
- **TYPE B**—with aggressive hypertensive treatment, 1-month survival >90%, 10-year survival 56%

MANAGEMENT

ABC—O₂ to keep sat >95%, **IV, antihypertensive therapy** (keep HR <60 bpm and SBP <120 mmHg. *Labetalol* 2 mg/min IV loading drip, then 2–8 mg/min (target heart rate 55–60 bpm) or 20–80 mg IV q10 min, maximum 300 mg, then 200–400 mg PO BID. If SBP still >120 mmHg, *sodium nitroprusside* 0.25–0.5 µg/kg/min IV initially, then 0.25–3 µg/kg/min, maximum 10 µg/kg/min)

TREAT UNDERLYING CAUSE—**Type A** (emergent surgical repair, endovascular stenting, long-term blood pressure control). **Type B** (medical blood pressure control; surgical repair if complicated by occlusion of branch arteries). Monitor over time with serial CT/MR chest

Related Topics

Acute Coronary Syndrome (p. 30)
Stroke (p. 321)

Acute Coronary Syndrome

2015 ACC/AHA/SCAI STEMI Guidelines
2014 AHA/ACC UA/NSTEMI Guidelines
2012 ACCF/AHA UA/NSTEMI Focused Update
2019 CCS/CAIC STEMI Focused Update
2018 CCS Atrial Fibrillation Focused Update

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN**CARDIAC**

- **MYOCARDIAL**—myocardial infarction, angina (atherosclerosis, vasospasm, anomalous origin or intramural segment of coronary arteries), myocarditis
- **VALVULAR**—aortic stenosis
- **PERICARDIAL**—pericarditis
- **VASCULAR**—aortic dissection, vasculitis

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN (CONT'D)**RESPIRATORY**

- **PARENCHYMAL**—pneumonia, cancer
- **PLEURAL**—pneumothorax, pneumomediastinum, pleural effusion, pleuritis
- **VASCULAR**—pulmonary embolism, pulmonary hypertension

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN (CONT'D)

GI—esophageal spasm, esophagitis, esophageal cancer, GERD, peptic ulcer disease, Boerhaave syndrome, cholecystitis, pancreatitis

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN (CONT'D)

OTHERS—musculoskeletal (costochondritis), shingles, anxiety

PATHOPHYSIOLOGY

	Pathologic changes	Clinical presentation
Pre-clinical	Atherosclerosis	Asymptomatic
Angina	Luminal narrowing	Central chest discomfort; worsened by exertion, emotion, and eating; relieved by rest and nitroglycerine
Unstable angina	Plaque rupture or thrombus	Worsening pattern or rest pain; no elevation in troponin, with or without ECG changes of ischemia
NSTEMI	Partial occlusion	Non-ST elevation MI; elevation in troponin, with or without ECG changes of ischemia (ST segment and or T wave changes)
STEMI	Complete occlusion	ST elevation MI; elevation in troponin, with distinct ST segment elevation in ≥ 2 contiguous leads, new LBBB, or posterior wall MI with reciprocal ST depression in precordial leads on ECG

PATHOPHYSIOLOGY (CONT'D)**THIRD UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION (MI)**

- **TYPE 1**—spontaneous MI due to a primary coronary event (atherosclerotic plaque rupture or erosion with acute thromboembolism)
- **TYPE 2**—MI secondary to an ischemic imbalance (supply demand mismatch)
- **TYPE 3**—MI resulting in death when biomarker values are unavailable (sudden unexpected cardiac death before serum biomarkers collected for measurement)
- **TYPE 4**—MI related to PCI (4A) or stent thrombosis (4B)
- **TYPE 5**—MI related to CABG

RISK FACTORS

- **MAJOR**—diabetes, hypertension, dyslipidemia, smoking, family history of premature CAD, advanced age, male gender
- **ASSOCIATED**—obesity, metabolic syndrome, sedentary lifestyle, high-fat diet
- **EMERGING**—lipoprotein abnormalities, inflammation (\uparrow CRP), chronic infections, chronic kidney disease

POST-MI COMPLICATIONS—arrhythmia (VT/VF, bradycardia), sudden death, papillary muscle rupture/dysfunction, myocardial rupture (ventricular free wall, interventricular septum), ventricular aneurysm, left ventricular thrombus, valvular

PATHOPHYSIOLOGY (CONT'D)

disease (especially acute mitral regurgitation), heart failure/cardiogenic shock, peri-infarction pericarditis, post-cardiac injury pericarditis (Dressler syndrome)

CLINICAL FEATURES

CHEST PAIN EQUIVALENTS—dyspnea, syncope, fatigue, particularly in patients with diabetic neuropathy who may not experience chest pain

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION FOR EXERTIONAL TOLERANCE

- **I**=no symptoms with ordinary physical activity
- **II**=mild symptoms with normal activity (walking >2 blocks or 1 flight of stairs)
- **III**=symptoms with minimal exertion
- **IV**=symptoms at rest

CANADIAN CARDIOVASCULAR SOCIETY (CCS) CLASSIFICATION FOR ANGINA

- **I**=angina with strenuous activity
- **II**=slight limitation, angina with meals/cold/stress
- **III**=marked limitation, angina with walking $<1-2$ blocks or 1 flight of stairs
- **IV**=unable to perform any physical activity without angina and symptoms may be present at rest

CLINICAL FEATURES (CONT'D)**KILLIP CLASS CLASSIFICATION FOR HEART FAILURE**

- **I**=no evidence of heart failure
- **II**=mild to moderate heart failure (S3, lung rales less than half way up, or jugular venous distension)
- **III**=overt pulmonary edema
- **IV**=cardiogenic shock

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT HAVING A MYOCARDIAL INFARCTION?

	LR+
History	
Pain radiation to the shoulder or both arms	4.1
Pain radiation to right arm	3.8
Radiation to left arm	2.2
Radiation to both arms	9.7
Vomiting	3.5
Ex-smoker	2.5
Diaphoresis	2.0
Pleuritic chest pain	0.2
Sharp or stabbing chest pain	0.3
Positional chest pain	0.3
Chest pain reproducible by palpation	0.2–0.4
Physical	
Hypotension	3.1
S3	3.2
Pulmonary crackles	2.1
ECG	
New ST elevation ≥ 1 mm	5.7–53.9
New Q wave	5.3–24.8
Any ST elevation	11.2
New conduction defect	6.3
New ST depression	3.0–5.2
Any Q wave	3.9
Any ST depression	3.2
T wave peaking or inversion ≥ 1 mm	3.1
New T wave inversion	2.4–2.8
Any conduction defect	2.7
Multivariate Prediction Models	
ACI-TIPI (<i>Acute Cardiac Ischemia Time Insensitive Predictive Instrument</i>)	3.9–12
Goldman Protocol	2.9–3.6

CLINICAL FEATURES (CONT'D)

APPROACH—radiation of chest pain, diaphoresis, hypotension, and S3 suggest acute MI. Chest pain that is pleuritic, sharp or stabbing, positional or reproduced by palpation decreases likelihood of acute MI. On ECG, any ST \uparrow , new Q waves, or new conduction changes make acute MI very likely. Normal ECG is very powerful to rule out MI

UPDATE—"After clinical symptoms are used to identify patients with possible ischemia, the ECG and troponin results take precedence in making the diagnosis." The presence of diabetes, HTN, or dyslipidemia "should not affect clinician's probability estimate that an episode of chest pain represents an ACI."

Panju et al. JAMA 1998;280(14)
Simel et al. The Rational Clinical Examination. McGraw-Hill; 2009

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, troponin/CK (at presentation and 3–6 hours after symptom onset), BNP or NT-pro-BNP, AST, ALT, ALP, bilirubin, INR/PTT, Mg, Ca, PO₄, albumin, lipase, fasting lipid profile, random and fasting glucose, HbA1C
- **IMAGING**—CXR, echocardiogram (first 72 h), **ECG**—q8h $\times 3$ or q15–30min in the first hour with chest pain
- **STRESS TESTS**—ECG, echocardiogram Stress tests, MIBI once stable (>48 h post-MI)
- **CORONARY CATHETERIZATION**

DIAGNOSTIC AND PROGNOSTIC ISSUES**RISK STRATIFICATION FOR STABLE CORONARY DISEASE**

- **ECG EXERCISE STRESS TEST**
 - **ABSOLUTE CONTRAINDICATIONS**—recent myocardial infarction (<4 days), unstable angina, severe symptomatic LV dysfunction, life-threatening arrhythmia, acute pericarditis, aortic dissection, acute PE, severe symptomatic aortic stenosis

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **GOAL**—keep on treadmill until subject reaches $\geq 85\%$ of age-predicted heart rate (220-age)
- **ISCHEMIA CRITERIA**— ≥ 1 mm horizontal or down-sloping ST depression over multiple leads, or ST elevation \rightarrow myocardial ischemia (sens 68%, spc 77%) \rightarrow consider more accurate screening modality (MIBI, stress echo, or angiogram)
- **INCONCLUSIVE**—premature termination due to chest pain/poor exercise tolerance (inability to reach target heart rate) \rightarrow proceed to pharmacological stress test
- **DUKE TREADMILL SCORE**—(exercise time in minutes) $- 5 \times$ (maximum ST \downarrow in mm) $- 4 \times$ (treadmill angina index [0=none, 1=non-limiting, 2=exercise limiting]).
Low risk $\geq +5$ (4-year survival 98–99%),
moderate risk -10 to $+4$, **high risk** ≤ -11 (4-year survival 71–79%)
- **DIPYRIDAMOLE/ADENOSINE MIBI**—dipyridamole (Persantine) causes vasodilation. In CAD, the coronary artery is already maximally dilated to compensate, so addition of dipyridamole will not change perfusion to diseased vessel(s) further. This results in a relative perfusion mismatch compared to areas with normal dilatory reaction. Contraindicated in asthma/COPD. Antidote is aminophylline or caffeine
- **DOBUTAMINE ECHOCARDIOGRAPHY**—assesses wall motion abnormalities. Compared to MIBI, echocardiogram is more specific and less sensitive. Contraindicated in severe hypertension and arrhythmias

APPROACH TO DIAGNOSIS OF STABLE CAD—start with history, physical, rest ECG, and CXR. If low probability, do not investigate further. If high probability, proceed with management. If intermediate probability \rightarrow stress test \rightarrow cardiac CT, MIBI or stress echo \rightarrow angiography

DIFFERENTIAL DIAGNOSIS OF TROPONIN ELEVATION

- **CARDIAC**—myocardial infarction, myocarditis, congestive heart failure, ventricular hypertrophy, pericarditis, vasospasm, tachycardia with supply-demand mismatch, drug/cocaine ingestion, stress (takotsubo) cardiomyopathy, vasculitis
- **PULMONARY**—pulmonary embolism, pulmonary hypertension, COPD exacerbation
- **HEPATIC**—liver failure
- **RENAL**—chronic kidney disease

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **NEUROLOGIC**—stroke, intracranial hemorrhage
- **SYSTEMIC**—sepsis, prolonged strenuous exercise

SERUM MARKERS

- **TROPONIN I/T**—rises within 4–6 h, peaks at 18–24 h, remains elevated 7–10 days (sens 40% at presentation, 40–70% after 6–9 h of symptoms)
- **CK/CKMB**—rises within 4–6 h, peaks at 18–24 h, remains elevated 3–4 days (sens 35–50% at presentation, 90% after 3 h in ER)
- **MYOGLOBIN**—rises within 1–2 h, peaks in few hours

Therefore, measure markers (e.g. troponin) at least twice separated by 6–8 h with serial ECG. Despite all appropriate investigations, missed MI rate is 2–5%

ECG CHANGES IN ACUTE MI—see APPROACH TO ECG p. 78

TIMI SCORE FOR PATIENTS WITH UNSTABLE ANGINA/NSTEMI

- **SCORING** (out of 7)—age ≥ 65 , ≥ 3 CAD risk factors, known CAD (stenosis $>50\%$), ASA use within prior 7 days, ≥ 2 angina episodes within 24 h, \uparrow cardiac markers, ST deviation ≥ 0.5 mm
- **RISK GROUPS**—**low** = 0–2, **intermediate** = 3–4, **high** = 5–7. Consider anticoagulation and early angiography with revascularization in intermediate or high-risk groups
- **RISK OF DEATH, MI OR REVASCULARIZATION IN 14 DAYS**—0/1 = 4.7%, 2 = 8.3%, 3 = 13.2%, 4 = 19.9%, 5 = 26.2%, 6/7 = 40.9%

GRACE RISK SCORE FOR PATIENTS WITH UNSTABLE ANGINA/NSTEMI

- **SCORING** (based on regression model)—age, SBP, HR, creatinine, Killip class, cardiac arrest at admission, presence of ST segment deviation, elevation in serum cardiac enzymes/markers. Risk score calculated using online software: [Grace ACS Risk Score 2.0](#)

Risk category	GRACE risk score	In-hospital death (%)
Low	≤ 108	<1
Intermediate	109–140	1–3
High	>140	>3
Risk category	GRACE risk score	6-month death (%)
Low	≤ 88	<3
Intermediate	89–118	3–8
High	>118	>8

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

TIMI SCORE FOR PATIENTS WITH STEMI

- **SCORING** (out of 14)—age (3 points = ≥ 75 , 2 points = 65–74), any of diabetes, hypertension, or angina (1 point), systolic BP ≤ 100 mmHg (3 points), HR > 100 (2 points), Killip class II–IV (2 points), weight < 67 kg (1 point), anterior ST elevation or LBBB (1 point), time to reperfusion > 4 h (1 point)
- **RISK OF DEATH IN 30 DAYS**—0 = 0.8%, 1 = 1.6%, 2 = 2.2%, 3 = 4.4%, 4 = 7.3%, 5 = 12.4%, 6 = 16.1%, 7 = 23.4%, 8 = 26.8%, > 8 = 35.9%

IN-HOSPITAL OUTCOMES

	NSTEMI (%)	STEMI (%)
Death	4	6
Reinfarction	0.9	1.1
Cardiogenic shock	2.8	6.4
Stroke	0.7	0.8
Major bleeding	10	12

ACTION registry® 2008/2009 data

ACUTE MANAGEMENT

ABC—avoid routine administration of supplemental O₂ if saturations $\geq 90\%$, IVs, inotropes, consider balloon pump or ventricular assist devices if hemodynamically unstable

PAIN CONTROL—nitroglycerin (*nitro drip* 25 mg in 250 mL D5W, start at 5 μ g/min IV, then \uparrow by 5–10 μ g/min every 3–5 min to 20 μ g/min, then \uparrow by 10 μ g/min every 3–5 min up to 200 μ g/min, or until relief of pain, stop titration if SBP is < 100 mmHg. *Nitro patch* 0.4 mg/h daily. *Nitro spray* 0.4 mg SL q5min $\times 3$. Beware if suspect right ventricular infarction or if patients on sildenafil as the addition of nitroglycerin in these scenarios could cause significant hypotension). **Morphine** 2–4 mg IV every 5–15 min PRN for severe pain (avoid routine use of IV opioids as they can cause nausea and delay gastric emptying which may compromise absorption of antiplatelet drugs)

CLOT CONTROL

- **ANTIPLATELET**—**ASA** 162–325 mg PO chew $\times 1$ dose, then 81 mg PO daily indefinitely. **P₂Y₁₂ receptor blockade** with *clopidogrel* 300–600 mg $\times 1$ dose then 75 mg PO daily for 1 year; or *ticagrelor* 180 mg $\times 1$ dose, then 90 mg PO BID for 1 year; or *prasugrel* (with PCI

ACUTE MANAGEMENT (CONT'D)

only; do not give if history of CVA or TIA, or age ≥ 75 years) 60 mg $\times 1$ dose then 10 mg daily for 1 year. Combination ASA plus P₂Y₁₂ receptor blocker for minimum of 1 month (ideally 1 year)—post PCI with bare-metal stent, or minimum 6–12 months (possibly indefinitely) for drug-eluting stents. Consider **GPIIb/IIIa inhibitor** for patients who have not received oral antiplatelets pre-PCI or when there is thrombotic complications post-PCI (e.g. large residual thrombus burden)

- **ANTICOAGULATION**—options include **LMWH** (*enoxaparin* 30 mg IV bolus, then 1 mg/kg SC BID for STEMI [no IV bolus for NSTEMI], caution if renal failure or age > 75) or **unfractionated heparin** (*unfractionated heparin* 70 U/kg [up to 4,000 U] IV bolus, then 18 U/kg/h [up to 1,000 U/h] and adjust to 1.5–2.5 \times normal PTT for 48 h or until PCI completed). **Factor Xa inhibitors** (*fondaparinux* 2.5 mg SC daily until discharge or 8 days, caution if renal failure). **Direct thrombin inhibitors** (*bivalirudin* 0.1 mg/kg IV bolus then 0.25 mg/kg/h initially, followed by second 0.5 mg/kg bolus before PCI and 1.75 mg/kg/h during PCI, then continue infusion for up to 4 h post-PCI, if needed)
- **REPERFUSION THERAPY**—see **PCI** for details. **Fibrinolytics** for STEMI (*alteplase* 15 mg IV over 2 min, then 0.75 mg/kg over 30 min [maximum 50 mg], then 0.5 mg/kg over 60 min [overall maximum 100 mg]; or *tecteplase* IV bolus over 5 sec, weight-based dosing: 30 mg for weight < 60 kg, 35 mg for 60–69 kg, 40 mg for 70–79 kg, 45 mg for 80–89 kg, 50 mg for ≥ 90 kg])
- **RATE CONTROL**—start with *metoprolol tartrate* [immediate release] 25 mg PO q6–12 h. Titrate as tolerated up to maximum dose of *metoprolol tartrate* [immediate release] 100 mg PO q12h. Alternatively, *carvedilol* 6.25 mg PO BID and titrate as tolerated up to 25 mg PO BID. The goal heart rate is 50–60 with normal activity. If ongoing ischemia or refractory hypertension at the time of presentation, may also consider *metoprolol tartrate* 5 mg IV q5min, up to 3 doses. Avoid if acute HF, low-output state, presence of prolonged first-degree or high-grade AV block, history of reactive airways disease, or MI precipitated by cocaine use. If β -blocker contraindicated, consider non-dihydropyridine calcium channel blockers (*diltiazem* 30–120 mg PO QID or

ACUTE MANAGEMENT (CONT'D)

verapamil 80–120 mg PO TID [contraindicated if LV dysfunction])

LIPID CONTROL—high-intensity statin such as *atorvastatin* 80 mg PO daily or *rosuvastatin* 40 mg PO daily

ACUTE MANAGEMENT (CONT'D)

BLOOD PRESSURE SUPPORT—for patients with cardiogenic shock, consider IV fluids, inotropes (dobutamine/dopamine), balloon pump, ventricular assist devices, and early revascularization

OVERALL APPROACH

	Stable angina	Unstable angina or NSTEMI	STEMI
ASA	✓	✓	✓
Nitrates	✓	✓	✓
Morphine	±	±	±
β-blockers	✓	✓	✓
ACE inhibitors or ARBs	✓	✓	✓
HMG-CoA inhibitors	✓	✓	✓
Heparin or antithrombin	NO	✓	✓
P2Y ₁₂ inhibitors	NO	✓	✓
GPIIb/IIIa inhibitors	NO	±	±
Fibrinolytics or PCI ^a	NO	NO	✓
Cardiology consult	Outpatient ^b	CCU ^c	CCU ^c

^aIf initial presentation is to a PCI-capable hospital, then primary PCI should be performed within 90 min from time of first medical contact (FMC). If initial presentation is to a non-PCI-capable hospital, then arrange urgent transfer to PCI-capable hospital if primary PCI can be performed within 120 min from time of FMC. If timely PCI cannot be provided, administer fibrinolytic within 30 min of FMC. Urgent CABG is also an option post-catheterization

^bOutpatient cardiology for stress test

^cCCU consult for risk stratification, monitoring, PCI, and/or CABG

ACUTE MANAGEMENT (CONT'D)

CAUTIONS IN TREATMENT OF ACUTE MYOCARDIAL INFARCTION—avoid negative inotropic agents such as β-blockers and nondihydropyridine calcium channel blockers if acute or decompensated heart failure. Avoid administration of nitroglycerin, morphine, and diuretics to patients with right ventricular infarction as these medications can cause venodilation and decrease preload, leading to hypotension

LONG-TERM MANAGEMENT OF CORONARY ARTERY DISEASE

ANTIANGINAL—**nitroglycerin** (*nitro patch* 0.4–0.8 mg/h daily; *nitro spray* 0.4 mg SL q5 min × 3; *isosorbide mononitrate* 30 mg PO daily, maximum 240 mg), **β-blocker** (*metoprolol tartrate* [immediate release] 25–100 mg PO BID, *metoprolol succinate* [extended release] 50–200 mg PO daily, *carvedilol* 6.25–25 mg PO BID, *bisoprolol* 5–10 mg PO daily), **calcium**

LONG-TERM MANAGEMENT OF CORONARY ARTERY DISEASE (CONT'D)

channel blocker (*amlodipine* 5–10 mg PO daily)

ACE INHIBITOR—*ramipril* 2.5–10 mg PO BID, *lisinopril* 2.5–10 mg PO daily, *trandolapril* 0.5–4 mg PO daily, *perindopril* 2–8 mg PO daily. If ACE inhibitor not tolerated, use ARB

ANTIPLATELET—**ECASA** 81 mg PO daily indefinitely. **P₂Y₁₂ receptor blockade** (*clopidogrel* 75 mg PO daily; *ticagrelor* 90 mg PO BID, or *prasugrel* 10 mg PO daily) generally for 1 year after ACS. Combination ASA plus clopidogrel for minimum of 1 month (ideally 1 year)-post PCI with bare-metal stent, or minimum 6–12 months (possibly indefinitely) for drug-eluting stents. Consider ticagrelor or prasugrel if received PCI

ANTICOAGULATION—controversial especially in combination with ASA and/or P₂Y₁₂ inhibitor. May be considered for patients post-STEMI or NSTEMI with one of the following criteria: (1) atrial

LONG-TERM MANAGEMENT OF CORONARY ARTERY DISEASE (CONT'D)

fibrillation (AF), (2) left ventricular thrombus, (3) significant left ventricular dysfunction with extensive regional wall motion abnormalities. In patients with AF that have an indication for anticoagulation for stroke prevention (see ATRIAL FIBRILLATION p. 48) in addition to having had a recent ACS with PCI, triple therapy with oral anticoagulation + ASA + P₂Y₁₂ inhibitor is recommended for the first 1–6 months (duration depends on risk of stroke, stent thrombosis, and bleeding risk) followed by a step down to dual therapy with oral anticoagulation + P₂Y₁₂ inhibitor for up to 12 months post PCI; beware of bleeding risk on dual and triple therapy. Following the 12 month period, patients with AF and stable CAD who have an indication for anticoagulation for stroke prevention can discontinue the antiplatelet agent and remain on oral anticoagulation only; an antiplatelet agent can be continued with oral anticoagulation in these patients if there is an additional indication for its use (e.g. in patients with a mechanical valve + AF). If possible, minimize duration of triple therapy and consider GI protection with proton-pump inhibitor; if warfarin is used instead of a novel anticoagulant, target lower INR (e.g. 2.0–2.5)

RISK REDUCTION ★ABCDEF★

- **ASA/ACE INHIBITOR/ARB**
- **BLOOD PRESSURE CONTROL** (see HYPERTENSION p. 70)
- **CHOLESTEROL CONTROL** (see DYSLIPIDEMIA p. 75)
- **DIABETIC CONTROL** (see DIABETES p. 365)
- **EXERCISE** (30 min of moderate-intensity exercise 3–4 ×/week)
- **FAT REDUCTION** (see OBESITY ISSUES p. 449)
- **GET GOING TO QUIT SMOKING!** (see SMOKING ISSUES p. 490)

DRIVINGPOST-MYOCARDIALINFARCTION—see p. 492 for details

TREATMENT ISSUES

RIGHT VENTRICULAR INFARCTION—evidence of inferior MI should automatically trigger one to check right-sided leads (V_{4R}) to assess for the possibility of RV infarction, which occurs in about 50% of patients with inferior MI. May see increased JVP, Kussmaul sign, and clear lungs clinically. ST elevation in V_{4R} is diagnostic and prognostic. Hypotension should be treated with fluid bolus to ensure good preload. Inotropic support can also be considered (e.g. dobutamine)

TREATMENT ISSUES (CONT'D)

POSTERIOR INFARCTION—ST depression in V₁–V₂ in a regular ECG should automatically trigger one to request for posterior (V₇–V₉) leads to check for posterior MI. Posterior infarct may be associated with inferior infarcts (90%) and lateral infarcts (10%) as the PDA may be supplied by the right or left circumflex coronary artery

POTENTIAL COMPLICATIONS POST-MI—ventricular septal defect (typically in elderly patients with a large infarct), free wall rupture (typically in elderly patients with large infarct), acute mitral regurgitation due to papillary muscle rupture (more common in inferior vs. anterior infarct), heart failure, heart block (may be transient if early reperfusion), atrial fibrillation, ventricular arrhythmias (VT and/or VF)

POST-MI RISK STRATIFICATION

- **EXTENT OF INFARCT/RESIDUAL FUNCTION**—assessment is based on clinical factors (↑ HR, ↓ BP, Killip class, diabetes, renal failure, ↑ WBC, GRACE risk score, TIMI risk score), ECG, biomarkers (CK, troponin), imaging (echocardiogram, MIBI, cardiac MRI), and angiography. Early measurement of LV function, although of prognostic importance, is misleading as myocardium function may improve in first 2 weeks. Medical management according to risk
- **EXTENT OF MYOCARDIUM AT RISK**—assessment is based on exercise stress test, stress echocardiogram, stress sestamibi (ischemic tissue), thallium scan (viable tissue), PET scan, cardiac MRI, angiography. Angioplasty or CABG should be considered
- **RISK OF ARRHYTHMIA**—high risk of VF/VT within the first 48 h, therefore monitor with telemetry. If it occurs after 48 h, consider antiarrhythmics and early ICD, especially if the arrhythmia is monomorphic VT (suggestive of scar substrate)

BALLOON PUMP—a long balloon in the descending aorta that deflates during systole and inflates during diastole to augment coronary perfusion and cardiac output as well as decrease afterload. Considered for severe refractory ischemia and hemodynamic instability. May be used in conjunction with inotropes. Contraindicated in aortic regurgitation, AAA, aortic dissection, uncontrolled sepsis bleeding disorder, and severe PVD. Intraaortic balloon pump not in common use because it has no effect on mortality (Intraaortic Balloon Pump in Cardiogenic Shock II trial)

TREATMENT ISSUES (CONT'D)**FIBRINOLYTICS USE**

- **INDICATIONS**—>120 min anticipated delay from first medical contact to primary PCI, ≥ 30 min of chest pain, patient presentation within 12 h (ideal door to needle time <30 min), ECG criteria (>1 mm ST \uparrow in ≥ 2 contiguous leads, or new LBBB with suggestive history, age <75)
- **ABSOLUTE CONTRAINDICATIONS**—any intracranial hemorrhage; ischemic stroke within 3 months (except acute ischemic stroke within first 4.5 h); structural cerebral vascular lesion; malignant intracranial neoplasm; closed-head or facial trauma within 3 months; intracranial or intra spinal surgery within 2 months; severe uncontrolled hypertension (unresponsive to emergency therapy); suspected aortic dissection; bleeding diathesis or active bleeding (excluding menses)
- **RELATIVE CONTRAINDICATIONS**—chronic, poorly-controlled, severe hypertension; severe hypertension on presentation ($>180/110$ mmHg); ischemic stroke >3 months; dementia; other intracranial pathology (not already specified above); internal bleeding within 2–4 weeks; active peptic ulcer; major surgery within 3 weeks; non-compressible vascular punctures; use of anticoagulation therapy; pregnancy; traumatic CPR >10 min; prior exposure to streptokinase (if planning to use this fibrinolytic again)
- **PRACTICAL CONSIDERATIONS**—effective fibrinolysis requires adequate coronary perfusion. As such, maintaining mean arterial pressure >60 mmHg with vasopressors after fibrinolysis is advised
- **RISK OF BLEEDING**—average risk of severe bleed is 1.8%. Increased risk with women, BP $>165/95$ mmHg, age >65 , weight <70 kg [<154 lbs], and lysis with TPA (+0.5% absolute risk/factor)
- **PERSISTENT ST ELEVATION**—look for resolution of symptoms and ST elevation to decrease by $>50\%$ within 90 min of fibrinolytic therapy. Persistent ST elevation may suggest failed fibrinolytic therapy, and requires urgent rescue catheterization. Other causes of ST elevation include pericarditis, ventricular aneurysm, hyperkalemia, LBBB, and early repolarization abnormality

TREATMENT ISSUES (CONT'D)**Related Topics**

Aortic Dissection (p. 29)
 Asystole (p. 499)
 Diabetes Mellitus (p. 365)
 ECG (p. 78)
 Hyperlipidemia (p. 75)
 Hypertension (p. 70)
 Pericarditis (p. 38)
 Shock (p. 116)
 Smoking Cessation (p. 490)

PERCUTANEOUS CORONARY INTERVENTION (PCI, PTCA)

- **INDICATIONS FOR ACUTE STEMI**—patient presents within 12 h of chest pain (at a PCI-capable hospital, ideal time from first medical contact to device or “FMC-to-device time” ≤ 90 min; if at a non-PCI-capable hospital requiring transfer for primary PCI, then ideal “FMC-to-device time” ≤ 120 min), ECG criteria (>1 mm ST \uparrow in ≥ 2 contiguous leads, new or presumed new left bundle branch block), contraindications to fibrinolysis, or in patients in cardiogenic shock irrespective of time of MI onset
- **INDICATIONS FOR CHRONIC STABLE CAD**—single/double vessel disease refractory to medical therapy. Decision for revascularization (PCI vs. CABG) should follow assessment by heart team (interventional cardiology and cardiac surgery)
- **ADVERSE EVENTS**—access site (bleeding, hematomas, arteriovenous fistulae, pseudoaneurysms), contrast nephropathy, arrhythmia (VT, VF), stroke, dissection, myocardial infarction, death
- **BARE METAL STENTS VS. DRUG-ELUTING STENTS**—in-stent restenosis is due to fibrosis of coronary vasculature and usually happens 3 months post-procedure. Drug-eluting stents (sirolimus, paclitaxel, everolimus, or zotarolimus) are designed to inhibit cell proliferation and decrease the risk of in-stent restenosis. There has been some controversy regarding higher adverse events in patients with first generation drug-eluting stents (sirolimus or paclitaxel). The most recent outcomes research analysis suggests that newer-generation drug-eluting stents (everolimus or zotarolimus) are associ-

TREATMENT ISSUES (CONT'D)

ated with a decreased rate of repeat revascularization, stent thrombosis, and no significant difference in mortality

- **BENEFITS**—primary PCI is generally preferred given the superior outcomes compared to fibrinolysis, particularly if (1) fibrinolysis contraindicated, (2) previous history of CABG, or (3) cardiogenic shock. However, patients who are able to seek medical attention within 1 h of chest pain onset, have allergy to contrast dye, or do not have access to PCI in a timely fashion should consider fibrinolytics

OUTCOMES FOR FIBRINOLYTICS VS. PRIMARY PCI

	Fibrinolytics (%)	Primary PCI (%)
Non-fatal reinfarction	7	3
Stroke	2	1
Death (4–6 weeks)	7–9	5–7
Combined endpoint of death–fatal reinfarction and stroke	14	8

Keeley et al. NEJM 2007;356(1)

Lagerqvist et al. NEJM 2007;356(10)

Nallamothu et al. NEJM 2007;357(16)

CORONARY ARTERY BYPASS GRAFT SURGERY

- **CORONARY ANATOMY**
 - **RIGHT CORONARY (RCA)**—gives rise to right marginal (RMA), right posterior descending (RPDA), and right posterolateral branches (RPL 1, 2, 3)
 - **LEFT MAIN (LM)**—gives rise to left anterior descending (LAD) → diagonal (D1, 2, 3) and septals; ramus intermediate (Ram Int); and left circumflex (LCX) → obtuse marginal (OM 1, 2, 3)

TREATMENT ISSUES (CONT'D)

- **DOMINANT ARTERY**—defined as the artery that supplies PDA and at least one posterolateral (PL) artery
- **INDICATIONS**—studies suggest CABG provides mortality benefit for specific subgroups, including patients with (1) left main disease >50% occlusion, (2) two vessel disease with significant involvement of proximal left anterior descending, and (3) diffuse triple vessel disease. Diabetic patients and those with reduced left ventricular function derive more benefit from bypass surgery. Angiographic disease severity should be assessed using the SYNTAX score. Decision for revascularization (PCI vs. CABG) should follow assessment by heart team (interventional cardiology and cardiac surgery)
- **MORBIDITY BENEFIT**—95% have improvement of symptoms immediately after surgery, 75% symptom free at 5 years. Recurrent disease more common in vein grafts than artery grafts
- **GRAFTS**—saphenous veins from calf or thigh (SVG), internal mammary arteries (LIMA/RIMA), radial arteries (RA), and gastroepiploic artery from stomach (GA). A total of 90% of arterial graft and 50% of vein graft remain patent by 10 years
- **COMPLICATIONS**
 - **CARDIAC**—MI 2–4%, arrhythmia (AF 40%, sustained VT/VF 2–3%), AV block requiring pacemaker 0.8–4%, pericarditis/tamponade, aortic dissection
 - **NEUROLOGICAL**—stroke, postoperative delirium, cognitive impairment, depression, phrenic nerve damage, intercostal nerve damage
 - **OTHERS**—renal failure, bleeding, infection, pleural effusions, death
- **MEDICATIONS**—hold clopidogrel or ticagrelor 5–7 days prior to CABG. Continue ASA before and after surgery

Pericardial Diseases: Pericarditis and Tamponade**DIFFERENTIAL DIAGNOSIS**★ **MINT★**

METABOLIC—uremia, dialysis, hypothyroidism
MEDICATIONS—procainamide, hydralazine, INH, phenytoin, penicillin

DIFFERENTIAL DIAGNOSIS (CONT'D)

INFARCTION—MI (early, late)

INFECTIOUS—viral (e.g. HIV, Coxsackie, echovirus, adenovirus), bacterial (e.g. TB, *Staphylococcus aureus*, *Streptococcus*)

DIFFERENTIAL DIAGNOSIS (CONT'D)

pneumoniae), fungal (e.g. *Candida* species, histoplasmosis)

INFLAMMATORY—psoriatic arthritis, enteric arthritis, rheumatoid arthritis, SLE, mixed connective tissue disease, scleroderma

DIFFERENTIAL DIAGNOSIS (CONT'D)**IDIOPATHIC**

NEOPLASTIC—primary (mesothelioma), metastasis (breast, lung, melanoma), leukemia, lymphoma

TRAUMA—stab, gunshot wound, blunt, CPR, postpericardiotomy, radiation

CLINICAL FEATURES**RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH A PERICARDIAL EFFUSION HAVE CARDIAC TAMPONADE?**

	Sens (%)
History	
Dyspnea	87–89
Fever	25
Chest pain	20
Cough	7–10
Physical	
Tachycardia	77
Pulsus paradoxus >10 mmHg ^a	82
Elevated JVP	76
↓ heart sounds	28
Hypotension	26
Hypertension	33
Tachypnea	80
Peripheral edema	21–28
Pericardial rub	19–29
Hepatomegaly	28–55
Kussmaul sign	26
ECG	
Low voltage	42
Atrial arrhythmia	6
Electrical alternans	16–21
ST elevation	18–30
PR depression	18

^aPulsus paradoxus LR+ 3.3, LR– 0.03

APPROACH—“Among patients with cardiac tamponade, a minority will not have dyspnea, tachycardia, elevated JVP, or cardiomegaly on chest radiograph. A pulsus paradoxus >10 mmHg among patients with a pericardial effusion helps distinguish those with cardiac tamponade from those without. Diagnostic certainty of the presence of tamponade requires additional testing.”

Roy et al. *JAMA* 2007;297(16)

CLINICAL FEATURES (CONT'D)**DISTINGUISHING FEATURES OF ACUTE TAMPONADE AND CHRONIC CONSTRICTIVE PERICARDITIS**

	Acute tamponade	Constrictive pericarditis
Vitals	Tachycardia, hypotension +++, pulsus paradoxus	Hypotension, pulsus paradoxus (rare)
JVP	Elevated, Kussmaul (rare) Prominent x' descent but blunted y descent	Elevated, Kussmaul Prominent x' and y descent (Friedrich sign)
Apex beat	Impalpable	Impalpable
Heart sounds	Distant	Distant, early S3/knock
Other features	Dullness and bronchial breath sounds over left base (Ewart sign)	Hepatosplenomegaly, edema

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, troponin, CK
- **IMAGING**—CXR (calcification if constrictive disease), echocardiogram
- **ECG**—may have sinus tachycardia, low voltages, and electrical alternans in tamponade/effusion; diffuse ST elevation (concave up) and PR depression may be seen in pericarditis

SPECIAL

- **PERICARDIOCENTESIS**—diagnostic or therapeutic (for tamponade, TB/bacterial pericarditis, or large persistent effusion)
- **PERICARDIOSCOPY**
- **CT/MRI CHEST**—if suspect constrictive pericarditis

MANAGEMENT

ACUTE PERICARDITIS—**NSAIDs** (*indomethacin* 25–50 mg PO TID, *ibuprofen* 600–800 mg PO TID × 2–4 weeks, or until resolution of pain) for most cases of idiopathic or viral pericarditis, but avoid after acute MI. If post-MI, **ASA** 650 mg PO TID × 3–4 weeks. Adjuvant **colchicine** 0.6 mg PO BID × 3 months in addition to NSAID/ASA to reduce risk of recurrence. **Prednisone** 0.25–0.5 mg/kg PO daily × 2 weeks (followed by taper) may be considered for connective tissue-mediated disease, although symptoms may recur upon withdrawal

RECURRENT PERICARDITIS—**ASA** 650 mg PO TID × 4–8 weeks or **NSAIDs** (*indomethacin* 25–50 mg PO TID, *ibuprofen* 600–800 mg PO TID × 4–8 weeks). Add **colchicine** (0.6 mg PO BID × 3–6 months) for longterm prophylaxis.

MANAGEMENT (CONT'D)

Avoid anticoagulation as risk of hemopericardium. **Prednisone** 0.25–0.5 mg/kg PO daily may also be useful, although symptoms may recur upon withdrawal

TAMPONADE—**ABC**, **O₂**, IVs, bolus IV fluids, **pericardiocentesis** (subxyphoid blind approach, echocardiogram-guided parasternal or apical approach), **pericardiectomy**, **pericardial window** if recurrent/malignant effusion. Avoid nitroglycerin and morphine if tamponade as they may decrease preload, leading to worsening of cardiac output

CONSTRICTIVE PERICARDITIS—consider diuresis if evidence of volume overload. Severe, medically-refractory cases may require surgical pericardiectomy

SPECIFIC ENTITIES

ACUTE PERICARDITIS—may be preceded by upper respiratory tract infection. Diagnosis is based on any two of the following inflammatory signs (LR+ 5.4): fever, pericardial friction rub (three components), characteristic chest pain (better with upright position and leaning forward, or pleuritic), PR depression, and diffuse ST elevation. Large effusion without inflammatory signs or tamponade suggests chronic idiopathic pericardial effusion (LR+ 20)

RECURRENT PERICARDITIS—returns in days to weeks upon stopping medications. Likely causes include rheumatologic disorders, Dressler syndrome, and post-pericardiectomy syndrome

TAMPONADE—a clinical diagnosis based on dyspnea, tachycardia, hypotension, pulsus paradoxus, and elevated JVP. Tamponade causes

SPECIFIC ENTITIES (CONT'D)

restriction in left or right ventricular diastolic filling. Tamponade with inflammatory signs suggests malignant effusion (LR+ 2.9)

CONSTRICTIVE PERICARDITIS—contraction of pericardium due to chronic inflammation,

SPECIFIC ENTITIES (CONT'D)

leading to left and/or right heart failure. May follow pericarditis or radiation. May be difficult to distinguish from restrictive cardiomyopathy clinically

Heart FailureJessup et al. *NEJM* 2003;348(20)

2006 CCS Heart Failure Guidelines

Canadian Heart Failure Guidelines Updates 2013–2020

DIFFERENTIAL DIAGNOSIS OF HF EXACERBATION/DYSPNEA**CARDIAC**

- **MYOCARDIAL**—HF exacerbation, myocardial infarction
- **VALVULAR**—aortic stenosis, acute aortic regurgitation, mitral regurgitation/stenosis, endocarditis
- **PERICARDIAL**—tamponade, constrictive pericarditis
- **DYSRHYTHMIA**

RESPIRATORY

- **AIRWAY**—COPD exacerbation, asthma exacerbation, acute bronchitis, bronchiectasis, foreign body obstruction
- **PARENCHYMA**—pneumonia, cryptogenic organizing pneumonia, ARDS, interstitial lung disease exacerbation
- **VASCULAR**—pulmonary embolism, pulmonary hypertension
- **PLEURAL**—pneumothorax, pleural effusion

SYSTEMIC—sepsis, ARDS, metabolic acidosis, anemia, neuromuscular, psychogenic, anxiety

PATHOPHYSIOLOGY**ANATOMIC/PHYSIOLOGIC CLASSIFICATION OF CARDIOMYOPATHY**

- **DILATED** (dilatation and impaired contraction of one or both ventricles)—idiopathic, ischemic, valvular, viral, genetic, late manifestation of hypertrophic heart disease, tachycardia induced, alcohol induced, peripartum
- **HYPERTROPHIC** (disorder with disproportionate hypertrophy of the left ventricle and occasionally right ventricle)—**idiopathic** (autosomal dominant inheritance with incomplete penetrance), **storage disease** (Fabry disease, Pompe disease, Hurler syndrome, Noonan syndrome), athlete's heart (usually reversible), obesity, amyloid

PATHOPHYSIOLOGY (CONT'D)

- **RESTRICTIVE** (non-dilated ventricles with impaired ventricular filling)—idiopathic familial, **infiltrative** (amyloidosis, hemochromatosis, sarcoidosis), drugs, radiation, endomyocardial fibrosis
- **ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA** (replacement of right ventricular free wall with fatty tissue)
- **UNCLASSIFIABLE**—endocardial fibroelastosis, left ventricular non-compaction

ETIOLOGIC CLASSIFICATION OF CARDIOMYOPATHY

- **ISCHEMIC CARDIOMYOPATHY** (mostly dilated)—varying degrees of persistent ischemia, infarction, and left ventricular remodeling
- **VALVULAR CARDIOMYOPATHY** (mostly dilated)—abnormal loading conditions and secondary left ventricular remodeling and dysfunction
- **HYPERTENSIVE CARDIOMYOPATHY** (dilated, restrictive)—left ventricular hypertrophy and dysfunction
- **DIABETIC CARDIOMYOPATHY** (dilated)—left ventricular dysfunction in the absence of atherosclerosis or hypertension
- **INFLAMMATORY CARDIOMYOPATHY** (mostly dilated)—**infectious** (e.g. diphtheria, rheumatic fever, scarlet fever, typhoid fever, meningococcal, TB, Lyme disease, Leptospirosis, RMSF, poliomyelitis, influenza, mumps, rubella, rubeola, variola, varicella, EBV, Coxsackie virus, echovirus, CMV, hepatitis, rabies, mycoplasma, psittacosis, arboviruses, histoplasmosis, cryptococcosis, Chagas disease), **autoimmune, idiopathic** myocardial inflammatory diseases
- **METABOLIC CARDIOMYOPATHY** (dilated, restrictive, and/or hypertrophic)—**endocrine** (thyrotoxicosis, hypothyroidism, acromegaly, pheochromocytoma), **storage diseases** (glycogen storage disease, Fabry disease, Gaucher dis-

PATHOPHYSIOLOGY (CONT'D)

- ease, Niemann–Pick disease), **nutritional deficiencies** (Beriberi, Kwashiorkor, pellagra), **deposition** (amyloidosis, hemochromatosis, sarcoidosis)
- **MUSCULAR DYSTROPHIES** (mostly dilated)—Duchenne, Becker, myotonic dystrophy
 - **NEUROMUSCULAR**—Friedreich ataxia (hypertrophic), Noonan syndrome, lentiginosis
 - **GENERAL SYSTEMIC DISEASE** (mostly dilated)—**connective tissue diseases** (rheumatoid heart disease, ankylosing spondylitis, SLE, scleroderma, dermatomyositis), granulomatous (sarcoidosis, granulomatosis with polyangiitis, granulomatous myocarditis), **other inflammatory** (giant cell myocarditis, hypersensitivity myocarditis), **neoplasm** (primary, secondary, restrictive pattern)
 - **SENSITIVITY AND TOXIC REACTIONS** (mostly dilated)—alcohol, amphetamine, arsenic, catecholamines, cocaine, anthracyclines, zidovudine, radiation (restrictive as well)
 - **PERIPARTUM** (dilated)—see p. 467

FUNCTIONAL CLASSIFICATION OF HEART FAILURE

- **SYSTOLIC DYSFUNCTION** (HFmEF [heart failure with a mid-range ejection fraction; LVEF 41–49%] and HFrfEF [heart failure with reduced ejection fraction; LVEF \leq 40%])—S3 (dilated ventricle with

PATHOPHYSIOLOGY (CONT'D)

- volume overload). Mechanisms include decreased contractility and increased afterload. Causes include MI, cardiomyopathy (dilated, infiltrative), valvular (aortic regurgitation, mitral regurgitation, “burned out” aortic stenosis), “burned out” hypertension and myocarditis
- **DIASTOLIC DYSFUNCTION** (HFpEF [heart failure with preserved ejection fraction; normal LVEF])—S4 (stiff ventricle), LVH, \downarrow ventricular relaxation, normal LVEF, \uparrow chamber pressures). Mechanisms include decreased active relaxation and passive relaxation (stiff ventricle). Causes include ischemia, hypertension, valvular (aortic stenosis), cardiomyopathy (restrictive, hypertrophic), and pericardial disease
 - **MIXED DYSFUNCTION**—in many cases, diastolic dysfunction is present with systolic heart failure

PRECIPITANTS OF HF ★FAILURE★

- **FORGET TO TAKE MEDICATIONS** (non-adherence)
- **ARRHYTHMIA, ANEMIA**
- **INFECTION, ISCHEMIA, INFARCTION**
- **LIFESTYLE CHANGE** (e.g. high salt and/or fluid intake)
- **UPREGULATORS** (thyroid, pregnancy)
- **RHEUMATIC HEART DISEASE, ACUTE VALVULAR DISEASE**
- **EMBOLISM**

CLINICAL FEATURES**DISTINGUISHING FEATURES BETWEEN COPD AND HEART FAILURE**

	COPD	Heart Failure
History	Previous COPD Medications	Previous HF Medications
Inspect	Nicotine stain, barrel chest Laryngeal height <4 cm	
Cardiac exam	Subxyphoid cardiac pulse	Elevated JVP, S3, S4
Resp. exam	Hyperresonance Prolonged expiratory time	Bilateral crackles
Investigations	CXR shows hyperinflation ABG shows hypercapnia and hypoxemia	CXR shows redistribution and cardiomegaly ABG shows hypoxemia Elevated BNP

CLINICAL FEATURES (CONT'D)

LEFT HEART FAILURE—left-sided S₃, rales, wheezes, tachypnea. Causes include previous MI, aortic stenosis, and left-sided endocarditis

RIGHT HEART FAILURE—right-sided S₃, ↑ JVP, ascites, hepatomegaly, peripheral edema. Causes include left heart failure, pulmonary hypertension, right ventricular MI, mitral stenosis, and right-sided endocarditis

CLINICAL FEATURES (CONT'D)

GRADING OF PITTING EDEMA—**0**=no edema, **1**=trace edema, **2**=moderate edema disappears in 10–15 s, **3**=stretched skin, deep edema disappears in 1–2 min, **4**=stretched skin, fluid leaking, very deep edema present after 5 min

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS DYSPNEIC PATIENT IN THE EMERGENCY DEPARTMENT HAVE CONGESTIVE HEART FAILURE?

	Sens (%)	Spc (%)	LR+	LR-
History				
Initial clinical judgment	61	80	4.4	0.45
Hx heart failure	60	90	5.8	0.45
Myocardial infarction disease	40	87	3.1	0.69
Coronary artery	52	70	1.8	0.68
Dyslipidemia	23	87	1.7	0.89
Diabetes	28	83	1.7	0.86
Hypertension	60	56	1.4	0.71
Smoker	62	27	0.84	1.4
COPD	34	57	0.81	1.1
PND	41	83	2.6	0.70
Orthopnea	50	77	2.2	0.65
Edema	51	76	2.1	0.64
Dyspnea on exertion	84	34	1.3	0.48
Fatigue and weight gain	31	70	1.0	0.99
Cough	36	61	0.93	1.0
Physical				
S ₃	13	99	11	0.88
AJR	24	96	6.4	0.79
JVD	39	92	5.1	0.66
Rales	60	78	2.8	0.51
Any murmur	27	90	2.6	0.81
Lower extremity edema	50	78	2.3	0.64
Valsalva maneuver	73	65	2.1	0.41
SBP <100 mmHg	6	97	2.0	0.97
S ₄	5	97	1.6	0.98
SBP ≥150 mmHg	28	73	1.0	0.99

CLINICAL FEATURES (CONT'D)

	Sens (%)	Spc (%)	LR+	LR-
Wheezing	22	58	0.52	1.3
Ascites	1	97	0.33	1.0
CXR				
Pulmonary venous congestion	54	96	12	0.48
Interstitial edema	34	97	12	0.68
Alveolar edema	6	99	6.0	0.95
Cardiomegaly	74	78	3.3	0.33
Pleural effusions	26	92	3.2	0.81
Any edema	70	77	3.1	0.38
Pneumonia	4	92	0.50	1.0
Hyperinflation	3	92	0.38	1.1
ECG				
Atrial fibrillation	26	93	3.8	0.79
New T wave changes	24	92	3.0	0.83
Any abnormal finding	50	78	2.2	0.64
ST elevation	5	97	1.8	0.98
ST depression	11	94	1.7	0.95
BNP				
BNP ≥ 250 pg/mL			4.6	
BNP ≥ 100 pg/mL ^a			2.7	
BNP ≥ 50 pg/mL			1.7	0.06

^aFor patients with an estimated GFR of 15–60 mL/min/1.73 m², a threshold of 201 pg/mL can be used

APPROACH—“The features evaluated in more than one study with the highest LRs (>3.5) for diagnosing heart failure were the following: the overall clinical judgment, history of heart failure, S3, jugular venous distension, pulmonary venous congestion or interstitial edema on CXR, and atrial fibrillation on ECG. The features evaluated in more than one study with the lowest LRs (<0.60) for diagnosing heart failure were the following: the overall clinical judgment, no prior history of heart failure, no dyspnea on exertion, the absence of rales, and the absence of radiographic pulmonary venous congestion, or cardiomegaly. The single finding that decreased the likelihood of heart failure the most was a BNP <100 pg/mL.” While the findings of this study are useful when assessing dyspneic patients suspected of having heart failure, “no individual feature is sufficiently powerful in isolation to rule heart failure in or out. Therefore, an overall clinical impression based on all available information is best. If the appropriate constellation of findings with high LRs for heart failure are present, that may be sufficient to warrant empirical treatment without further urgent investigations.”

Wang et al. *JAMA* 2005;294(15)
Simel et al. *The Rational Clinical Examination*. McGraw-Hill; 2009

CLINICAL FEATURES (CONT'D)**RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ABNORMAL CENTRAL VENOUS PRESSURE?**

JVP VS. CAROTID—JVP has biphasic waveforms, is non-palpable, is occludable, decreases with inspiration, changes with position, and increases with abdominogastric reflux (AJR). To perform the AJR, the blood pressure cuff is pumped 6 × and then pressed against the abdomen at 20–35 mmHg for 15–30 s. Normal = no change in JVP, or transient increase of >4 cm that returns to baseline before 10 s, or sustained increase <3 cm throughout. Positive AJR occurs when abdominal compression causes a sustained increase in JVP >4 cm (sens 24%, spc 96%, LR+ 4.4)

Cook et al. *JAMA* 1996;275(8)

UPDATE—a JVP height ≥3 cm above the sternal angle in any position indicates an abnormal CVP. Clinical assessment of high JVP has a LR+ for high CVP of 3.1. An assessment of low JVP has a LR+ for low CVP of 3.4

Simel et al. *The Rational Clinical Examination*. McGraw-Hill; 2009

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, troponin/CK×3, BNP or NT-pro-BNP, D-dimer, TSH, albumin
- **IMAGING**—CXR, echocardiogram (check E/A ratio if diastolic dysfunction)
- **ECG**

SPECIAL

- **FURTHER IMAGING**—MIBI, MUGA, cardiac MRI
- **STRESS TEST**—to assess ischemic heart disease
- **CARDIAC CATHETERIZATION**
- **ABG**—if severe dyspnea

DIAGNOSTIC AND PROGNOSTIC ISSUES**B-TYPE NATRIURETIC PEPTIDE/N-TERMINAL PROHORMONE OF BRAIN NATRIURETIC PEPTIDE**

- **DIAGNOSIS**—BNP and NT-proBNP levels are elevated with HF, PE, pulmonary hypertension, LVH, ACS, AF, renal failure, overload, and sepsis. Generally, can rule-out HF if BNP <100 pg/mL or NT-proBNP <300 pg/mL; may rule-in if BNP >500 pg/mL, NT-proBNP >900 pg/mL (if age 50–75 years), or NT-proBNP >1,800 pg/mL (if

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

age >75 years). Best used in combination with clinical scoring system when diagnosis is uncertain

- **BAGGISH CLINICAL SCORING SYSTEM**—elevated NT-proBNP [>450 pg/mL if age <50 years, or >900 pg/mL if age ≥50 years] (+4), interstitial edema on CXR (+2), orthopnea (+2), lack of fever (+2), age >75 years (+1), lack of cough (+1), use of loop diuretic prior to presentation (+1), rales (+1). If score 0–5, low likelihood of HF; if 6–8, intermediate likelihood of HF; if 9–14, high likelihood of HF
- **PROGNOSIS**—BNP >80th percentile is associated with a >50% increase in long-term mortality

HF PROGNOSIS—33% 1-year mortality, 75% 6-year mortality

ACUTE MANAGEMENT

ABC—O₂ to keep sat >95%, IVs

SYMPTOM CONTROL—★**LMNOP**★ *Lasix/furosemide* 20–120 mg IV PRN, *Morphine* 2–5 mg IV PRN, *Nitroglycerin* 0.4 mg SL PRN, **O₂**, **Position** (upright)

LONG-TERM MANAGEMENT

DIET—**low salt** (<100 mmol/day, 1.5–2 g/day), **fluid restriction** (1.5–2 L/day)

DIURETICS—**furosemide** 20–120 IV/PO daily-BID with daily adjustments (try to use smallest dose possible to allow ACE inhibitor) ± **metolazone** 2.5–5 mg PO 30 min before furosemide, **spironolactone** 12.5–50 mg PO daily or **eplerenone** 25–50 mg PO daily

VASODILATORS—**ACE inhibitor** (*captopril* 6.25–50 mg PO TID, *enalapril* 1.25–10 mg PO BID, *ramipril* 2.5–10 mg PO BID, *lisinopril* 2.5–20 mg PO daily, *perindopril* 2–8 mg PO daily). **ARB** (*valsartan* 40–160 mg PO BID, *candesartan* 8–32 mg PO daily). **Hydralazine** 10–50 mg PO QID and **nitrate** (*nitroglycerin* 0.4 mg topical daily or *isosorbide mononitrate* 30–90 mg PO daily)

RATE CONTROL—**β-blockers** (*metoprolol tartrate* 50–100 mg PO BID, *carvedilol* 3.125–25 mg PO BID, *bisoprolol* 2.5–10 mg PO daily). **HCN**

(**hyperpolarization-activated cyclic nucleotide-gated channel blocker**) (*ivabradine* 5–7.5 mg PO BID) can be considered in patients with sinus rhythm and heart rate ≥70 bpm on maximal tolerated dose of β-blocker or in whom a β-blocker is contraindicated

DIGITALIS—**digoxin** 0.0625–0.25 mg PO daily

LONG-TERM MANAGEMENT (CONT'D)

SGLT2 inhibitors—empagliflozin, canagliflozin, or dapagliflozin. May be beneficial, especially in patients with type 2 diabetes and/or atherosclerosis

TREAT UNDERLYING CAUSE—CAD (PCI/CABG), **aortic stenosis** (AV replacement), **sleep apnea** (CPAP)

DEVICES—if ejection fraction <30–35%, consider **cardiac resynchronization therapy** (CRT/biventricular pacing) \pm **implantable cardioverter defibrillators** (ICD). Percutaneous mitral valve repair can be considered for symptomatic heart failure with reduced EF and severe MR if refractory to medical therapy. **Ventricular assist devices** may also be considered in selected cases of refractory HF

TREATMENT ISSUES

ACE INHIBITOR (Garg, JAMA 1995)—hazard ratios for total mortality 0.77 and mortality/hospitalization 0.65 for any patients with LVEF <40%. Target dose = maximum tolerated. Contraindications include SBP <80 mmHg, bilateral renal artery stenosis, severe renal failure, and hyperkalemia

ARB (CHARM)—consider substitution with ARB if ACE inhibitor *not tolerated* (e.g. cough). May also be used as adjunct to ACE inhibitor if β -blocker not tolerated. Contraindications similar to ACE inhibitor

HYDRALAZINE/NITRATES (VHEFT I and II, A-HeFT)—less effective than ACE inhibitor. Particularly useful for pregnant patients, Black patients, or those who developed renal insufficiency while on ACE inhibitor, or as add-on therapy

ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITOR (ARNI) (McMurray NEJM 2014, PARADIGM-HF)—combination sacubitril-valsartan demonstrated 16% reduction in all-cause mortality, 20% reduction in death from cardiovascular causes, and 21% reduction heart failure hospitalizations compared to enalapril

β -BLOCKERS (Foody, JAMA 2002)—hazard ratios for total mortality 0.65 and mortality/hospitalization 0.64. May worsen symptoms in first few weeks and may take up to 1 year to see full effect in LVEF. Useful for patients with NYHA II–III (and stable IV) and LVEF <40%, also NYHA I, LVEF <40%, and post-MI. Contraindications include fluid overload and severe asthma. Start only when patient euolemic

IVABRADINE (SHIFT 2010)—26% relative risk reduction of heart failure hospitalization. Useful for patients with LVEF \leq 40%, NYHA II–IV, and sinus rhythm with HR \geq 70 bpm despite β -blocker

TREATMENT ISSUES (CONT'D)

optimization or intolerance. Only useful if patients are in sinus rhythm given its direct effect on the sinus node and is therefore not indicated if patients are in atrial fibrillation or if develop atrial fibrillation while on ivabradine

SPIRONOLACTONE (RALES 1999, EPHEUS 2003, EMPHASIS-HF 2011)—hazard ratios for all-cause mortality 0.7 and hospitalization for HF, 0.65 for patients with NYHA III–IV, LVEF <35%, and already on maximum medical therapy. Hazard ratios for cardiovascular death/HF hospitalization 0.63 and cardiovascular mortality 0.76 for patients with NYHA II and LVEF \leq 30% (or LVEF 31–35% *plus* QRS duration >130 msec), and already on maximum medical therapy. Caution in elderly and renal failure patients as higher risk of hyperkalemia

DIGOXIN (DIG 1997)—hazard ratios for total mortality 0.99 and mortality/hospitalization 0.92. Particularly useful for patients with both HF and atrial fibrillation, or symptomatic HF despite maximum medical therapy

OVERALL APPROACH—treat underlying cause if possible. Non-pharmacological treatments (diet, exercise, smoking cessation) \rightarrow add ACE inhibitor if LVEF \leq 40% (or hydralazine/nitrates if renal failure, ARB if cough secondary to ACE inhibitor) \rightarrow add β -blocker when euolemic if LVEF \leq 40% \rightarrow if NYHA II–IV and sinus rhythm with HR \geq 70 bpm despite β -blocker optimization or intolerance add ivabradine \rightarrow add spironolactone/epplerenone if NYHA II–IV if LVEF \leq 30% (or \leq 35% and QRS duration >130 msec) \rightarrow if ongoing symptoms with NYHA II–IV despite optimization of ACE inhibitor, β -blocker, ivabradine, and mineralocorticoid receptor antagonists dose optimization, consider switching ACE inhibitor or ARB to ARNI \rightarrow add digoxin \pm ARB if still symptomatic. If ejection fraction is <30–35% despite optimal medical therapy, consider revascularization, implantable cardioverter defibrillator, and cardiac resynchronization (if QRS is wide with underlying LBBB). For end stage cases consider ventricular-assist device/heart transplant. Consider palliative care referral for symptomatic patients with advanced heart failure

SPECIFIC ENTITIES

CAUSES OF FLASH PULMONARY EDEMA—cardiac (ischemic heart disease, acute aortic regurgitation, acute mitral regurgitation, mitral stenosis/obstruction, arrhythmia), **pulmonary** (pulmonary embolism, pneumonia), **renal** (bilateral renal artery stenosis), **systemic** (hypertension crisis, fever, sepsis, anemia, thyrotoxicosis)

SPECIFIC ENTITIES (CONT'D)**HYPERTROPHIC OBSTRUCTIVE
CARDIOMYOPATHY (HOCM)**

- **PATHOPHYSIOLOGY**—autosomal dominant condition with mutated cardiac sarcomere, leading to massive ventricular hypertrophy (particularly septum). This results in left ventricular outflow tract obstruction, mitral regurgitation, diastolic dysfunction, and subsequently myocardial ischemia and overt heart failure. Cardiac arrhythmias may lead to sudden death (<1%/year). Other complications include atrial fibrillation and infective endocarditis
- **RISK FACTORS FOR SUDDEN DEATH**—major risk factors include history of cardiac arrest (VF), sustained VT, unexplained syncope, non-sustained VT on Holter, abnormal BP response on exercise test, left ventricular wall thickness >30 mm, and family history of sudden death. Minor risk factors include left ventricular outflow obstruction (gradient ≥ 30 mmHg), diastolic dysfunction, microvascular obstruction, late gadolinium enhancement on cardiac MRI, and high-risk genetic defect

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—most are asymptomatic although dyspnea, chest pain, syncope, and sudden death may develop. Family history should be obtained. Physical findings include brisk carotid upstroke, bifid carotid pulse, double apical impulse, systolic ejection murmur (LLSB, louder with standing and Valsalva) \pm mitral regurgitation murmur
- **DIAGNOSIS**—echocardiogram (septal thickening, systolic-anterior motion of mitral valve). Further workup includes 48 h Holter monitor and exercise testing annually
- **TREATMENTS**—**avoidance** (dehydration and strenuous exercise), **medical** (β -blockers and non-dihydropyridine calcium channel blockers as first line, disopyramide as second line), **interventional/surgical** (septal myomectomy, alcohol septal ablation, dual-chamber pacing), **prophylaxis** (implantable cardioverter defibrillator for high-risk patients to prevent sudden cardiac death, anticoagulation if atrial fibrillation)

Nishimura et al. *NEJM* 2004;350(13)

Digoxin Intoxication

Gheorghide et al. *Circulation* 2004;109(24)

CAUSES

OVERDOSE—intentional, accidental (digoxin, foxglove, yellow oleander)

DRUG INTERACTIONS—quinidine, amiodarone, verapamil, diltiazem, tetracycline, erythromycin, rifampin, cyclosporine, SSRIs

PHARMACOKINETICS (see precipitants below)

- **OLD AGE**
- **RENAL FAILURE**
- **CARDIAC**—ischemia, myocarditis, cardiomyopathy, amyloidosis, cor pulmonale
- **METABOLIC**—hypokalemia, hypomagnesemia, hypernatremia, hypercalcemia, hypoxemia, acid–base imbalance

PATHOPHYSIOLOGY

DIGOXIN LEVEL—measurement of serum levels is not routinely necessary as dosing can usually be titrated according to clinical and hemodynamic effects. When measured, serum level should be collected at 12–24 h after the last dose (post-distribution phase). While the upper normal limit is 2.6 nmol/L [2.0 ng/mL], higher digoxin levels may be seen in asymptomatic patients. Low-dose

PATHOPHYSIOLOGY (CONT'D)

digoxin, resulting in serum levels 0.5–0.9 nmol/L [0.4–0.7 ng/mL] is associated with possible survival benefit compared to ≥ 1 nmol/L [≥ 0.78 ng/mL] in HF patients

MECHANISM—digitalis acts by inhibiting the membrane-bound Na/K ATPase transport system. This leads to intracellular loss of K and gain of Na. Increase in intracellular Ca leads to \uparrow cardiac contractility. Digoxin also exerts a vagotonic action, which slows conduction through the SA and AV node and helps to control heart rate

PRECIPITANTS OF DIGOXIN TOXICITY—toxicity is not merely related to serum levels, but also digoxin dosing (e.g. acute overdose), other medications (e.g. non-potassium sparing diuretics), and conditions (e.g. renal insufficiency, acute coronary syndromes, cardiac amyloidosis, hypothyroidism). For instance, hypokalemia, hypernatremia, hypomagnesemia and acidosis predispose to toxicity even at low-serum digoxin levels because of their depressive effects on the Na/K ATPase pump. In contrast, hyperkalemia occurs in acute toxicity and is directly related to prognosis

CLINICAL FEATURES**SIGNS AND SYMPTOMS**

- **NEUROLOGICAL**—delirium, hallucination, blurred vision with altered color perception, headaches, dizziness
- **CARDIAC**—bradycardia, high-degree AV block, paroxysmal atrial tachycardia (often 2:1 AV conduction), unifocal or multifocal PVCs, bidirectional ventricular tachycardia, accelerated junctional tachycardia
- **GI**—anorexia, N&V, diarrhea, abdominal pain
- **METABOLIC**—hyperkalemia

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, Ca, Mg, albumin, serum digoxin level
- **ECG**
- **ABG**

DIAGNOSTIC ISSUES**ECG CHANGES ASSOCIATED WITH DIGOXIN**

- **THERAPEUTIC LEVELS**—sagging of ST segments, flattened T waves, U waves, and shortened QT. Not to be confused with digoxin toxicity
- **TOXIC LEVELS**—first degree heart block, paroxysmal atrial tachycardia (often 2:1 AV conduction), regularized atrial fibrillation (i.e. with complete heart block), unifocal or multifocal PVCs, ventricular bigeminy, bidirectional VT

MANAGEMENT

ACUTE—ABC, O₂, IV, **treat arrhythmia**

TREAT UNDERLYING CAUSE—**observe, cardiac monitoring, activated charcoal** (if ingestion within 4 h). **Correct** electrolyte disturbances

MANAGEMENT (CONT'D)

and reverse acidosis. **Atropine** for bradycardia. **Digibind/purified antidigoxin FAB fragments** (if acute ingestion of 10 mg or more in adults, or digoxin level >13 nmol/L [10 ng/mL], K >5 mM and life-threatening arrhythmia, hemodynamic instability, unstable arrhythmia [e.g. symptomatic bradycardia], or end-organ hypoperfusion [e.g. acute renal failure]). May see response in 20 min and complete response up to 4 h. Monitor potassium levels after treatment with Digibind)

TREATMENT ISSUES**AVOID**

- **IV CALCIUM**—indicated for other causes of severe hyperkalemia, calcium may precipitate VT/sudden death and should **not** be given for hyperkalemia of digoxin toxicity
- **CARDIOVERSION**—relatively contraindicated because asystole or ventricular fibrillation may be precipitated
- **TRANSVENOUS PACING**—can precipitate arrhythmias and deterioration

HALF-LIVES—plasma t_{1/2} for digoxin 1.6 days, digitoxin 5 days

INDICATIONS FOR DIGOXIN THERAPY—in patients with **symptomatic systolic HF and sinus rhythm** (digoxin may be especially useful in patients with severe symptoms despite standard medical therapy, LVEF <25%, or cardiomegaly), **diastolic HF** (with rapid atrial fibrillation or severe symptoms despite standard medical therapy), and **rapid atrial fibrillation** (with or without heart failure). Use with extreme caution or avoid in the elderly, patients with severe conduction abnormalities, acute coronary syndromes, or renal failure

Atrial Fibrillation

Ozcan et al. *NEJM* 2001;344(14)

Alboni et al. *NEJM* 2004;351(23)

2019 AHA/ACC/HRS Focused Update Atrial Fibrillation

2018 CCS Focused Update Atrial Fibrillation

DIFFERENTIAL DIAGNOSIS OF PALPITATIONS**★PPP★**

PHYSIOLOGIC (high output states)—anemia, pregnancy, fever, exercise, stress

PATHOLOGIC★CDE★

- **CARDIAC**—**arrhythmia** (see tachycardia below), **myocardial** (cardiomyopathy, atrial myxoma, shunts), valvular, transplanted heart

DIFFERENTIAL DIAGNOSIS OF PALPITATIONS (CONT'D)

- **DRUGS**—sympathomimetic agents, vasodilators, anticholinergic agents, β-blocker withdrawal, illicit (cocaine, amphetamines)
- **ENDOCRINE**—hypoglycemia, hyperthyroidism, pheochromocytoma
- **PSYCHIATRIC**—panic attack/disorder, generalized anxiety disorder, somatization disorder

DIFFERENTIAL DIAGNOSIS OF NARROW COMPLEX TACHYCARDIA

REGULAR NARROW COMPLEX TACHYCARDIA—sinus tachycardia, atrial flutter with fixed block, supraventricular tachycardia (atrial tachycardia, AV nodal reentry, orthodromic AV reentrant/WPW), accelerated junctional tachycardia

IRREGULAR NARROW COMPLEX TACHYCARDIA—sinus tachycardia/arrhythmia, premature atrial contractions, multifocal atrial tachycardia, atrial flutter with variable block, atrial tachycardia with variable block, atrial fibrillation

DIFFERENTIAL DIAGNOSIS OF IRREGULARLY IRREGULAR RHYTHM

ATRIAL—sinus arrhythmia (rate 60–100), wandering pacemaker (rate 60–100), premature atrial rhythm/beat, multifocal atrial tachycardia (rate >100), ectopic atrial tachyarrhythmia with variable block, atrial flutter with variable block, atrial fibrillation

VENTRICULAR—premature ventricular contraction, polymorphic ventricular tachycardia, ventricular fibrillation

PATHOPHYSIOLOGY**CAUSES OF ATRIAL FIBRILLATION**

- **CARDIOVASCULAR**—**myocardial** (hypertension, CAD, HF, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, infiltration [amyloidosis, sarcoidosis, hemochromatosis], ASD), **valvular** (rheumatic, acquired, endocarditis), **arrhythmia** (WPW), **pericardial** (pericarditis), cardiac surgery
- **PULMONARY**—COPD, pulmonary embolism, pleural effusion, pulmonary hypertension, obstructive sleep apnea
- **METABOLIC**—thyrotoxicosis, obesity
- **DRUGS**—theophylline, adenosine, digitalis, β -agonists, alcohol, caffeine, cocaine
- **IDIOPATHIC** (10%)

CLASSIFICATION OF ATRIAL FIBRILLATION

- **PAROXYSMAL ATRIAL FIBRILLATION**—episodes of AF last <7 days (usually <24 h). Terminates spontaneously or with intervention. May variably recur
- **PERSISTENT ATRIAL FIBRILLATION**—continuous AF sustained >7 days
- **LONG-STANDING PERSISTENT ATRIAL FIBRILLATION**—continuous AF >12 months
- **PERMANENT ATRIAL FIBRILLATION**—a classification determined by clinician and patient to stop further attempts to restore and/or maintain sinus

PATHOPHYSIOLOGY (CONT'D)

rhythm. A therapeutic attitude rather than inherent pathophysiological attribute of AF

- **NONVALVULAR ATRIAL FIBRILLATION**—AF in the absence of moderate or severe rheumatic mitral stenosis, mechanical or bioprosthetic heart valve, or mitral valve repair
- **LONE ATRIAL FIBRILLATION**—AF in patients <60 years, no structural heart disease or risk factors, including hypertension

CLINICAL FEATURES OF NARROW COMPLEX TACHYCARDIA

HISTORY—palpitations, chest pain, dyspnea, dizziness, syncope, past medical history (AF, SVT, WPW, CAD, HF, hypertension, diabetes, stroke, TIA, thyroid dysfunction), medications (antihypertensives, antiarrhythmics), DVT/PE risk factors

PHYSICAL—vitals (pulse rate and rhythm, BP), cardiac and pulmonary examination for heart failure

CAROTID SINUS MASSAGE, VALSALVA, OR ADENOSINE—SVT may spontaneously terminate, while the ventricular response in AF or atrial flutter may slow down allowing better analysis of the atrial rhythm. Avoid adenosine if suspect pre-excitation syndrome (atrial fibrillation or atrial flutter with WPW)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, Mg, TSH, INR, PTT, D-dimer, troponin
- **IMAGING**—CXR, echocardiogram (enlarged left atrium)
- **ECG**
- **24-H HOLTER**
- **EXERCISE STRESS TEST**

SPECIAL

- **ELECTROPHYSIOLOGY STUDIES**
- **URINARY OR PLASMA METANEPHRINES**—if suspect pheochromocytoma

ACUTE MANAGEMENT

ABC—O₂ to keep sat >95%, IV

SYNCHRONIZED CARDIOVERSION—pre-medicate if possible with *midazolam* 1–2 mg IV q2–3 min, *fentanyl* 50–150 μ g IV \times 1, shock 50, 100, 200, 300, 360 J, prepare to intubate and give IV anti-arrhythmics PRN

AV NODAL BLOCKING AGENTS ★ ABCD★

- **AMIODARONE**—*amiodarone* 150 mg IV bolus over 10 min, q10–15 min. Alternatively, infu-

ACUTE MANAGEMENT (CONT'D)

sion 60 mg/h over 6 h, then 30 mg/h over 18 h. Maximum 2.2 g/day

- **β-BLOCKERS**—*metoprolol* 5 mg IV over 1 min q5min × 3 PRN, *esmolol* 500 µg/kg IV over 1 min, maintenance dose 50–200 µg/kg/min IV
- **CALCIUM CHANNEL BLOCKERS**—*diltiazem* 15–20 mg IV over 2 min, repeat in 15 min at 20–25 mg PRN, maintenance dose 5–20 mg/h IV; *verapamil* 2.5–5.0 mg IV over 1–2 min, followed by 5–10 mg in 15–30 min PRN with maximum of 30 mg, maintenance dose 0.05–0.2 mg/min IV
- **DIGITALIS**—*digoxin* 0.25–0.5 mg IV q6h to a total dose of 1 mg, maintenance dose 0.125–0.25 mg PO/IV daily

OVERALL APPROACH

- **UNSTABLE ATRIAL FIBRILLATION**—perform cardioversion immediately
- **STABLE ATRIAL FIBRILLATION <48 H—rate control** (β-blockers, calcium channel blockers, digoxin) and consider **rhythm control** (DC cardioversion, amiodarone, propafenone, flecainide); immediate initiation of anticoagulation prior to cardioversion preferred and anticoagulate at least × 4 weeks post-cardioversion. Anticoagulation for 3 weeks prior to cardioversion is recommended for patients with recent stroke or TIA even if AF duration is <48 h
- **STABLE ATRIAL FIBRILLATION >48 H OR UNKNOWN DURATION—rate control** (β-blockers, calcium channel blockers, digoxin) and consider **rhythm control**. IV unfractionated heparin → TEE to exclude atrial thrombus → cardioversion within 24 h → anticoagulate × 4 weeks; ALTERNATIVELY anticoagulate × 3 weeks → cardioversion → anticoagulate at least × 4 weeks
- **TREAT UNDERLYING CAUSE/PRECIPIANT**—infection, myocardial infarction, ischemia, drugs, pulmonary embolism, thyrotoxicosis

LONG-TERM MANAGEMENT

RATE CONTROL—target resting HR <80 and exercise HR <110 in patients with significant symptoms. (Consider target resting HR <110 in asymptomatic patients with preserved LVEF). **β-blocker** (*metoprolol tartrate* [immediate release] 50–100 mg PO BID, *metoprolol succinate* [extended release] 100–200 mg PO daily, *carvedilol* 6.25–50 mg PO BID, *bisoprolol* 5–10 mg PO daily). **Calcium channel blockers** (*diltiazem CD* 120–480 mg PO daily, *verapamil ER* 180–540 mg PO daily). **Digitalis** (*digoxin* 0.5 mg PO × 1 dose, then 0.25 mg × 2 doses q6–12 h, then 0.0625–0.25 mg daily)

LONG-TERM MANAGEMENT (CONT'D)

RHYTHM CONTROL—elective cardioversion (only after a 3-week course of therapeutic anticoagulation or atrial thrombus excluded by TEE. Cardioversion should be followed by 4 weeks of anticoagulation). **Antiarrhythmics** (*amiodarone* 200–400 mg PO daily, *sotalol* 40–160 mg PO BID, especially if CAD; *flecainide* 50 mg PO q12h, especially if no structural heart disease; *propafenone* 150 mg PO q8h, especially if no structural heart disease)

STROKE PREVENTION

- **LOWEST RISK** (e.g. nonvalvular disease, CHADS₆₅=0, and **absence** of CAD or arterial vascular disease)—no antithrombotic therapy
- **LOW RISK** (e.g. nonvalvular disease, CHADS₆₅=0, and **presence** of CAD or arterial vascular disease)—**ASA** 81 mg daily
- **MODERATE TO HIGH RISK—anticoagulation** (*warfarin* 5 mg PO daily to target INR between 2–3, *dabigatran* 110–150 mg PO BID, *rivaroxaban* 15–20 mg PO daily, *apixaban* 2.5–5 mg PO bid, or *edoxaban* 60 mg PO daily). Direct oral anticoagulants (DOACs) preferred over warfarin except for valvular AF (e.g. moderate to severe mitral stenosis) or patients with mechanical valves. In patients with moderate to severe CKD, a reduced dose of dabigatran, rivaroxaban, apixaban, or edoxaban is recommended; in patients with end-stage CKD or on dialysis, the use of dabigatran, rivaroxaban, or edoxaban is not recommended. Patients at higher risk of bleeding may require lower doses. Bridging anticoagulation (for initiation/interruption of warfarin therapy) not routinely required but should be considered in those at high risk for acute thrombosis (e.g. mechanical heart valves). Percutaneous left atrial appendage occlusion may be considered in patients with contraindication for anticoagulation but who would still benefit from stroke prevention

PROCEDURES—radiofrequency ablation

for AF includes isolation of the pulmonary veins along with other complex ablation approaches. If this approach is unsuccessful, radiofrequency ablation of the AV node with insertion of a permanent pacemaker to activate the ventricles may be considered as a last resort. AF ablation is mainly associated with symptom improvement. In patients who also have heart failure and left ventricular systolic dysfunction, there may be additional mortality benefit. Long-term anticoagulation based on stroke risk needs to be considered in all patients regardless of the rate or rhythm strategy that is used. **Surgical** (corridor

LONG-TERM MANAGEMENT (CONT'D)

and maze procedures can be considered but long-term success unclear)

Wyse et al. *NEJM* 2002;347(23)

Connolly et al. *NEJM* 2009;361(12)

Van Gelder et al. *NEJM* 2010;362(15)

Patel et al. *NEJM* 2011;365(10)

Mega *NEJM* 2011;365(11)

TREATMENT ISSUES**STROKE RISK FACTORS IN PATIENTS WITH ATRIAL FIBRILLATION****★CHADS₆₅★**

- **CHF** (any history, 1 point)
- **HYPERTENSION** (any history, 1 point)
- **AGE** ≥65 (1 point)
- **DIABETES** (1 point)
- **STROKE OR TIA** (2 points)

★CHADS₂★

- **CHF** (any history, 1 point)
- **HYPERTENSION** (any history, 1 point)
- **AGE** ≥75 (1 point)
- **DIABETES** (1 point)
- **STROKE OR TIA** (2 points)
- **RISK OF STROKE (IF UNTREATED)**—0 points = 1.9%/year, 1 = 2.8%, 2 = 4.0%, 3 = 5.9%, 4 = 8.5%, 5 = 12.5%, 6 = 18.2%

★CHA₂DS₂-VASc★

- **CHF** (any history, 1 point)
- **HYPERTENSION** (any history, 1 point)
- **AGE** ≥75 (2 point)
- **DIABETES** (1 point)
- **STROKE OR TIA** (2 points)
- **VASCULAR DISEASE (coronary, aortic, or peripheral)** (1 point)
- **AGE 65–74** (1 point)
- **SEX, female** (1 point)
- **RISK OF STROKE (IF UNTREATED)**—0 points = 0%/year, 1 = 1.3%, 2 = 2.2%, 3 = 3.2%, 4 = 4.0%, 5 = 6.7%, 6 = 9.8%, 7 = 9.6%, 8 = 6.7%, 9 = 15.2%
- **MAIN INDICATIONS FOR ANTICOAGULATION**—CHADS₂ score ≥1, CHADS₆₅ score ≥1, CHA₂DS₂-VASc score ≥2 in men, or CHA₂DS₂-VASc score ≥3 in women
- **OTHER RISK FACTORS**—CAD, echocardiography abnormalities (atrial size >5 cm, LV dysfunction), thyrotoxicosis, rheumatic valvular disease (RR 17). *All* moderate to severe mitral stenosis and HOCM patients with AF should have chronic anticoagulation (regardless of CHADS₂, CHADS₆₅, or CHA₂DS₂-VASc score)
- **RISK REDUCTION**—anticoagulation decreases risk of stroke by ~60%

TREATMENT ISSUES (CONT'D)

- **FACTORS INCREASING RISK OF BLEEDING WITH WARFARIN USE**—advanced age, female sex, diabetes, prior hemorrhage, uncontrolled hypertension, alcoholism or liver disease, cancer, bleeding disorder, chronic kidney disease, ASA/clopidogrel/NSAIDs (including COX-2 inhibitors). Note that risk of fall by itself is not a contraindication to warfarin use
- **RISK OF BLEEDING ON ANTICOAGULATION**—as CHADS₂ score increases so does risk of major bleeding (but risk of stroke usually remains higher than risk of bleeding). Benefit-to-risk ratio for anticoagulation generally becomes even more favorable as risk factors for stroke accumulate. Risk calculation for bleeding usually unnecessary. Existing risk models do not reliably predict individual risk. Use clinical judgment

★HASBLED★

- **HYPERTENSION**, SBP >160 mmHg (1 point)
- **ABNORMAL LIVER FUNCTION** (1 point)
- **ABNORMAL RENAL FUNCTION** (1 point)
- **STROKE** (1 point)
- **BLEEDING TENDENCY/PREDISPOSITION** (1 point)
- **LABILE INR ON WARFARIN** (1 point)
- **ELDERLY**, age >65 (1 point)
- **DRUGS** (ASA, clopidogrel, NSAIDs) (1 point)
- **DRUGS** (alcohol abuse) (1 point)
- **RISK OF BLEEDING**—0 = 1.13 bleeds/100 patient-years, 1 = 1.02, 2 = 1.88, 3 = 3.74, 4 = 8.70, 5 = 12.50, insufficient data for scores ≥6

IMPORTANT TOXICITIES OF AMIODARONE

- **CARDIAC** (5%)—sinus bradycardia and AV nodal block. QT prolongation leading to torsades de pointes may rarely occur
- **THYROID**—amiodarone-induced thyrotoxicosis (3%). Type 1 from increased thyroid hormone synthesis from excess iodine (usually with underlying multinodular goiter or Graves' disease). Type 2 from destructive thyroiditis and thyroid hormone release. Doppler US showing goiter and ↑ vascularity favors type 1 (hyperthyroidism), but normal sized gland and normal/↓ vascularity favor type 2 (thyroiditis). Presence of (any) radioiodine uptake favors hyperthyroidism (type 1), but absence of uptake does not reliably differentiate between type 1 or type 2. Patients on amiodarone may not develop classic symptoms of thyrotoxicosis. Treatment includes anti-thyroid drugs (for type 1) and steroids (for type 2). Hypothyroidism also common (20%)

TREATMENT ISSUES (CONT'D)

- **PULMONARY** (<3%)—chronic interstitial pneumonia (most common), cryptogenic organizing pneumonia, ARDS, and solitary pulmonary nodule. Histologically characterized by foamy macrophages in the air space. DLCO is often decreased. CT chest may show diffuse/localized interstitial or alveolar opacities. Treat with steroids and stop amiodarone
- **HEPATIC** (15%)—non-alcoholic steatohepatitis which in severe cases may lead to cirrhosis
- **NEUROLOGIC** (30%)—ataxia, tremor, peripheral polyneuropathy, insomnia, and impaired memory
- **VISION** (100%)—corneal microdeposits may result in halo vision, photophobia, and blurred vision. Optic nerve injury (1–2%) may cause blindness

TREATMENT ISSUES (CONT'D)

- **DERMATOLOGIC** (25–75%)—photosensitivity, gray-bluish discoloration (blue man syndrome), and alopecia. This is reversible upon discontinuation of amiodarone, but may take a few years
- **MONITORING**—baseline TSH, LFTs, PFT and CXR. TSH and LFTs every 6 months, CXR yearly, and PFT as needed

Zimetbaum NEJM 2007;356(9)

Related Topics

ACLS (p. 499)

Digoxin (p. 47)

ECG (p. 78)

Wolff-Parkinson-White Syndrome (p. 81)

Syncope**DIFFERENTIAL DIAGNOSIS****★SVNCOPE★**

SITUATIONAL—micturition, defecation, coughing, laughing

VASOVAGAL—painful, emotional stimulus, head turning

NEUROGENIC—vestibular stroke, seizures, autonomic insufficiency

CARDIOGENIC

- **CONDUCTION**—VT, AV block/Stokes-Adams, prolonged QT, carotid sinus hypersensitivity (shaving, tight collars)

- **VALVULAR**—aortic stenosis, mitral stenosis, pulmonary stenosis, tricuspid stenosis

- **VASCULAR**—pulmonary hypertension, pulmonary embolism

- **PERICARDIAL**—tamponade

- **MYOCARDIAL**—myocardial infarction, hypertrophic cardiomyopathy

ORTHOSTATIC**PSYCHOGENIC****ETC**—drugs**CLINICAL FEATURES**

HISTORY—N&V before collapse, syncope with exertion, seizure features (tongue biting, incontinence, post-collapse disorientation), last meal, history of cardiac disease (arrhythmias, heart failure, ischemic heart disease, aortic stenosis), previous syncope, seizures, or psychiatric problems, current medications, family history of unexplained syncope or sudden death

CLINICAL FEATURES (CONT'D)

PHYSICAL—orthostatic hypotension, irregular or slow-rising pulse, apical-carotid delay, soft or paradoxically split S2, presence of S4, murmurs (particularly aortic stenosis), carotid sinus massage, injuries, decreased level of consciousness, any focal neurological signs

OVERALL—history is most useful for diagnosis especially from reliable witness, revealing causes in ~45% of cases. Despite different investigations, cause of syncope remains undiagnosed in 50%. Mostly benign (e.g. vasovagal), but 1-year mortality up to 30% in high-risk patients. Highest diagnostic yield from postural BP measurement. Lowest diagnostic yields from head CT, carotid ultrasound, EEG, and cardiac enzymes

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, Cr, CK, troponin

- **IMAGING**—CXR, echocardiogram, carotid dopplers, CT head

- **OTHERS**—ECG, 24 h Holter

SPECIAL

- **EEG**—if suspect seizures

- **STRESS TEST**

- **TILT TABLE TEST**—to confirm vasovagal syncope

MANAGEMENT

ACUTE—ABC, O₂, IV

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

REFLEX SYNCOPE—consists of situational syncope, vasovagal syncope, and carotid sinus syndrome

NEUROCARDIOGENIC (VASOVAGAL) SYNCOPE

- **PATHOPHYSIOLOGY**—prolonged standing, vigorous exercise, emotional distress, severe pain → excessive peripheral venous pooling → decreased venous return → compensation with cardiac hypercontractile state → activation of mechanoreceptors (and this is seen by brain as hypertension-like) causing paradoxical reflex bradycardia and drop in peripheral vascular resistance → decreased output to brain → syncope
- **CLINICAL FEATURES**—pre-syncope symptoms may include weakness, light-headedness, diaphoresis, visual blurring, headache, nausea, and feeling warm or cold. Syncope lasts about 30 s to 5 min. Recovery is rapid with minimal postictal state
- **DIAGNOSIS**—tilt-table test (spc 90%), implantable loop recorders
- **TREATMENTS**—lie down if pre-syncope, adequate fluids and salt intake, SSRI (*paroxetine* 20 mg PO daily), vasoconstrictor (*midodrine* 2.5–10 mg PO TID), permanent cardiac pacing if recurrent

NEJM 2005;352:10

SITUATIONAL SYNCOPE—similar to vasovagal syncope in pathophysiology, but due to mechanoreceptors in esophagus, lungs, bladder, and rectum triggered by coughing, swallowing, urination, and defecation, respectively

NEUROGENIC ORTHOSTATIC HYPOTENSION

- **PATHOPHYSIOLOGY**—standing leads to pooling of blood (500–1000 mL) in legs → decreased venous return to right atrium → decreased cardiac output. Normally, this triggers the autonomic response via baroreceptors in carotid

SPECIFIC ENTITIES (CONT'D)

sinus and aortic arch, resulting in increased peripheral vascular resistance and cardiac output. In orthostatic hypotension, this response is dampened or lost with autonomic failure, leading to hypoperfusion of various organs → light-headedness, dizziness, syncope, weakness, fatigue, angina, orthostatic dyspnea. Typically happens in older individuals and exacerbated by prolonged standing, strenuous exercises, high temperature, and meals

- **CAUSES**—physical deconditioning, medications (alpha-blockers, antihypertensives, diuretics), Parkinson disease, Lewy body dementia, multi-system atrophy, pure autonomic failure
- **CLINICAL FEATURES**—pre-syncope symptoms may include weakness, light-headedness, diaphoresis, visual blurring, headache, nausea and feeling warm or cold. Syncope lasts about 30 s to 5 min. Recovery is rapid with minimal postictal state
- **DIAGNOSIS**—SBP drop of ≥ 20 mmHg or DBP drop of ≥ 10 mmHg during first 3 min of standing, or a head-up tilt on tilt table. Autonomic failure may be assessed by heart rate variability testing
- **TREATMENTS**—gradual staged movements with postural changes, exercises, increase salt/fluid intake, elastic stockings, and minimize antihypertensive medication use. Medications include *fludrocortisone* 0.05–0.1 mg PO daily, *midodrine*, *pseudoephedrine*, *ephedrine*, and potentially *pyridostigmine*

Freeman NEJM 2008;358(6)

Related Topics

Arrhythmia (p. 48)
Dizziness (p. 341)
Falls (p. 425)
Stroke (p. 321)
Valvular Heart Disease (p. 58)

Cardiac Examination**PULSE**

PULSUS TARDUS ET PARVUS (low carotid upstroke and amplitude)—aortic stenosis

BRISK PULSE (rapid carotid upstroke)—hypertrophic cardiomyopathy

BOUNDING PULSE (rapid carotid upstroke and descent)—↑ left ventricular volume (aortic regurgitation, mitral regurgitation, VSD, PDA, severe bradycardia), ↓ peripheral resistance (fever, anemia, thyrotoxicosis, rigid arteries, pregnancy)

PULSE (CONT'D)

PULSUS BISFERIENS (double-peaked)—combination aortic stenosis and regurgitation

REGULARLY IRREGULAR PULSE—sinus arrhythmia, pulsus bigeminus (PVC, PAC)

IRREGULARLY IRREGULAR PULSE—atrial fibrillation, premature atrial or ventricular contractions

BLOOD PRESSURE

CORRECT CUFF SIZE—width of bladder $\geq 40\%$ of arm circumference and length of bladder $\geq 80\%$ of arm circumference

AUSCULTATORY GAP—defined as the gap between the first Korotkoff sound (which may disappear briefly) and its reappearance. Missing the higher reading can lead to an underestimation of systolic blood pressure. Thus, the systolic blood pressure should always be palpated first before auscultation

WIDE PULSE PRESSURE—isolated systolic hypertension, aortic regurgitation, hyperdynamic states (sympathetic hyperactivity, fever/sepsis, anemia, thyrotoxicosis, large AV fistula, PDA, beriberi, pregnancy)

PSEUDOHYPERTENSION—false elevation of systolic blood pressure secondary to rigid arteries. The Osler maneuver may be useful for determining the presence of pseudohypertension

PULSUS ALTERNANS (alternating fluctuation in pulse pressure)—initially hear only the more prominent beats. As cuff pressure decreases, start to hear the less intense beats (1:1 ratio). This may be detected in severe LV dysfunction and aortic stenosis

PULSUS PARADOXUS—inspiratory drop in systolic blood pressure >10 mmHg. Causes include asthma, COPD, **tamponade**, restrictive cardiomyopathy, constrictive pericarditis, hypovolemic shock, and rarely pulmonary embolism, SVC obstruction, and morbid obesity

JUGULAR VENOUS PRESSURE

A WAVE—atrial contraction

- **PROMINENT A WAVE**—tricuspid stenosis, pulmonary stenosis, pulmonary hypertension, hypertrophic cardiomyopathy, and Ebstein anomaly
- **CANNON A WAVE**—AV dissociation (complete heart block, ventricular tachycardia) (right atrium contracts against closed tricuspid valve)
- **DECREASED A WAVE**—dilated right atrium
- **ABSENT A WAVE**—atrial fibrillation

X DESCENT—atrial relaxation. S1 starts

- **DECREASED X DESCENT**—atrial fibrillation
- **X DESCENT DEEPER THAN Y DESCENT**—tamponade
- **C WAVE**—bulging of tricuspid valve into right atrium during ventricular isometric contraction
- **X' DESCENT**—descent of the base of the heart during systole

V WAVE—atrial filling. S2 just before peak of v

- **DOMINANT V WAVE**—tricuspid regurgitation (cv wave), right heart failure, atrial septal defect

JUGULAR VENOUS PRESSURE (CONT'D)

Y DESCENT—opening of tricuspid valve/atrial emptying

- **RAPID STEEP Y DESCENT**—constrictive pericarditis (square root sign), severe right heart failure
- **DECREASED Y DESCENT**—tricuspid stenosis
- **BLUNTED/ABSENT Y DESCENT**—tamponade

ABDOMINOJUGULAR REFLUX (AJR)—blood pressure cuff pumped $6 \times$, then pressed against abdomen at 20–35 mmHg for 15–30 s. Positive AJR occurs when abdominal compression causes a sustained increase in JVP >4 cm [>1.6 in.] and predicts elevated left atrial pressure (≥ 15 mmHg, LR+ 8.0, LR– 0.3)

KUSSMAUL SIGN—paradoxical increase in JVP during inspiration. Causes include right ventricular failure, restrictive cardiomyopathy, constrictive pericarditis, SVC obstruction, and pulmonary embolism

PRECORDIAL EXAMINATION

INSPECTION—apex, right ventricular heave

PALPATION—apex, heaves, thrills, palpable heart sounds

- **DISPLACED APICAL BEAT** (lateral to mid-clavicular line)—left ventricular dilatation, LR+ 8.0
- **ENLARGED APICAL BEAT** (≥ 2.5 cm)—left ventricular dilatation, LR+ 4.7
- **SUSTAINED APICAL BEAT** (outward impulse extends to, or past, S2)—left ventricular pressure overload (aortic stenosis), volume overload (aortic regurgitation, VSD), severe cardiomyopathy, or ventricular aneurysm
- **RETRACTING APICAL BEAT** (retraction during systole; inward motion begins at S1, outward impulse after S2)—constrictive pericarditis (up to 90%), tricuspid regurgitation
- **SUSTAINED LEFT PARASTERNAL MOVEMENT** (“lift/heave”)—tricuspid regurgitation, mitral regurgitation
- **PALPABLE P2**—pulmonary hypertension in mitral stenosis, LR+ 3.6

HEART SOUNDS

TECHNIQUE—S1, S2, and physiological splitting of S2 are best heard over the base. Identification of S3 and S4 requires conscious effort listening for low pitched sounds over the apex (using the bell)

DISTINGUISHING S1 FROM S2—time with carotid pulse, diastole longer than systole, S2 louder than S1 at the base, S1 is low pitched and longer while S2 is high pitched and shorter, S2 often split

HEART SOUNDS (CONT'D)**INTENSITY OF S1 AND S2**

- **LOUD P2 >A2 AT PULMONIC AREA**—increased pulmonary pressure (left ventricular failure, mitral stenosis, pulmonary hypertension), increased pulmonary flow (atrial septal defect)
- **LOUD S2 AT AORTIC AREA**—hypertension, hyperdynamic states (fever, hyperthyroidism, anemia)
- **SOFT S2 OVER AORTIC AREA**—severe aortic stenosis
- **LOUD S1 AT MITRAL AREA**—mitral stenosis
- **SOFT S1**—mitral regurgitation, left bundle branch block, short PR interval

HEART SOUNDS (CONT'D)**SPLITTING OF S2**

- **FIXED SPLITTING** (splitting same degree during both inspiration and expiration)—atrial septal defect, right ventricular failure
- **WIDE SPLITTING** (splitting greater during inspiration than expiration)—right bundle branch block, pulmonary stenosis, pulmonary hypertension
- **PARADOXICAL (REVERSED) SPLITTING** (splitting only during expiration)—left bundle branch block, severe aortic stenosis, RV pacing

NORMAL AND EXTRA HEART SOUNDS

Sound	Heard	Pitch	Others
S1	LUSB	High	
Early systolic click	RUSB	High	Aortic stenosis
Mid-systolic click	Apex	High	MVP, louder standing
S2	LUSB	High	Splitting
Opening snap (early diastolic)	Apex	High	Mitral stenosis
S3 (early diastolic)	Apex	Low	Heart failure
S4 (late diastolic)	Apex	Low	HTN, aortic stenosis

Note: high pitch sounds are best heard with the diaphragm, while low pitch sounds are best heard with the bell

HEART SOUNDS (CONT'D)**DISTINGUISHING FEATURES BETWEEN P2 AND OPENING SNAP**

1. P2 is best heard at LUSB while opening snap is best heard at the apex
2. P2 separates from A2 on inspiration, while opening snap tends to move closer to S2 on inspiration

DISTINGUISHING FEATURES BETWEEN S4 AND S1

1. S4 is usually best heard at apex with the bell while S1 is best heard at base
2. S4 is usually more widely separated from S1 than splitting of S1
3. S4 is loudest at the start of expiration, softest at mid-inspiration
4. S4 may be accentuated by lying down, exercise, or forced inspiration with closed glottis
5. S4 has a lower pitch than S1

DISTINGUISHING FEATURES BETWEEN S3 AND OPENING SNAP

1. S3 has a lower pitch than opening snap
2. S3 occurs later than opening snap

HEART SOUNDS (CONT'D)**DISTINGUISHING FEATURES BETWEEN S3 AND S4**

1. S3 has a lower pitch than S4
2. S3 is closer to S2 while S4 is closer to S1
3. Left ventricular S3 is louder at the apex while right ventricular S3 or S4 is usually best heard at left sternal border or at the base

MURMURS**TIMING**

- **MID-SYSTOLIC**—aortic stenosis, aortic sclerosis, pulmonary stenosis, hypertrophic obstructive cardiomyopathy, atrial septal defect, flow murmurs (fever, pregnancy, hyperthyroidism, anemia, aortic regurgitation due to high flow)
- **PANSYSTOLIC**—mitral regurgitation, tricuspid regurgitation, ventricular septal defect, aorto-pulmonary shunts

MURMURS (CONT'D)

- **LATE SYSTOLIC**—mitral valve prolapse, papillary muscle dysfunction
- **EARLY DIASTOLIC**—aortic regurgitation, pulmonary regurgitation
- **MID-DIASTOLIC**—mitral stenosis, tricuspid stenosis, atrial myxoma, Austin Flint murmur of aortic regurgitation, Carey Coombs murmur during acute phase of rheumatic fever
- **PRE-SYSTOLIC**—mitral stenosis, tricuspid stenosis, atrial myxoma
- **CONTINUOUS MURMURS**—patent ductus arteriosus, arteriovenous fistula, aortopulmonary connection, venous hum, mammary souffle

INTENSITY—grade I (barely audible), grade II (faint but can be heard immediately), grade III (easily heard), grade IV (loud **and** associated with palpable thrill), grade V (very loud, can be heard with the stethoscope half off chest), grade VI (very loud, can be heard with stethoscope off chest wall)

QUALITY—depends on the pitch, may be musical, harsh, blowing, rumbling, scratchy, grunting, or squeaky

CONFIGURATION—crescendo, decrescendo, crescendo–decrescendo, plateau, holosystolic

LOCATION—aortic valve (RUSB), pulmonary valve (LUSB), tricuspid valve (LLSB), mitral valve (apex)

RADIATION—aortic valve (carotids), pulmonary valve (left shoulder), tricuspid valve (xyphoid, right of sternum), mitral valve (axilla)

MANEUVERS

- **RESPIRATION**—**right-sided** murmurs typically increase with inspiration (except pulmonic click) or sustained abdominal pressure (↑ venous return), while **left-sided** murmurs are generally louder during expiration

MURMURS (CONT'D)

- **VALSALVA MANEUVER** (↓ venous return and ↑ systemic arterial resistance)—most murmurs decrease in length and intensity during the Valsalva maneuver. Two exceptions are the systolic murmur of **hypertrophic cardiomyopathy**, which usually becomes much louder, and the systolic murmur of **mitral valve prolapse**, which becomes longer and often louder (click moves closer to S1)
- **POSITIONAL CHANGES**—most murmurs diminish with standing due to reduced preload. However, the murmur of **hypertrophic cardiomyopathy** becomes louder and the murmur of **mitral valve prolapse** lengthens and often is intensified. Squatting (or usually passive leg raising, both ↑ venous return and ↑ systemic arterial resistance) produces opposite effect
- **ISOMETRIC EXERCISE** (↑ systemic arterial resistance)—murmurs caused by blood flow across normal or obstructed valves (e.g. **mitral or pulmonic stenosis**) become louder. Murmurs of **mitral and aortic regurgitation** and **ventricular septal defect** also increase with handgrip exercise
- **TRANSIENT ARTERIAL OCCLUSION** (↑ systemic arterial resistance)—transient external compression of both arms by bilateral cuff inflation to 20 mmHg greater than peak systolic pressure augments the murmurs of **mitral regurgitation, aortic regurgitation, and ventricular septal defect**, but not murmurs due to other causes

DISTINGUISHING FEATURES AMONG COMMON SYSTOLIC AND DIASTOLIC MURMURS

	Systolic murmurs					Diastolic murmurs				
Findings*	Tricuspid Regurgitation	Mitral valve Prolapse	Mitral Regurgitation	Aortic Sclerosis	Aortic Stenosis	Hypertrophic Cardiomyopathy	Tricuspid Stenosis	Pulmonary Regurgitation	Mitral Stenosis	Aortic Regurgitation
Inspection	Dyspnea Cyanosis Cachexia Jaundice	Pectus excavatum Marfan scoliosis	Dyspnea	Normal	Dyspnea Sustained apex	Dyspnea Double apex	Normal	Dyspnea	Mitral facies Cyanosis Dyspnea	Argyll Robertson Marfan Ank. spond
Radial pulse	Irregular (AF)	Normal	Irregular (AF)	Normal	Brachio-radial delay	Brisk	Irregular (AF)	Normal	Irregular (AF)	Water-hammer

MURMURS (CONT'D)

Systolic murmurs						Diastolic murmurs					
BP	Normal	Normal	Normal	Normal	Narrow PP	Normal	Normal	Normal	Narrow PP	Wide PP	
Carotid	Normal	Normal	Bounding Irregular (AF)	Normal	Pulsus parvus et tardus	Brisk bifid	Irregular (AF)	Normal	Irregular (AF)	Bounding/collapsing pulse	
JVP	Increased V wave Prominent a wave PAH, no a wave (AF)	Normal	Absent a wave (AF)	Normal	Normal	Prominent a wave	Prominent a wave, slow y descent, absent a wave (AF)	Prominent a wave PAH	Absent a wave (AF) Prominent a wave PAH, cv wave (TR)	Normal	
Palpation	Palpable P2 PAH, thrill RV heave	Normal	Enlarged, displaced apex, thrill RV heave	Normal	Sustained apex, thrill LV heave	Double apical impulse Thrill LV heave	Normal	Palpable P2 PAH, thrill RV heave	RV heave Palpable P2 PAH	Sustained, displaced apex, thrill LV heave	
S1 ^a	Soft	Normal	Soft	Normal	Normal	Normal	Wide splitting S1	Normal	Loud S1	Split (chronic) Absent (acute)	
S2 ^b	Loud PAH	Normal	Normal	Normal	Paradoxical split, soft	Paradoxical split	Normal	Loud PAH	Palpable P2 PAH	Soft	
S3	R sided	Normal	L sided	Normal	Normal	L sided	Normal	R sided	Absent	L sided	
S4	None	Normal	Normal	Normal	L sided	L sided	Normal	R sided	Normal	L sided	
Clicks or snaps	None	Mid-systolic click	None	None	Early systolic click	None	Opening snap (LLSB)	None	Opening snap (apex)	None	
Murmur ^c	LLSB High pitch Holosystolic	Apex High pitch Late systolic	Apex High pitch Holo systolic	RUSB High pitch Mid-systolic	RUSB High pitch Mid-systolic	LLSB , apex High pitch Mid-systolic	LLSB Mid-diastolic	LUSB High pitch Early diastolic	Apex Low pitch Mid-diastolic ^e	RUSB High pitch Early diastolic	
Radiation	Xyphoid	None	Axilla	None	Clavicle Carotids	Base of heart	None	None	None	Apex Sternum	
Maneuvers	↑ inspiration, sustained abdominal pressure	↑ standing, Valsalva^d ↓ squatting	↑ isometric, transient art. occlusion	None	↑ squatting, leg raise ↓ standing, Valsalva, isometric	↑ standing, Valsalva ↓ squatting	↑ inspiration	↑ inspiration	↑ isometric ↓ standing, Valsalva	↑ isometric, transient art. occlusion Best heard sitting up in end expiration	
Other associated murmurs/clinical features	Graham Steell murmur PAH Ascites, pulsatile liver, edema	Mitral regurgitation (holosystolic at apex)	Pulmonary edema	None	Gallavardin phenomenon (mid-systolic murmur at apex)	Mitral regurgitation (mid-systolic at apex)	Mitral stenosis may also be present	PR murmur called Graham Steell m. if secondary to PAH	Pulmonary and tricuspid regurg. Murmurs PAH	Austin Flint Murmur (mid-diastolic over apex) Mid-systolic flow m Other signs ^f	

^aNot all findings listed for each condition may be present on examination
^bLoud heart sounds are usually due to mild-moderate stenotic lesions, while light heart sounds are usually due to regurgitant or severe stenotic lesions
^cRegurgitant murmurs usually start early, while stenotic murmurs tend to start mid-way
^dFor mitral valve prolapse, maneuvers that increase murmur intensity also move both the click and murmur closer to S1
^eFor mitral stenosis, the murmur is classically described as mid-diastolic with presystolic accentuation
^fAll the following special signs for aortic regurgitation are related to increased pulse pressure. These include Quincke sign (pulsatile refill in capillary bed of finger nails), Becker sign (pulsatile retinal artery), deMusset sign (head bob), Mueller sign (pulsatile uvula), Mayne sign (DBP ↓ 15 mmHg with arm raised), Gerhardt sign (pulsatile spleen), Rosenbach sign (pulsatile liver), Traube sign (pistol shot sound over femoral arteries), Duroziez sign (femoral artery bruit with compression), Hill sign (popliteal SBP > brachial SBP by 60 mmHg)

MURMURS (CONT'D)**RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN ABNORMAL SYSTOLIC MURMUR?**

AORTIC STENOSIS—presence of any of following significantly increases the likelihood of aortic stenosis: effort syncope, slow carotid upstroke, late or mid peaking systolic murmur, decreased or absent S2, apical-carotid delay, brachioradial delay. “The presence of AS requires detection of a systolic murmur, generally radiating to the right clavicle.”

Update for Clinical Signs for Detecting Aortic Stenosis

	LR+	LR-
Slow carotid upstroke	9.2	0.56
Murmur radiating to right carotid	8.1	0.29
Reduced or absent S2	7.5	0.50
Murmur over the right clavicle	3.0	0.10
Reduced carotid volume	2.0	0.64

Simel et al. *The Rational Clinical Examination*. McGraw-Hill; 2009

MITRAL REGURGITATION—“For cardiologists, absence of a mitral area murmur or a late systolic/holosystolic murmur significantly reduces the likelihood of mitral regurgitation, except in the setting of acute MI. Cardiologists can accurately distinguish left-sided regurgitant murmurs, such as mitral regurgitation and ventricular septal defect, using transient arterial occlusion.”

TRICUSPID REGURGITATION—“Cardiologists can accurately detect the murmur of tricuspid regurgitation. Cardiologists can accurately rule in and rule out tricuspid regurgitation using the quiet inspiration and sustained abdominal pressure maneuvers.”

MURMURS (CONT'D)

HYPERTROPHIC CARDIOMYOPATHY—“Cardiologists can rule in or rule out hypertrophic cardiomyopathy by evaluating for decreased murmur intensity with passive leg elevation or increased murmur intensity when the patient goes from a **squatting to standing position**.”

MITRAL VALVE PROLAPSE—“A **systolic click, with or without systolic murmur**, is sufficient for the diagnosis of mitral valve prolapse. . . . The absence of both a systolic click and murmur significantly reduces the likelihood of echocardiographic mitral valve prolapse. In patients with echocardiographic mitral valve prolapse, a holosystolic murmur without a systolic click significantly increases the likelihood of long term complications, whereas absence of both a systolic click and murmur significantly reduces the likelihood of long term complications”

Etchells et al. *JAMA* 1997;277(7)

INNOCENT MURMURS—in otherwise healthy younger patients. Systolic murmurs tend to be mid-systolic, grade 1 or 2 (possibly 3), loudest over LUSB, and do not radiate. Murmurs that are associated with systolic thrill (LR+ 12), holosystolic (LR+ 8.7), loud (LR+ 6.5), or plateau-shaped (LR+ 4.1) are more likely to be significant. Diastolic murmurs are always abnormal

INVESTIGATIONS

ECHOCARDIOGRAM—if cardiac symptoms, murmur grade ≥ 3 , diastolic murmur, or when other cardiac findings are present

Aortic Stenosis

2014 AHA/ACC Valvular Heart Disease Guideline
2017 AHA/ACC Focused Update Valvular Heart Disease

Carabello et al. *Lancet* 2009;373(9667)

Carabello *NEJM* 2002;346(9)

DIFFERENTIAL DIAGNOSIS**VALVULAR**

- **CONGENITAL MALFORMATIONS**—unicuspid, bicuspid
- **CALCIFICATION**—degenerative or senile, atherosclerosis, Paget disease, chronic renal failure

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **INFECTIONS**—rheumatic fever, *Chlamydia pneumoniae*
- **RHEUMATOID ARTHRITIS**

DIFFERENTIAL DIAGNOSIS (CONT'D)

SUBVALVULAR

- **DISCRETE LESIONS**—membranous diaphragm, fibromuscular ring
- **OBSTRUCTIVE**—hypertrophic cardiomyopathy

SUPRAVALVULAR—localized or discrete narrowing of the ascending aorta (Williams syndrome)

LOW GRADIENT AORTIC STENOSIS—resulting from low cardiac output

PATHOPHYSIOLOGY

COMPLICATIONS ★BEE★

- **BLEEDING** (angiodyplasia + aortic stenosis + acquired vWD type IIa = Heyde syndrome)
- **ENDOCARDITIS**
- **EMBOLIC EVENTS** (cerebral, systemic)

CLINICAL FEATURES

PHYSICAL—tachypnea, decreased pulse pressure, brachioradial delay, pulsus parvus et tardus (slow rise and low amplitude), apical-carotid delay, hyperdynamic apical beat, systolic thrill at the base of heart, narrowly split or paradoxical splitting of S2 or absent S2, harsh mid-systolic ejection murmur (radiation to carotids), Gallavardin phenomenon

GALLAVARDIN PHENOMENON—aortic stenosis murmur is usually harsh and loudest over the right upper sternal border, whereas a Gallavardin murmur is musical and may be heard over apex. It is due to radiation of the high-frequency components of the aortic stenosis murmur to the apex

DISTINGUISHING FEATURES BETWEEN AORTIC SCLEROSIS AND AORTIC STENOSIS MURMUR

	Aortic sclerosis	Aortic stenosis
Pathophysiology	Abnormally thickened valve leaflets but minimal outflow obstruction	Decreased functional area of valve to cause decreased outflow
Carotid pulse	Normal	Pulsus parvus et tardus
S2	Normal	Soft single S2 (P2)
Murmur	Mid-systolic murmur	Late peaking of systolic murmur

DISTINGUISHING FEATURES BETWEEN AORTIC STENOSIS, MITRAL REGURGITATION, AND HYPERTROPHIC CARDIOMYOPATHY

	Aortic stenosis	Mitral regurgitation	HOCM
Carotid upstroke	Slow, low amplitude	Normal or low amplitude	Brisk
S1	Normal	Soft	Normal
S2	Single if severe	Normal	Often reversed
S3	No	Loud	No
S4	If severe	No	Yes
Loudest murmur	RUSB	Apex	LLSB and apex
Maneuvers			
Standing	↓	↓	↑
Squatting	↑	↑	↓
Valsalva	↓	↓	↑

INVESTIGATIONS**BASIC**

- **CXR**
- **ECHOCARDIOGRAM**—TTE to evaluate etiology and assess severity
- **ECG**—left ventricular hypertrophy
- **EXERCISE TESTING**—may help quantify symptoms but contraindicated in severe AS

SPECIAL

- **CARDIAC CATHETERIZATION**—to assess valve area and hemodynamics

DIAGNOSTIC AND PROGNOSTIC ISSUES**AORTIC VALVE AREA AND SEVERITY**

- **NORMAL**= peak velocity <2 m/s, area = 3–4 cm²
- **MILD**= peak velocity 2.0–2.9 m/s, mean gradient <20 mmHg, area = 1.5–2 cm²
- **MODERATE**= peak velocity 3.0–3.9 m/s, mean gradient 20–39 mmHg, area = 1–1.5 cm²
- **SEVERE**= peak velocity ≥4 m/s, mean gradient >40 mmHg, area = ≤1 cm² (or indexed area ≤0.6 cm²/m²)
- **SYMPTOMS**—usually do not appear until valve ≤1 cm². The significance of valve area depends on patient size (larger patient = more severe for same valve area)
- **PROGRESSION**—valve area decreases by ~0.1 cm²/year and the mean gradient increases by 7 mmHg/year (particularly if cardiac risk factors)

PROGNOSIS OF AORTIC STENOSIS ★ASH★

(Angina, Syncope, Heart failure)

- **SEVERE AORTIC STENOSIS WITH NO SYMPTOMS**—1–2% die in short period
- **SEVERE AORTIC STENOSIS WITH ANGINA PRESENTATION**—50% die in 5 years
- **SEVERE AORTIC STENOSIS WITH SYNCOPE PRESENTATION**—50% die in 3 years
- **SEVERE AORTIC STENOSIS WITH HEART FAILURE PRESENTATION**—50% die in 2 years
- **SEVERE AORTIC STENOSIS AFTER VALVE REPLACEMENT**—survival similar to normal individuals

MANAGEMENT**MILD OR MODERATE AORTIC STENOSIS**

—follow clinically and with echocardiogram (every 3–5 years for mild, every 1–2 years for moderate, every year for severe)

SEVERE OR SYMPTOMATIC AORTIC STENOSIS

—**aortic valve replacement** (transcatheter or surgical, see criteria below), balloon valvuloplasty (offers no survival benefit and is only a temporizing measure until surgical or percutaneous aortic valve replacement can be performed)

MANAGEMENT (CONT'D)

VASODILATORS—use with caution in the setting of hypertension or HF. ACE inhibitors preferred over β-blockers because of risk of reduced inotropy; start low dose and titrate slowly; risk of hypotension and syncope

TREATMENT ISSUES**AORTIC VALVE REPLACEMENT (AVR)**

- **RECOMMENDED INDICATIONS (CLASS I)**—if severe AS with symptoms of HF, syncope, exertional dyspnea, angina, or presyncope (by history or on exercise testing); asymptomatic severe AS and LVEF <50%; or severe AS and undergoing cardiac surgery for other reasons
- **REASONABLE INDICATIONS (CLASS II a)**—if asymptomatic but very severe AS (i.e. peak velocity ≥5 m/s or mean gradient ≥60 mmHg); severe AS and exercise test with ↓ exercise tolerance or ↓ in SBP; symptomatic low-flow/low-gradient severe AS (i.e. valve area ≤1 cm²) with LVEF <50%, and severe/high gradients on dobutamine stress test; symptomatic low-flow/low-gradient severe AS (i.e. valve area ≤1 cm²) with normal LVEF ≥50% and valve obstruction as most likely cause of symptoms (based on clinical, hemodynamic, and anatomic data); or moderate AS and undergoing cardiac surgery for other reasons
- **POSSIBLE INDICATIONS (CLASS II b)**—if severe AS and rapid disease progression and low surgical risk
- **PREOPERATIVE CONSULT**—AVR should be done before elective non-cardiac surgeries in symptomatic patients
- **RISK OF AVR**—mortality 1–2%, morbidity 1%/year (venous thromboembolic disease, bleeding, deterioration of prosthetic valve, endocarditis)

SURGICAL VS. TRANSCATHETER VALVE

—transcatheter aortic valve replacement (TAVR) should be considered for patients with an indication for AVR who have intermediate-to-high or prohibitive risk for surgical AVR. A multidisciplinary heart valve team should collaborate in the decision making process

MECHANICAL VS. BIOPROSTHETIC VALVE

—compared to human tissue valves, mechanical valves have prolonged durability, but higher chance of thromboembolism and bleeding from chronic anticoagulation. Overall, long-term outcomes are better with a mechanical valve. Main indications for bioprosthetic valve include patients who cannot or will not tolerate warfarin or for whom compliance is uncertain, patients ≥65 years of age who do not have risk factors for thromboembolism, and women of childbearing age

Aortic Regurgitation

2014 AHA/ACC Valvular Heart Disease Guideline

DIFFERENTIAL DIAGNOSIS

VALVE ABNORMALITY—rheumatic heart disease, infective endocarditis, SLE, calcifications, congenital (bicuspid or unicuspid aortic valve), flail leaflet, osteogenesis imperfecta, drugs (fenfluramine)

AORTIC DILATION—aortic dissection, ankylosing spondylitis, syphilis, Marfan, Ehlers Danlos, hypertension, bicuspid aortic valve, cystic medial necrosis

PATHOPHYSIOLOGY

PATHOPHYSIOLOGY—leaky aortic valve → initial compensation with left ventricular dilatation and eccentric hypertrophy (palpitations, atypical chest pain), wide pulse pressure (due to increased stroke volume with elevation in SBP and regurgitation with rapid collapse of the arteries and a low diastolic blood pressure) → eventually decompensation leading to left ventricular dysfunction (heart failure)

CLINICAL FEATURES

PHYSICAL

- GENERAL APPEARANCE**—Marfan syndrome, ankylosing spondylitis, **Quincke sign** (pulsatile refill in capillary bed of finger nails), digital throb, **Becker sign** (visible pulsations of the retinal arteries and pupils), **deMusset sign** (head bob occurring with each heart beat), **Müller sign** (systolic pulsations of the uvula)
- VITALS**—wide pulse pressure, “**water hammer**” or Corrigan pulse (tapping impulse in forearm, especially when arm is raised vertically due to rapid rise and fall in pressure), **Mayne sign** (>15 mmHg decrease in diastolic

CLINICAL FEATURES (CONT'D)

blood pressure with arm elevation above the head)

- CARDIAC**—soft S1, left-sided S3 (heart failure), **diastolic murmur** (early diastolic or holodiastolic, blowing, over left upper sternal border), **Austin Flint murmur** (mid/late diastolic rumble, over apex) and **mid-systolic flow murmur**
- OTHERS**—**Gerhardt sign** (systolic pulsations of the spleen), **Rosenbach sign** (systolic pulsations of the liver), **Traube sign** (pistol shot pulse with systolic and diastolic sounds heard over the femoral arteries when compressed distally), **Duroziez sign** (systolic and diastolic bruit heard when the femoral artery is partially compressed), **Hill sign** (popliteal cuff systolic pressure exceeding brachial pressure by >60 mmHg). Note that all the special signs are due to increased pulse pressure

DISTINGUISHING FEATURES BETWEEN AORTIC REGURGITATION AND PULMONARY REGURGITATION MURMUR

- PULMONARY REGURGITATION MURMUR**—high pitch decrescendo diastolic murmur (Graham Steell murmur) loudest over **left upper sternal border**. **Increases with inspiration**. May be associated with signs of pulmonary hypertension
- AORTIC REGURGITATION MURMUR**—early diastolic decrescendo murmur loudest over **right and/or left upper sternal border**. No change or decreases with inspiration. May be associated with **Austin Flint murmur** and the other signs of aortic regurgitation

DISTINGUISHING FEATURES BETWEEN AUSTIN FLINT AND MITRAL STENOSIS MURMUR

	Austin Flint	Mitral stenosis
Sex	M > F	F > M
Hemoptysis	Almost never	Likely mitral stenosis
Rhythm	Sinus	Atrial fibrillation
M1	Usually faint	Usually loud
P2	Normal or ↑	Usually loud
Ventricular gallop/S3	Always present	Absent
Diastolic murmur	Usually early or mid-diastolic	Often presystolic accentuation (if in sinus rhythm)
Opening snap	Absent	Present
CXR	Boot shaped	LAE
ECG	Sinus, LVH, prolonged PR	Atrial fibrillation, P mitrale

INVESTIGATIONS**BASIC**

- **CXR**—cardiomegaly ± aortic root dilatation
- **ECHOCARDIOGRAM**—TTE to evaluate etiology and assess severity
- **ECG**—LVH
- **EXERCISE TESTING**—may help quantify symptoms

SPECIAL

- **CARDIAC CATHETERIZATION**—to assess valve area and hemodynamics

PROGNOSTIC ISSUES**ASYMPTOMATIC WITH NORMAL LV SYSTOLIC FUNCTION**

- **PROGNOSIS**—development of symptoms and/or LV dysfunction <6%/year; asymptomatic LV dysfunction <3.5%/year; sudden death <0.2%/year

ASYMPTOMATIC WITH LV DYSFUNCTION

- **PROGNOSIS**—progression to cardiac symptoms >25%/year

SYMPTOMATIC

- **PROGNOSIS**—mortality >10%/year

MANAGEMENT

ACUTE CONSIDERATIONS—with acute AR, immediate priority is to rule out life-threatening etiologies (e.g. aortic dissection, myocardial infarction, and severe valvular endocarditis)

LIFESTYLE CHANGES—salt restriction/diuretics

MANAGEMENT (CONT'D)

MEDICATIONS—afterload reduction with vasodilators (nifedipine, ACE inhibitors, ARBs) indicated for severe AR with symptoms, LV dysfunction, or LV dilatation, but not for long-term management of asymptomatic mild to moderate AR and normal LV function. Vasoconstricting agents should be avoided as they can worsen the degree of AR

FOLLOW-UP—asymptomatic mild AR with normal LV function and little/no LV dilatation can be followed annually with clinical exam and echocardiogram every 2–3 years (sooner if symptoms emerge). Asymptomatic severe AR with normal LV function and LV dilatation (>60 mm) should be seen every 6 months with echocardiogram every 6–12 months

PROCEDURES—intraaortic balloon pumps should be avoided

AORTIC VALVE REPLACEMENT (AVR)

- **RECOMMENDED INDICATIONS (CLASS I)**—if symptomatic severe AR; asymptomatic chronic severe AR (regurgitant fraction ≥50%, regurgitant volume ≥60 mL/beat, Doppler jet width ≥65% of LVOT) and LVEF <50%; or severe AR and undergoing cardiac surgery for other reasons
- **REASONABLE INDICATIONS (CLASS IIa)**—if asymptomatic severe AR with normal LVEF ≥50% but severe LV dilatation (LVESD >50 mm); or moderate AR and undergoing other cardiac surgery
- **POSSIBLE INDICATIONS (CLASS IIb)**—if asymptomatic severe AR and normal LVEF ≥50% but with progressive severe LV dilatation (LVEDD >65 mm) and low surgical risk

Mitral Stenosis

Gerber et al. *Circulation* 2009;119(11)
2014 AHA/ACC Valvular Heart Disease Guideline

DIFFERENTIAL DIAGNOSIS

RHEUMATIC HEART DISEASE
MITRAL ANNULAR CALCIFICATION
CONGENITAL
ENDOCARDITIS
ATRIAL MYXOMA
PROSTHETIC VALVE DYSFUNCTION
COR TRIANGULUM

PATHOPHYSIOLOGY

STENOTIC MITRAL VALVE—left ventricular inlet obstruction → left atrial overload and left ventricle output failure → atrial fibrillation, pulmonary hypertension and eventually right heart failure

CLINICAL FEATURES

HISTORY—symptoms related to pulmonary hypertension (dyspnea, hemoptysis, chest pain), symptoms related to right heart failure (hepatomegaly,

CLINICAL FEATURES (CONT'D)

ascites, edema), hoarseness (Ortner syndrome, due to enlarged left atrium compressing on recurrent laryngeal nerve), complications (endocarditis, thromboembolism), past medical history (congenital valvular heart disease, rheumatic fever, connective tissue diseases [e.g. lupus]), medications

PHYSICAL

- **GENERAL APPEARANCE**—tachypnea, peripheral cyanosis, mitral facies (purple patches on cheeks secondary to vasoconstriction)
- **VITALS**—decreased pulse volume
- **JVP**—prominent a wave (pulmonary hypertension), absent a wave (atrial fibrillation), cv wave (tricuspid regurgitation)
- **CARDIAC**—right ventricular heave, palpable P2 (pulmonary hypertension), loud S1 (valve cusps widely apart at the onset of systole) in early disease, soft S1 in severe disease (valves

CLINICAL FEATURES (CONT'D)

rigid), loud S2, absent S3, opening snap (over apex and left lower sternal border; the earlier the opening snap, the more severe the stenosis), low pitch diastolic rumble (over apex, left decubitus position in expiration) \pm pre-systolic accentuation, tricuspid regurgitation

- **ABDOMINAL**—hepatomegaly, ascites, edema

INVESTIGATIONS**BASIC**

- **CXR**—signs of left atrial enlargement (splaying of carina, double density sign, prominent left atrial appendage, narrowing of the esophagus with barium swallow)
- **ECHOCARDIOGRAM**—TTE to evaluate etiology and assess severity. TEE to exclude left atrial thrombus before treatment
- **ECG**—left atrial enlargement, \pm RVH or atrial fibrillation

SPECIAL

- **CARDIAC CATHETERIZATION**—to assess valve area and hemodynamics

DIAGNOSTIC AND PROGNOSTIC ISSUES**MITRAL STENOSIS AND SEVERITY**

- **PROGRESSIVE**—evidence of mitral stenosis but not significant; mitral valve area (MVA) remains >1.5 cm², diastolic pressure half-time <150 ms
- **SEVERE**—MVA ≤ 1.5 cm² (MVA ≤ 1.0 cm² with very severe MS), diastolic pressure half-time ≥ 150 ms (diastolic pressure half-time ≥ 220 ms with very severe MS); associated with severe left atrial enlargement and pulmonary artery systolic pressure >30 mmHg. Note: transmitral mean gradient often >5 – 10 mmHg but mean pressure gradient varies greatly according to heart rate
- **SYMPTOMS**—often present when MVA ≤ 1.5 cm² (i.e. with severe MS). Onset of symptoms may be precipitated by exercise, emotional stress, infection, pregnancy, or rapid atrial fibrillation

PROGRESSION—approximately 0.1–0.3 cm²/year. Initially slow stable course (latent period) of 20–40 years between rheumatic fever and symptoms. From onset of symptoms (accelerated period), around 10 years until disability. Overall 10-year survival is 50–60% in untreated symptomatic MS, $>80\%$ in asymptomatic. Median survival <3 years with severe pulmonary hypertension

MANAGEMENT

LIFESTYLE CHANGES—salt restriction/diuretics
MEDICATIONS—**negative chronotropic agents** and HR control to prolong diastolic filling (β -blockers, non-dihydropyridine calcium channel blockers). **Anticoagulation** for patients with

MANAGEMENT (CONT'D)

moderate-severe MS and concomitant atrial fibrillation (irrespective of CHADS₂ score), left atrial thrombus, or prior embolic event (even if in sinus rhythm). **Prophylaxis for rheumatic fever** (secondary prevention)

FOLLOW-UP—any change in symptoms warrant reevaluation and echocardiogram. Otherwise, yearly evaluation in asymptomatic patients including CXR and ECG. Yearly echocardiogram for severe MS

PROCEDURES—indicated when symptomatic severe mitral stenosis. **Percutaneous balloon mitral valvuloplasty** (particularly for patients with non-calcified mitral valve, no left atrial thrombus, mild mitral regurgitation, and no other cardiac interventions) is equivalent to **surgical valvuloplasty** in terms of success; surgical repair or replacement favoured if percutaneous approach contraindicated. Average increase in valve area is 1.0 cm²

SPECIFIC ENTITIES**ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE**

- **PATHOPHYSIOLOGY**—group A *Streptococcus* infection \rightarrow non-suppurative inflammation with cardiac, joints, and CNS manifestations 2–4 weeks later. Post-*Streptococcus* glomerulonephritis and scarlet fever may also occur separately as complications of group A *Streptococcus* infection
- **JONES CRITERIA** for acute rheumatic fever
 - **MAJOR CRITERIA** ★♥NES★
 - **JOINT-MIGRATORY POLYARTHRITIS**
 - **♥CARDITIS** (pericarditis, myocarditis, valvulitis)
 - **NODULES** (subcutaneous)
 - **ERYTHEMA MARGINATUM**
 - **SYDENHAM CHOREA**
 - **MINOR CRITERIA**—clinical (fever, polyarthralgias), laboratory (\uparrow ESR, prolonged PR interval)
 - **DIAGNOSIS**—either two major criteria or one major criterion and two minor criteria, **plus** evidence of antecedent streptococcal infection (e.g. positive throat culture or rapid antigen detection test or elevated streptococcal antibody test)
- **INVESTIGATIONS**—anti-streptolysin O antibodies, anti-DNase B, antihyaluronidase, positive throat culture, echocardiogram
- **TREATMENTS**—patients with rheumatic disease are at high risk of recurrent rheumatic fever. Recurrent disease causes additional valve damage, and thus these patients should receive **secondary prophylaxis** for rheumatic fever (*benzathine penicillin G* 1.2 M U IM

SPECIFIC ENTITIES (CONT'D)

q4weeks, *penicillin V* 250 mg PO BID, or *azithromycin* 250 mg PO daily if allergic to penicillin). For patients with valvular involvement, therapy should continue for at least 10

SPECIFIC ENTITIES (CONT'D)

years, or until age 40 (whichever is longer). With a history of carditis in the absence of persistent valvular disease, treat for 10 years, or until age 21 (whichever is longer)

Mitral Regurgitation

2014 AHA/ACC Valvular Heart Disease Guideline
2017 AHA/ACC Focused Update Valvular Heart Disease

DIFFERENTIAL DIAGNOSIS

PRIMARY MR (VALVE ABNORMALITY)—rheumatic heart disease, infective endocarditis, mitral valve prolapse, myxomatous degeneration (Barlow valve), fibroelastic deficiency disease, mitral annular calcification, ruptured chordae tendineae, drugs (fenfluramine), congenital, iatrogenic

SECONDARY MR (LEFT VENTRICULAR DILATATION)—myocardial infarction, dilated cardiomyopathy

PATHOPHYSIOLOGY

LEAKY MITRAL VALVE—left atrial and ventricle volume overload → atrial fibrillation and left heart failure

CLINICAL FEATURES

CLINICAL FEATURES—exertional dyspnea, fatigue, decreased S1, widely split S2, S3, holosystolic murmur (over apex), displaced and enlarged apex

INVESTIGATIONS**BASIC**

- **CXR**—cardiomegaly, LAE
- **ECHOCARDIOGRAM**—TTE to evaluate etiology and assess severity
- **ECG**—LAE, LVH ± atrial fibrillation

SPECIAL

- **CARDIAC CATHETERIZATION**—to assess valve area and hemodynamics

MANAGEMENT

MEDICATIONS—in acute decompensated MR, priority is to identify and treat the underlying etiology (e.g. acute myocardial infarction, infectious endocarditis), reducing afterload (e.g. nitroprusside), and avoiding vasoconstrictive agents. Treat concomitant atrial fibrillation if present

FOLLOW-UP—asymptomatic mild MR with normal LV function and no LV dilatation can be followed annually. Asymptomatic severe MR should be seen every 6–12 months with echocardiogram at the time of assessment

MANAGEMENT (CONT'D)

PROCEDURES—**mitral valve repair** (generally better outcome if technically possible) or **replacement** if symptomatic, atrial fibrillation, pulmonary hypertension, end-systolic dimension ≥40 mm, or LVEF 30–60%. Transcatheter mitral valve repair may be considered for severely symptomatic, severe primary MR with prohibitive surgical risk

SPECIFIC ENTITIES**TRICUSPID REGURGITATION**

- **PATHOPHYSIOLOGY**—leaky tricuspid valve → right atrium and ventricle volume overload → eventually decompensation leading to right heart failure (hepatosplenomegaly, ascites, peripheral edema)
- **CAUSES**—right ventricular dilatation (left heart failure, pulmonary hypertension, Eisenmenger syndrome, pulmonic stenosis), valve abnormality (rheumatic heart disease, infective endocarditis, Ebstein anomaly, tumor). Rarely is it due to isolated tricuspid valve abnormality
- **CLINICAL FEATURES**—cachexia, jaundice (congestive hepatomegaly), JVP cv wave, RV heave, S3 (with dilated RV), S4 (with stiff RV), holosystolic murmur (over left lower sternal border), edema
- **INVESTIGATIONS**—ECG (right atrial enlargement, RVH ± atrial arrhythmias), CXR (cardiomegaly), echocardiogram (TTE to evaluate etiology and assess severity), cardiac catheterization (to assess valve hemodynamics and rule out intracardiac shunts)
- **TREATMENTS**—valve repair or replacement especially if severe and symptomatic

MITRAL VALVE PROLAPSE

- **PATHOPHYSIOLOGY**—prevalence 0.6–2.5% of population. May be sporadic or familial connective tissue disorder with morphologic abnormalities of the mitral valve (increased leaflet thickness and redundancy, chordal elongation, and sagging of the leaflets into the left atrium in systole)
- **TREATMENTS**—consider anticoagulation for AF based on stroke risk (see ATRIAL FIBRILLATION, p. 48)

SPECIFIC ENTITIES (CONT'D)**TWO SUBTYPES OF MITRAL VALVE PROLAPSE**

	Mild subtype	Severe subtype
Demographics	Mainly women (age 20–50)	Mainly men (age 40–70)
Pathology	Mild leaflet abnormalities Minimal MR	Myxomatous disease Considerable leaflet thickening and MR
Symptoms	Orthostatic hypotension Palpitations	Atrial fibrillation
Physical findings	Mid-systolic click with or without a late systolic murmur	MR murmur Chordal rupture may lead to sudden worsening of MR
Prognosis	Few patients have progressive MR	Progressive MR requiring surgery Increased risk of sudden death

Endocarditis

2015 AHA Scientific Statement Infective Endocarditis
 2017 AHA/ACC Focused Update Valvular Heart Disease
 Mylonakis et al. *NEJM* 2001;345(18)

DIFFERENTIAL DIAGNOSIS**INFECTIVE ENDOCARDITIS**

- **COMMON**—*Streptococcus viridans* (*S. sanguinis*, *S. mutans*, *S. mitis*), *S. pneumoniae*, *Streptococcus bovis*, *Enterococcus* (*E. faecalis*, *E. faecium*), *S. aureus*, Gram-negative bacilli
- **LONG INCUBATION TIME (7–21) days ★HACEK★**
 - *HAEMOPHILUS*
 - *ACTINOBACILLUS*
 - *CARDIOBACTERIUM*
 - *EIKENELLA*
 - *KINGELLA*
- **SPECIAL MEDIA**—*Mycoplasma*, *Chlamydia*, *Legionella*, *Brucella*, *Bartonella*, *Coxiella burnetii* (Q fever), *Histoplasma*, *Tropheryma whipplei*, fungi

MARANTIC ENDOCARDITIS—non-bacterial thrombotic endocarditis secondary to malignancy (usually adenocarcinoma) or SLE (Libman–Sacks endocarditis)

PATHOPHYSIOLOGY

SUBTYPES—classified as acute vs. subacute, native valve vs. prosthetic valve, and right sided vs. left sided

- **NATIVE HEART VALVE**—usually *S. viridans*, *S. bovis*, enterococci
- **PROSTHETIC HEART VALVE**—<2 months (usually coagulase negative staphylococci, may need to treat surgically), >1 year (usually *S. viridans*, *S. bovis*, enterococci)
- **INJECTION DRUG USE**—usually *S. aureus* and Gram-negative rods. Can also have fungal endocarditis

PATHOPHYSIOLOGY (CONT'D)

(especially if immunocompromised). Tricuspid valve most commonly affected

- **CANCER**—about 50% of patients with *S. bovis* endocarditis also have neoplasms of the GI tract

RISK FACTORS FOR ENDOCARDITIS

- **HIGH RISK**—complex cyanotic congenital heart disease (unrepaired or incompletely repaired cyanotic congenital heart disease, including palliative shunts and conduits; completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure; repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device), surgically constructed systemic pulmonary shunts, previous infective endocarditis, prosthetic heart valve, cardiac transplantation recipients who develop cardiac valvulopathy
- **MODERATE RISK**—most other congenital heart diseases, acquired valvular disease (rheumatic heart disease, mitral/aortic/pulmonary/tricuspid stenosis or regurgitation), mitral valve prolapse with valvular regurgitation or leaflet thickening, hypertrophic cardiomyopathy
- **LOW OR NO RISK**—secundum ASD or surgically repaired ASD, VSD, PDA, mitral valve prolapse with thin leaflets in the absence of regurgitation, ischemic heart disease, previous CABG
- **NON-CARDIAC**—IDU, poor dental hygiene, long-term hemodialysis, long-term indwelling catheter, procedures (GU, GI, surgical wound infection), diabetes, HIV, immunocompromise

CLINICAL FEATURES

HISTORY—fever, murmur, dyspnea, chest pain, anorexia, weight loss, malaise, night sweats, complications (painful nodules, rash, stroke, myocardial infarction, any infections), past medical history (structural heart disease, recent procedures [dental, GI, GU], IDU, SLE, malignancy, immunocompromised state), medications

PHYSICAL—fever, splinter hemorrhages, clubbing, Osler nodes (tender, subcutaneous nodules in pulp of digits or thenar eminence), Janeway lesions (nontender, erythematous, hemorrhagic pustular lesions on palms or soles), needle track marks, petechiae over conjunctivae and oral mucosa, Roth spots (pale areas surrounded by hemorrhage on fundoscopic examination), lymphadenopathy, respiratory examination (HF), murmur (regurgitant), splenomegaly, petechiae over legs

HIGH INDEX OF SUSPICION—always consider endocarditis in the differential when dealing with fever of unknown origin, persistent bacteremia, HF, MI, myocarditis, pericarditis, stroke, pneumonia, pulmonary embolism, splenic infarction, glomerulonephritis, septic arthritis, and osteomyelitis. All patients with *S. aureus* bacteremia should undergo echocardiography (25% have IE)

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, ESR, ANA, serology (HBV, HCV, HIV), urinalysis
- **MICROBIOLOGY**—blood C&S × 3 (endocarditis protocol and blood C&S × 2 daily until culture negative), sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, C. diff toxin A/B
- **IMAGING**—CXR, echocardiogram (TEE >TTE), CT chest/abd
- **ECG**—heart block

DIAGNOSTIC AND PROGNOSTIC ISSUES

MODIFIED DUKE'S CRITERIA

- **MAJOR**—positive blood culture × 2 (or, if *C. burnetii*, then positive blood culture × 1 or anti-phase I IgG antibody titer ≥ 1:800), echocardiographic evidence (oscillating intracardiac mass, abscess, new partial dehiscence of a prosthetic valve), new murmur
- **MINOR**—fever (>38 °C [100.4 °F]), **risk factor** (cardiac conditions, IDU), **vascular phenomena** (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions), **immunologic phenomena** (glo-

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

merulonephritis, Osler nodes, Roth spots, rheumatoid factor), **positive blood culture** not meeting major criteria

- **DIAGNOSIS**—likely endocarditis if 2 major, 1 major plus 3 minor, or 5 minor criteria

ECHOCARDIOGRAM—transesophageal echocardiogram (TEE sens 90–100%, spc 95–100%) preferred over transthoracic echocardiogram (TTE sens 50–80%, spc 90%) for detecting vegetations, perivalvular extension of infection and abscesses, diagnosing prosthetic valve endocarditis, and for differentiating between uncomplicated *S. aureus* bacteremia and endocarditis

PROGNOSIS—mortality of 25–50% for prosthetic valve endocarditis, 35% for staphylococcal endocarditis and 10% for streptococcal endocarditis

Related Topics

Aortic Regurgitation (p. 61)

Mitral Regurgitation (p. 64)

Tricuspid Regurgitation (p. 64)

MANAGEMENT

EMPIRIC ANTIBIOTIC THERAPY—**native valve and non-IDU** (*ampicillin* 2 g IV q4h or *cloxacillin* 2 g IV q4h plus *gentamicin* 1 mg/kg IV q8h, or *vancomycin* 1 g IV q12h plus *gentamicin* 1 mg/kg IV q8h), **native valve and IDU** (*cloxacillin* 2 g IV q4h plus *gentamicin* 1 mg/kg IV q8h or *vancomycin* 1 g IV q12h plus *gentamicin* 1 mg/kg IV q8h), **prosthetic valve** (*vancomycin* 1 g IV q12h plus *gentamicin* 1 mg/kg IV q8h plus *rifampin* 600 mg PO daily)

TARGETED ANTIBIOTIC THERAPY (please refer to the *Sanford Guide to Antimicrobial Therapy* for up-to-date recommendations)—**Streptococci** (*penicillin G* 2–3MU IV q4h or *ceftriaxone* 2 g IV/IM q24h × 4 weeks. *Gentamicin* 1 mg/kg IV q24h × 2 weeks may be added in certain circumstances to shorten the course by 2 weeks).

Penicillin-sensitive enterococci (*ampicillin* 2 g IV q4h or *vancomycin* 1 g IV q12h × 4–6 weeks, plus *gentamicin* 1 mg/kg IV q8h × 4–6 weeks for native valve). **Penicillin-resistant enterococci** (*vancomycin* 1 g IV q12h × 6 weeks, plus *gentamicin* 1 mg/kg IV q8h × 6 weeks for native valve); linezolid or daptomycin can be considered in the setting of vancomycin resistance. ***S. aureus*** (*cloxacillin* 2 g IV q4h, or *nafcillin* or *oxacillin* 2 g IV q6h, or *cefazolin* 2 g IV q8h × 2–6 weeks

MANAGEMENT (CONT'D)

[depending on right- or left-sided valve]). **MRSA** (*vancomycin* 1 g IV q12h × 6 weeks for native valve). **HACEK** (*ceftriaxone* 2 g IV/IM q24h or *ampicillin-sulbactam* 3 g IV q6h or *ciprofloxacin* 500 mg PO BID × 4 weeks). For prosthetic valve infection, therapy is usually longer (by 2–4 weeks) with gentamicin

SURGERY—valvular replacement (<10% reinfection rate. See indications below)

TREATMENT ISSUES

INDICATIONS FOR SURGERY—in the acute period, refractory congestive heart failure due to valve dysfunction secondary to endocarditis is the most important indication. Other indications include perivalvular extension of infection with abscess, fistula, or heart block; failure of antibiotic therapy with persistent bacteremia; infection with fungi or untreatable pathogens; Staphylococci on a prosthetic valve; or recurrent embolic events with persistent vegetation(s) despite appropriate antibiotic therapy. Consider early surgical consult for mobile vegetation(s) >10 mm with or without emboli

OVERALL RECOMMENDATIONS FOR ENDOCARDITIS PROPHYLAXIS—only given to patients with the highest risk of developing endocarditis, which include the following:

TREATMENT ISSUES (CONT'D)

- **HIGH-RISK CONDITIONS**—prosthetic valve, prosthetic material used for valve repair, unrepaired cyanotic congenital heart defect, repaired cyanotic congenital heart defect with residual defects at the site or adjacent to the site of the prosthetic device, completely repaired cyanotic congenital heart defect with prosthetic material or device during first 6 months after procedure, cardiac transplant recipients with valvulopathy, previous endocarditis
- **PROCEDURES**
 - **ORAL CAVITY**—dental procedures that involve manipulation of gingival or peripical region of teeth, perforation of oral mucosa
 - **RESPIRATORY TRACT**—tonsillectomy, adenoidectomy, bronchoscopy with a rigid bronchoscope, or flexible bronchoscopy if biopsied
 - **GI/GU TRACT**—prophylaxis generally not recommended unless have ongoing GI or GU infection at time of instrumentation
- **PROPHYLAXIS REGIMENS**—give one of the following 30–60 min prior to procedure: *amoxicillin* 2 g PO, *ampicillin* 2 g IM/IV, *cefazolin* 1 g IV/IM, *ceftriaxone* 1 g IV/IM, *cephalexin* 2 g PO, *clindamycin* 600 mg PO/IM/IV, *azithromycin* 500 mg PO, *clarithromycin* 500 mg PO

Peripheral Vascular DiseaseWhite *NEJM* 2007;356(12)

2016 AHA/ACC Guideline Peripheral Artery Disease (see also 2005, 2013)

DIFFERENTIAL DIAGNOSIS OF CLAUDICATION**ARTERIAL**

- **ATHEROSCLEROSIS**
- **INTRALUMINAL OCCLUSION**—embolism, thrombosis, dissection, adventitial cystic disease, arterial fibrodysplasia, arterial tumor, occluded limb aneurysm
- **VASCULITIS**—Takayasu arteritis, temporal arteritis, thromboangiitis obliterans
- **VASOSPASM**
- **DRUGS**—ergot
- **FIBROSIS**—iliac endofibrosis, radiation fibrosis, retroperitoneal fibrosis
- **TRAUMA**

VENOUS—DVT, thrombophlebitis, venous congestion

NEUROPATHIC—spinal stenosis, peripheral neuropathy

OTHERS—arthritis (hips, knees), compartment syndrome, symptomatic Baker cyst

CLINICAL FEATURES

HISTORY—pain, discomfort, or fatigue that occurs in leg muscle with exercise and improves with resting (ischemic intermittent claudication is **not** sensitive for peripheral vascular disease), age, maximum walking distance, non-healing wounds, trauma, DVT risk factors, past medical history (CAD, HF, AF, stroke, TIA, renal disease, hypertension, cholesterol), medications

PHYSICAL—comprehensive pulse examination of lower extremity

- **ANKLE BRACHIAL INDEX (ABI)**—abnormally high measurement >1.40 associated with non-compressible calcified vessel (and unreliable), 1.00–1.40 normal, 0.91–0.99 borderline, and ≤0.90 abnormal. If ≤0.90 significant narrowing of one or more blood vessels in the legs likely present, <0.8 intermittent claudication, <0.4 resting claudication, <0.25 critical limb ischemia. An ABI that ↓ by 20% following exercise

CLINICAL FEATURES (CONT'D)

is diagnostic of peripheral vascular disease, while a normal ABI following exercise eliminates the diagnosis

- **BUERGER TEST**—raise legs to 90° with patient in supine position. Check for return of rubor as the legs are lowered. Abnormal if angle of circulation <0° i.e. legs below table)
- **DE WEESE TEST**—disappearance of previously palpable distal pulses after walking or exercise

VENOUS INSUFFICIENCY EXAMINATION—hemosiderin deposit, pitting edema, dermatitis, cellulitis, ulcer (with prominent granulation tissue over medial malleolus), superficial venous

CLINICAL FEATURES (CONT'D)

collaterals (DVT), varicose vein (palpate for tenderness or hardness that may suggest thrombophlebitis), Trendelenburg test (helps to determine whether venous reflux is related to the superficial or deep venous system. Occlude a collapsed superficial vein just below the site of suspected reflux from deep to superficial system. With patient standing, observe refilling of vein. Rapid refilling despite occlusion suggests incompetence of valves in the deep venous system, while slow refilling with occlusion and rapid refilling after occlusion is removed suggests incompetence of valves in the superficial venous system)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THE CLINICAL EXAMINATION PREDICT LOWER EXTREMITY PERIPHERAL ARTERIAL DISEASE?

	LR+	LR-
History		
Claudication	3.3	0.89
Inspection		
Wounds (ischemic ulcers and gangrene over lateral malleolus, tips of toes, metatarsal heads, bunion)	5.9	0.98
Discolouration	2.8	0.74
Atrophy	–	–
Absence of hair	–	–
Palpation		
Any palpable pulse abnormality (femoral, popliteal, posterior tibial, dorsalis pedis)	4.7	0.38
Coolness	5.9	0.92
Capillary refill time (firm pressure to planter aspect of great toe for 5 s. Abnormal if >5 s for normal skin)	1.9	–
Auscultation		
Any bruit (iliac, femoral, popliteal)	5.6	0.39

SPECIAL TESTS—**ankle brachial index** (ankle SBP by palpation/Doppler of posterior tibial or dorsalis pedis pulse divided by brachial SBP), **venous filling time** (raise leg to 45° for 1 min with patient supine position for vein to collapse. With patient then sitting up and legs dangling, determine the time for vein to refill. Abnormal if >20 s) (LR+ 3.6, LR– 0.8)

APPROACH—for screening patients who require further testing to diagnose peripheral arterial disease, the most useful individual symptoms and signs are: claudication, femoral bruit, and a pulse abnormality on palpation. The absence of claudication and the presence of normal pulses decrease the likelihood of moderate to severe disease. When considering patients who are symptomatic with leg complaints, the most useful individual findings are the presence of cool skin, the presence of at least 1 bruit, and any palpable pulse abnormality. The absence of any bruit (iliac, femoral and popliteal) and the presence of normal peripheral pulses reduce the likelihood of peripheral arterial disease

Khan et al. *JAMA* 2006;295(5)

DISTINGUISHING FEATURES OF COMMON CAUSES OF LEG PAIN

	Claudication	Spinal stenosis	Venous congestion
Pain	Cramp, tiredness	Cramp, tiredness, tingling	Tightness, bursting
Sites	Buttock, hip, thigh, calf, foot	Buttock, hip, thigh	Groin, thigh
Worse	Walking	Walking, standing	Walking
Better	Rest	Sitting or change in position	Leg elevation
Others	Vascular dx, ↓ pulse	Lower back pain	History of DVT

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, fasting glucose, lipid panel, HbA1C
- **ANKLE BRACHIAL INDEX**—with or without exercise
- **DUPLEX ULTRASOUND**
- **ECG**

SPECIAL

- **CT/MR angiography**
- **ANGIOGRAPHY**

DIAGNOSTIC ISSUES

DIAGNOSTIC APPROACH—ABI <0.90 is sufficient for the diagnosis of peripheral arterial disease as it suggests >50% stenosis of peripheral vasculature (sens 90%, spec 98%). Patients with large vessel disease (distal aorta or iliac arteries) may only have abnormal ABI after exercise. Patients with non-compressible vessels (as suggested by ABI >1.30–1.40) should have toe-brachial index done. Perform duplex US or CT/MR angiogram if the diagnosis is uncertain or if revascularization is being considered. Digital-subtraction angiograph remains the gold standard; do not perform invasive or non-invasive anatomic assessment for asymptomatic patients

MANAGEMENT**RISK REDUCTION ★ABCDEFG★**

- **ASA**
- **BLOOD PRESSURE CONTROL** (see HYPERTENSION p. 70)
- **CHOLESTEROL CONTROL** (see DYSLIPIDEMIA p. 75)
- **DIABETIC CONTROL** (see DIABETES p. 365)
- **EXERCISE** (30–45 min of moderate-intensity exercise 3–4 x/week)
- **FAT REDUCTION** (see OBESITY ISSUES p. 449)
- **GET GOING TO QUIT SMOKING!** (see SMOKING ISSUES p. 490)

MANAGEMENT (CONT'D)

MEDICAL—antiplatelet (ASA 75–325 mg PO daily, *clopidogrel* 75 mg PO daily), high-intensity **statin** (*atorvastatin* 80 mg PO daily, *rosuvastatin* 40 mg PO daily). Consider *cilostazol* 100 mg PO BID for life-limiting claudication (in the absence of heart failure). Anticoagulation is not recommended for peripheral vascular disease unless there is another clinical indication for its use (e.g. atrial fibrillation); the benefit of anticoagulation in patients requiring bypass grafting for peripheral vascular disease is uncertain

SURGICAL—revascularization (surgery or percutaneous transluminal angioplasty)

TREATMENT ISSUES

REVASCLARIZATION—indicated for patients with significant functional limitations (lifestyle or jobs) despite maximal lifestyle and medical treatment. Not optimal for patients <40 with atherosclerosis obliterans, with non-disabling symptoms, diabetes, significant coronary risk factors, or other diseases associated with high mortality

SPECIFIC ENTITIES

VASCULAR DISEASE FAMILY—CAD, CVD, PVD, AAA, renal artery stenosis, chronic mesenteric ischemia

ABDOMINAL AORTIC ANEURYSM—U.S. Preventative Services Task Force recommends one-time screening with abdominal US for men 65–75 who have smoked 100 cigarettes or more in their lifetime. Repair is controversial for 4–5 cm [1.6–2 in.]; >5 cm [>2 in.] warrants surgical intervention (risk of spontaneous rupture is 22%/year). Monitor lesions ≤5 cm [≤2 in.] with ultrasound regularly (every 6 months if lesions 4 cm [1.6 in.], more frequent for bigger lesions). Operative mortality is 4–6% for elective repair, 19% for urgent repair, and 50% for repair of a ruptured aneurysm. No driving if AAA >6 cm [2.4 in.] in men, >5.5 cm [2.2 in.] in women

Hypertension

2020 Hypertension Canada Guidelines

2017 ACC/AHA Hypertension Guideline

2014 JNC8 Hypertension Guidelines

August *NEJM* 2003;348(7); Moser et al. *NEJM* 2006;355(4); Chobanian *NEJM* 2007;357(8)

DIFFERENTIAL DIAGNOSIS

ESSENTIAL HYPERTENSION

RENAL

- **RENAL PARENCHYMAL DISEASE**—chronic renal failure, polycystic kidney disease
- **RENAL VASCULAR DISEASE**—atherosclerosis, fibromuscular dysplasia, scleroderma, vasculitis

ENDOCRINE

- **ADRENAL**—primary aldosteronism, Cushing syndrome, pheochromocytoma
- **“PSEUDO-ADRENAL”**—Liddle syndrome, apparent mineralocorticoid excess syndrome, Gordon syndrome, reninoma
- **ACROMEGALY**
- **HYPERPARATHYROIDISM**
- **THYROID**—hyperthyroidism, hypothyroidism

DRUGS—NSAIDs, corticosteroids, anabolic steroids, estrogen-containing oral contraceptives, cocaine, amphetamines, MAO inhibitors, SNRIs, SSRIs, levo-dopa, erythropoietin, cyclosporine, tacrolimus, midodrine, alcohol excess, licorice root

ANATOMIC

- **AORTA**—coarctation, aortic dissection

NEUROGENIC

- **BARORECEPTOR MALFUNCTION**—lateral medullary syndrome, posterior fossa lesion
- **CUSHING TRIAD**—increased ICP with hypertension, bradycardia, and respiratory depression

OTHER

- **GESTATIONAL HYPERTENSION**
- **OBSTRUCTIVE SLEEP APNEA**
- **POLYCYTHEMIA VERA**

PATHOPHYSIOLOGY

CLASSIFICATION

- **HYPERTENSION**—there is a log-linear relationship between BP and cardiovascular risk with an increase in risk at a threshold of ~115/75 mmHg. Specific cutoff for “high” BP varies according to different guidelines, measurement techniques (attended vs. unattended), devices (e.g. automated vs. manual), settings (e.g. ambulatory vs. office), and underlying conditions (e.g. absence vs. presence of diabetes). See below for diagnostic algorithm
- **ISOLATED SYSTOLIC HYPERTENSION**—younger people tend to have isolated diastolic hypertension (50–60% of patients under 40). With age, large

PATHOPHYSIOLOGY (CONT'D)

arteries tend to stiffen with decreased elasticity secondary to a combination of atherosclerosis, calcification, and elastin degradation. Thus, isolated systolic hypertension predominates with age (over 90% of patients over 70)

- **RESISTANT HYPERTENSION**—uncontrolled hypertension despite 3 different antihypertensive agents (of which one is a diuretic), or hypertension irrespective of control on 4 or more antihypertensive agents
- **MASKED HYPERTENSION**—BP consistently elevated with out-of-office measurements, but normotensive when measured in office; associated with ↑ cardiovascular risk
- **WHITE COAT HYPERTENSION**—BP consistently elevated with office measurements, but normotensive when out-of-office; possible slight ↑ cardiovascular risk (but still less than masked or sustained hypertension)
- **HYPERTENSIVE EMERGENCY**—severe hypertension (usually SBP \geq 180 and/or DBP \geq 120 mmHg) with end organ damage such as pulmonary edema, aortic dissection, myocardial infarction, cerebrovascular hemorrhage, papilledema, fundoscopic hemorrhages or exudates, acute renal failure, eclampsia of pregnancy, and hypertensive encephalopathy
- **HYPERTENSIVE URGENCY**—severe hypertension (usually SBP \geq 180 and/or DBP \geq 120 mmHg) without findings of hypertensive emergency

HYPERTENSIVE END ORGAN DAMAGE—ischemic heart disease, peripheral arterial disease, left ventricular hypertrophy, stroke, TIA, microalbuminuria or proteinuria, and chronic kidney disease

HYPERTENSIVE RETINOPATHY

- **MILD**—**focal arteriolar narrowing** (vasospasm), **generalized arteriolar narrowing** (increased vascular tone due to autoregulation, mild intimal hyperplasia, and hyaline degeneration in sclerotic stage). Subsequently, **arteriovenous nicking** (venous compression by a thickened arteriole, leading to dilation of vein around intersection), and **opacity of arteriolar wall** (widening and accentuation of the central light reflex leading to so-called copper wiring appearance)

PATHOPHYSIOLOGY (CONT'D)

- **MODERATE**—**hemorrhages** (blot, dot, or flame shaped due to disruption of the blood–retina barrier), **microaneurysms** (necrosis of the smooth muscles and endothelial cells), **hard exudates** (exudation of blood and lipids), and **soft exudates** (cotton wool spots, retinal ischemia)
- **MALIGNANT**—signs of moderate retinopathy plus swelling of the optic disc
- **UTILITY**—the retina provides a window of cerebral circulation. Risk of stroke (and death) increases with degree of retinopathy. Note that the stages may not be sequential

Wong et al. *NEJM* 2004;351(22)

CLINICAL FEATURES

HISTORY—blood pressure levels, ambulatory/home monitoring, complications and hypertensive end organ damage, other cardiac risk factors (smoking, diabetes, dyslipidemia, obesity), past medical history (thyroid, renal, or adrenal disorders), medications (antihypertensives, steroids, illicit drugs)

PHYSICAL—vitals (heart rate, blood pressure), obesity (sleep apnea), moon facies and thoracocervical fat pad (Cushing syndrome), low-pitched voice and acral enlargement (acromegaly), upper body better developed and continuous murmur over precordium/back (coarctation), narrowed oropharynx and ↑ neck circumference (OSA), goiter (hyperthyroidism), aortic regurgitation (aortic dissection), striae, renal bruits (renal artery stenosis), abdominal masses (polycystic kidney disease, adrenal tumors), radiofemoral delay and weak femoral pulses (coarctation). Assess complications including retinopathy, stroke, HF, AAA, and PVD. See references below on proper techniques to measure blood pressure

Williams et al. *NEJM* 2009;360(e6)

2020-2022 Highlights Hypertension
Canada

INVESTIGATIONS**BASIC**

- **LABS**—lytes, urea, creatinine, fasting glucose, HbA1C, lipid panel, urinalysis, urine microalbumin
- **24-H AMBULATORY BLOOD PRESSURE MONITOR**
- **ECG**

SECONDARY CAUSES WORKUP

- **HYPERALDOSTERONISM WORKUP**—if clinical features present (i.e. spontaneous hypokalemia <3.5 mmol/L; diuretic-induced hypokalemia <3.0 mmol/L; resistance to ≥3 antihypertensive drugs; adrenal incidentaloma with hypertension), consider screening aldosterone/renin ratio

INVESTIGATIONS (CONT'D)

- **PHEOCHROMOCYTOMA WORKUP**—if clinical features present (i.e. paroxysmal and/or severe hypertension refractory to usual antihypertensive drugs; symptoms of catecholamine excess; hypertension triggered by β-blockers, MAO inhibitors, micturition, or Valsalva maneuver; adrenal incidentaloma with hypertension; genetic syndrome [MEN2A, MEN2B, von Hippel-Lindau, neurofibromatosis]), consider 24-h urine metanephrine or plasma fractionated metanephrines
- **OTHER ENDOCRINE WORKUP** (guided by clinical suspicion)—Ca, albumin, PTH, TSH, free T4, 24-h urine cortisol, 1 mg dexamethasone suppression test, late night salivary cortisol, IGF-1
- **RENOVASCULAR WORKUP**—if ≥2 clinical features present (i.e. sudden-onset or worsening hypertension and age >55 or <30 years; presence of abdominal bruit; resistance to ≥3 antihypertensive drugs; ↑ serum Cr ≥30% with ACEi or ARB; other atherosclerotic disease; or recurrent flash pulmonary edema), consider renal Doppler US, CT/MR angiogram, renal angiogram
- **SLEEP OXIMETRY TEST**—if suspect sleep apnea

DIAGNOSTIC ISSUES**MEASUREMENT TECHNIQUES, DEVICES, AND SETTINGS**

- **AUTOMATED OFFICE BLOOD PRESSURE (AOBP)**—office measurement using an automated device with multiple readings with the patient *alone* in a private room
- **OFFICE BLOOD PRESSURE MEASUREMENT (OBPM)**—office measurement performed with the patient and provider in the room at the same time
- **AMBULATORY BLOOD PRESSURE MEASUREMENT (ABPM)**—ambulatory 24-h monitor with measurements collected at 20- to 30-minute intervals throughout the day and night
- **HOME BLOOD PRESSURE MEASUREMENT (HBPM)**—self-monitored home-based measurement, preferably using a validated device

OVERALL APPROACH TO DIAGNOSIS OF HYPERTENSION

1. **Hypertensive urgency or emergency during first visit?**
 - Yes → hypertension diagnosed
 - No → proceed to step 2
2. **What is the blood pressure during initial visit?**
 - Using AOBP or OBPM, SBP ≥180 mmHg and/or DBP ≥110 mmHg → repeat BP at least 2 more times at the same visit (discard

DIAGNOSTIC ISSUES (CONT'D)

first reading and average latter 2 readings). If mean BP 180/110 mmHg or greater, diagnosis of hypertension is confirmed

- For patients without diabetes, using AOBP, if SBP 135–179 mmHg and/or DBP 85–109 mmHg (or using OBPM, SBP 140–179 mmHg and/or DBP 90–109 mmHg), then obtain out-of-office readings before next visit
 - For patients with diabetes, using OBPM, if SBP 130–179 mmHg and/or DBP 80–109 mmHg for at least 3 measurements, then consider out-of-office readings before second visit → if BP remains elevated on multiple days, diagnosis of hypertension probable/confirmed
3. **Out-of-office readings can be measured using 24-h ABPM (preferred) or a HBPM series. Further information on how to perform these can be found at www.hypertension.ca**
 4. **What is the average blood pressure from the 24-h ABPM?**
 - Mean awake SBP \geq 135 mmHg or DBP \geq 85 mmHg → hypertension diagnosed
 - Mean 24-h SBP \geq 130 mmHg or DBP \geq 80 mmHg → hypertension diagnosed
 5. **What is the average blood pressure from the HBPM series?**
 - Average SBP \geq 135 or DBP \geq 85 mmHg → hypertension diagnosed

Average SBP <135 or DBP <85 mmHg → repeat HBPM series (to confirm average BP <135/85 mmHg), or consider 24-h ABPM monitoring **2020 Hypertension Canada Guidelines**

ACUTE MANAGEMENT

ACUTE—ABC, O₂, IV

HYPERTENSIVE EMERGENCY—*labetalol* 20 mg IV bolus initially, then 20–80 mg q10min, or 2 mg/min IV infusion (loading) then 2–8 mg/min, maximum total dose of 300 mg. *Nitroprusside* 0.25–0.5 µg/kg/min IV initially, increase by 0.5 µg/kg/min increments, to usually target 3 µg/kg/min (rarely >4 µg/kg/min, maximum 10 µg/kg/min). *Nicardipine* 5 mg/h IV initially, titrate to a maximum of 15 mg/h. *Fenoldopam* 0.1 µg/kg/min IV initially, titrate dose q15 min. Consider ICU admission. Workup and treatment of underlying causes once stabilized

HYPERTENSIVE URGENCY—*furosemide* 20–40 mg PO/IV \times 1 dose if in pulmonary edema or heart failure. *Clonidine* 0.1–0.3 mg PO BID. *Captopril* 25–50 mg PO TID. *Labetalol* 5–20 mg IV q15min or *hydralazine* 5–20 mg IV q15min to keep SBP <170 mmHg. Lower BP over hours to days, 25–30% lower than baseline; avoid lowering BP too rapidly (risk of stroke or MI if BP dropped to below minimum level

ACUTE MANAGEMENT (CONT'D)

required to maintain tissue perfusion). Workup and treatment of underlying cause once stabilized

LONG-TERM MANAGEMENT

LIFESTYLE CHANGES—**healthy diet** (high in fresh fruits, vegetables, and low fat dairy products; low in saturated fat and salt <100 mmol/day).

Physical activity (optimum 30–60 min of moderate cardiopulmonary activity 4–7 \times /week).

Reduction in alcohol (<2 drinks/day in men and <1 drink/day in women). **Weight loss** (in those with BMI >25 kg/m², lose >5 kg). **Smoke free environment**

ANTIHYPERTENSIVES ★ABCD★

- **ACE INHIBITOR**—*ramipril* 2.5–10 mg PO daily-BID, *enalapril* 5–20 mg PO daily-BID, *perindopril* 2–8 mg PO daily, *lisinopril* 2.5–10 mg PO daily, *trandolapril* 1–8 mg PO daily
- **ARB**—*candesartan* 8–32 mg PO daily, *losartan* 50–100 mg PO daily, *irbesartan* 150–300 mg PO daily, *valsartan* 80–320 mg PO daily, *telmisartan* 40–80 mg PO daily
- **β-BLOCKERS**—not recommended as first-line agent for uncomplicated hypertension in those \geq 60-years old. *Metoprolol* 50–100 mg PO BID, *atenolol* 50–100 mg PO daily, *labetalol* 100–400 mg PO TID, *bisoprolol* 5–10 mg PO daily, *carvedilol* 6.25–25 mg PO BID
- **CALCIUM CHANNEL BLOCKERS**—*amlodipine* 2.5–10 mg PO daily, *nifedipine ER* 30–90 mg PO daily, *diltiazem CD* 180–360 mg PO daily, *verapamil SR* 240–480 mg PO daily
- **THIAZIDE (AND THIAZIDE-LIKE) DIURETICS**—*chlorthalidone* 12.5–25 mg PO daily, *indapamide* 1.25–2.5 mg PO daily, *hydrochlorothiazide* 12.5–25 mg PO daily
- **POTASSIUM-SPARING DIURETICS**—*spironolactone* 12.5–50 mg PO daily
- **α1 BLOCKERS**—*TERAZOSIN* 1–20 mg PO daily, *doxazosin* 1–16 mg PO daily
- **CENTRAL α2 AGONIST**—*clonidine* 0.1–0.5 mg PO BID
- **OTHERS**—minoxidil, hydralazine

TREAT UNDERLYING CAUSE**TREATMENT ISSUES****ACE INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKERS**

- **INDICATIONS**—HF, post-MI, diabetes, proteinuria, renal failure (with caution), LVH
 - **CONTRAINDICATIONS**—pregnancy, ESRD, bilateral RAS
 - **ADVERSE EFFECTS**—cough (with ACE inhibitor), angioedema, hyperkalemia
- β-BLOCKERS**

TREATMENT ISSUES (CONT'D)

- **INDICATIONS**—resting tachycardia, HF, migraine, glaucoma, CAD/post-MI
- **CONTRAINDICATIONS**—asthma, severe PVD, Raynaud phenomenon, depression, bradycardia, second or third degree heart block, and hypoglycemia-prone diabetics
- **ADVERSE EFFECTS**—depression, ↓ exercise tolerance, bradycardia, hypotension

CALCIUM CHANNEL BLOCKERS

- **DIHYDROPYRIDINE** (potent vasodilators)—nifedipine, amlodipine, felodipine, nifedipine
- **NON-DIHYDROPYRIDINE** (heart rate control)—verapamil (cardiac depressant activity), diltiazem (some cardiac depressant, some vasodilator)
- **INDICATIONS**—angina pectoris, recurrent SVT (verapamil), Raynaud phenomenon (dihydropyridine), migraine, heart failure due to diastolic dysfunction, esophageal spasm
- **CONTRAINDICATIONS**—second or third degree heart block (non-dihydropyridine), HF with moderate to marked systolic dysfunction
- **ADVERSE EFFECTS**—nifedipine (dizziness, headache, flushing, and peripheral edema), verapamil (↓ cardiac contractility, conduction, and constipation), diltiazem (both side effects but a lot less severe)

THIAZIDE (AND THIAZIDE-LIKE) DIURETICS

- **INDICATIONS**—most patients (particularly Black patients)
- **CONTRAINDICATIONS**—allergy
- **ADVERSE EFFECTS**—↓ K, ↑ Ca, hyperuricemia, ↑ cholesterol, ↑ glucose, ↑ insulin resistance, impotence

TREATMENT ISSUES (CONT'D)**BLOOD PRESSURE TREATMENT TRIGGERS AND TARGETS**

Population	BP Thresholds for Drug Therapy (SBP/DBP, mmHg)	BP Treatment Targets (SBP/DBP, mmHg)
High risk (10-year Framingham risk score ≥15%, or cardiovascular disease, or CKD, or age ≥75 years)*	SBP ≥130	SBP <120
Moderate risk	≥140/90	<140/90
Low risk (no other cardiovascular risk factors or target organ damage)	≥160/100	<140/90
Comorbid diabetes mellitus	≥130/80	<130/80

* Intensive SBP target based on AOBP measurement. Intensive SBP target not recommended for institutionalized elderly adults; limited (or no) evidence for patients with HF, diabetes, stroke, or eGFR <20 mL/min/1.73 m².

Hypertension Canada 2020 Guidelines

OVERALL APPROACH TO CHOICE OF INITIAL THERAPY

Condition	Drug of Choice
HTN without other indications	A/B/C/D → AC/AD/BC/BD → ABC/ACD/BCD/ABD → ABCD Avoid B as first line if age ≥60 ACEi may be less effective in those of African descent
Isolated systolic hypertension	ARB/C1/D → ARB plus either C1 or D → ARB plus C1 plus D Avoid B
Angina	ACEi/B → ACEi plus B → add C1
Prior myocardial infarction	AB → ABC
Heart failure	AB → ABD (including spironolactone) → ACEi/ARB/B/D. Avoid hydralazine and minoxidil if LVH
Prior cerebrovascular disease	AD → add other agents
Peripheral vascular disease	A/B/C/D plus ASA. Avoid B if severe PVD
Diabetes without nephropathy	A/C1/D → AC1/AD → add B or C2
Diabetes with nephropathy	A → AC/AB/AD
CKD ± proteinuria	A → AD → add other agents
Asthma	A/C/D. Avoid B

TREATMENT ISSUES (CONT'D)

Condition	Drug of Choice
BPH	α -blockers
Migraine	B
Thyrotoxicosis	B
Essential tremor	B
Postural hypotension	Avoid vasodilators and diuretics
Raynaud phenomenon	C (dihydropyridine)
Gout	Avoid D
Hyperkalemia	C/D. Avoid ACE inhibitors, ARBs, and spironolactone
Hyponatremia	A/B/C. Avoid D
Pregnancy	Labetalol/methyldopa/nifedipine. Avoid ACE inhibitors and ARB (teratogenic)

where A = ACE inhibitors/ARBs, B = β -blockers, C = calcium channel blockers, C1 = long-acting dihydropyridine CCB, C2 = non-dihydropyridine CCB, D = diuretics

SPECIFIC ENTITIES

RENAL ARTERY STENOSIS (RAS)

- **PATHOPHYSIOLOGY**—causes include atherosclerosis and fibromuscular dysplasia
- **CLINICAL FEATURES**—systemic atherosclerosis, uncontrolled hypertension, flash pulmonary edema, asymmetrical kidneys, renal failure with ACE inhibitor, and renal bruits
- **DIAGNOSIS**—CT or MR angiogram (preferred as non-invasive and high sensitivity/specificity), duplex US (anatomic and functional information), contrast angiogram (gold standard)
- **TREATMENTS**—**medical** (cornerstone of management of atherosclerotic disease; risk factor reduction with blood pressure control [avoidance of ACE inhibitors/ARBs in severe bilateral renal artery stenosis], statin therapy, and antiplatelet agent), **angioplasty** (not routinely recommended for atherosclerotic disease because outcomes similar to medical therapy alone; consider if fibromuscular dysplasia, severe or refractory hypertension, recurrent flash pulmonary edema, or acute decline in renal function due to renal artery stenosis. Unlikely to restore renal function if small kidneys or high creatinine $>300 \mu\text{mol/L}$ [3.4 mg/dL]), **surgery**

DIFFERENTIAL DIAGNOSIS OF ABDOMINAL BRUITS

- **CARDIOVASCULAR**—abdominal aortic aneurysm, aortocaval fistula
- **RENAL VASCULAR**—renal artery stenosis
- **GI VASCULAR**—celiac artery compression syndrome, mesenteric ischemia
- **HEPATIC VASCULAR**—cirrhosis, hepatoma, AV malformation, arteriportal fistula, Cruveilhier–Baumgarten sign (cirrhosis, portal hypertension, and caput medusa)
- **SPLenic VASCULAR**—splenic AV fistula, splenic artery dissection, splenic enlargement
- **PANCREATIC VASCULAR**—pancreatic carcinoma

SPECIFIC ENTITIES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: IS LISTENING FOR ABDOMINAL BRUITS USEFUL IN THE EVALUATION OF RENOVASCULAR HYPERTENSION?

	LR+	LR-
Systolic and diastolic abdominal bruit	39	0.6
Any epigastric or flank bruit, including isolated systolic bruit	6.4	0.4
Systolic bruit	4.3	0.5
History of atherosclerotic disease	2.2	0.5

APPROACH—given the high prevalence (7–31%) of innocent abdominal bruits in younger age groups, it is recommended that “if a systolic abdominal bruit is detected in a young, normotensive, asymptomatic individual, no further investigations are warranted. In view of the low sensitivity, the absence of a systolic bruit is not sufficient to exclude the diagnosis of renovascular hypertension. In view of the high specificity, the presence of a systolic bruit (in particular a systolic–diastolic bruit) in a hypertensive patient is suggestive of renovascular hypertension. . . . In view of the lack of evidence to support characterizing bruits as to pitch, intensity and location, bruits should be reported only as systolic or systolic/diastolic.”

Turnbull *JAMA* 1995;274(16)

Simel et al. *The Rational Clinical Examination*.

McGraw-Hill; 2009

Related Topics

Aortic Dissection (p. 29)
 Hyperaldosteronism (p. 382)
 Pheochromocytoma (p. 383)

Hyperlipidemia

2013 ACC/AHA Guideline Blood Cholesterol
2019 ACC/AHA Guideline Primary Prevention Cardiovascular Disease
2016 Canadian Cardiovascular Society Guidelines Dyslipidemia

DIFFERENTIAL DIAGNOSIS
OF HYPERCHOLESTEROLEMIA

PRIMARY—polygenic, familial hypercholesterolemia (IIa; suspect when total cholesterol >6 mmol/L [>232 mg/dL], LDL >5 mmol/L [>193 mg/dL]), sitosterolemia

SECONDARY—obesity, diabetes, hypothyroidism, nephrotic syndrome, medications (thiazides), cholestatic liver disease (e.g. primary biliary cirrhosis)

DIFFERENTIAL DIAGNOSIS
OF HYPERTRIGLYCERIDEMIA

PRIMARY—dietary, familial hypertriglyceridemia (IV; suspect when TGL >5 mmol/L [>440 mg/dL]), LPL deficiency (I), dysbetalipoproteinemia (III), ApoCII deficiency

SECONDARY—obesity, diabetes, nephrotic syndrome, hypothyroidism, alcoholism, Cushing syndrome, and drugs (estrogen, tamoxifen, β -blockers, glucocorticoids, cyclosporine, glucocorticoids, novel antipsychotics, protease inhibitors, isotretinoin)

DIFFERENTIAL DIAGNOSIS OF COMBINED
HYPERCHOLESTEROLEMIA
AND HYPERTRIGLYCERIDEMIA

PRIMARY—familial combined hyperlipidemia (IIb), mixed hypertriglyceridemia (V), dysbetalipoproteinemia (III)

SECONDARY—diabetes, nephrotic syndrome, hypothyroidism, drugs (glucocorticoids, immunosuppressives, protease inhibitors), lipodystrophies

DIFFERENTIAL DIAGNOSIS OF LOW HDL

PRIMARY—familial hypoalphalipoproteinemia, Tangiers disease, apoA1 mutation, LCAT deficiency

SECONDARY—drugs (anabolic steroids, isotretinoin)

CLINICAL FEATURES

HISTORY—past medical history (diabetes, CAD, HF, stroke, TIA, renal disease, hypertension, liver disease, gallstones, hypothyroidism, HIV), medications

- **HYPERTRIGLYCERIDEMIA**—pancreatitis, chylomicronemia syndrome (nausea, vomiting, dyspnea, confusion), hyponatremia, transaminitis, milky plasma (with blood work)

CLINICAL FEATURES (CONT'D)

- **HYPERCHOLESTEROLEMIA**—premature atherosclerosis, aortic sclerosis/stenosis

PHYSICAL

- **HYPERTRIGLYCERIDEMIA**—lipemia retinalis (when TGL ≥ 22.6 mmol/L [>2000 mg/dL]), eruptive xanthomas (commonly on buttocks, extensor surfaces of arms, back; when TGL 11.3–22.6 mmol/L [1000 – 2000 mg/dL]), hepatosplenomegaly
- **HYPERCHOLESTEROLEMIA**—tendon xanthomas (most commonly in Achilles tendon and extensor surfaces of hands), xanthelasma, tuberosus xanthomas (over areas susceptible to trauma), corneal arcus (premature when <40-years of age)

INVESTIGATIONS

BASIC

- **LABS**—lipid profile (fasting optional if no hypertriglyceridemia), glucose, HbA1C, Cr, TSH, ALP, urine albumin/creatinine ratio \pm apoB (if hypertriglyceridemia)

SPECIAL

- **CORONARY ARTERY CALCIUM SCORE**—for risk stratification
- **LIPOPROTEIN(a)**—for risk stratification (e.g. intermediate risk patients where treatment decisions are uncertain, or for selective low-risk individuals with a family history of premature coronary heart disease) and prognosis

DIAGNOSTIC ISSUES

WHOM TO SCREEN FOR DYSLIPIDEMIA—men ≥ 40 years, women ≥ 40 years, or patients with any of the following conditions (irrespective of age): clinical evidence of atherosclerosis, abdominal aortic aneurysm, diabetes mellitus, hypertension, current smoker, stigmata of dyslipidemia, family history of premature cardiovascular disease or dyslipidemia, CKD, obesity, inflammatory disease, HIV, erectile dysfunction, COPD, gestational hypertension

MANAGEMENT

HYPERCHOLESTEROLEMIA—**dietary modification** (e.g. increased fruits and vegetables, avoiding organ meats). Pharmacological first-line treatment is **statin**, then add-on with **ezetimibe \pm bile-acid sequestrant** if needed. If LDL-cholesterol remains above target, use **PCSK9 inhibitor**, especially in high-risk patients

MANAGEMENT (CONT'D)

with clinical atherosclerotic cardiovascular disease and/or heterozygous familial hypercholesterolemia. Target LDL-cholesterol <1.8 mmol/L [70 mg/dL] (or 50% reduction), apoB <0.80 g/L (80 mg/dL), or non-HDL-cholesterol <2.6 mmol/L (100 mg/dL)

HYPERTRIGLYCERIDEMIA—**dietary modification** (e.g. reduced fat, simple sugars, and calories) and alcohol abstinence. Severe cases (TG >11.3 mmol/L [1,000 mg/dL]) should be treated pharmacologically because of associated risk of pancreatitis. Target uncertain

TREAT SECONDARY CAUSES/METABOLIC SYNDROME IF PRESENT**TREATMENT ISSUES**

LIFESTYLE—healthy lifestyle for all patients.

Diet (↑ fruit and vegetable intake, ↑ mono- and polyunsaturated fats, ↓ saturated fats and trans-fatty acid to <7% of calories, ↑ omega-3 fatty acid from fish and plant sources, *salmon oil* 3–9 g can ↓TGL), **regular exercise, smoking and alcohol avoidance, maintenance of healthy weight**

INDICATIONS FOR PHARMACOTHERAPY

- **MAJOR INDICATIONS FOR CHOLESTEROL TREATMENT**—clinical atherosclerotic disease (e.g. MI, angina, stroke, TIA, PAD), abdominal aortic aneurysm (>3 cm or prior surgery), diabetes mellitus (age ≥40 years, or >15 years duration for age ≥30 years [e.g. type 1 diabetes]), or with any microvascular disease), CKD (eGFR <60 mL/min/1.73m² or urine albumin/creatinine ratio >3.0 mg/mmol), LDL-cholesterol ≥5 mmol/L, or history of familial hypercholesterolemia
- **OTHER INDICATIONS**—perform risk assessment with adjusted **Framingham Risk Score** for 10-year risk of cardiovascular disease and treat all patients at high risk (≥20%). Consider treatment in those at intermediate risk (10–19%) with any one of the following: LDL-cholesterol ≥3.5 mmol/L (or apoB ≥1.2 g/L or non-HDL-cholesterol ≥4.3 mmol/L); men ≥50 years and women ≥60 years with at least 1 additional cardiovascular risk factor (e.g. low HDL-cholesterol, impaired fasting glucose, increased waist circumference, smoking, and hypertension)

MAJOR CHOLESTEROL-LOWERING DRUG CLASSES

- **STATINS (HMG-CoA REDUCTASE INHIBITORS; ↓↓ LDL ↑ HDL, ↓ TGL)**—considered first-line for hypercholesterolemia; *atorvastatin* 10–80 mg

TREATMENT ISSUES (CONT'D)

PO daily, *rosuvastatin* 5–40 mg PO daily, *simvastatin* 10–80 mg PO daily, *pravastatin* 10–40 mg PO daily. Main side effects include myalgias, myopathy, and transaminitis

- **NPC1L1 TRANSPORTER INHIBITOR (↓ LDL)**—*ezetimibe* 10 mg PO daily
- **BILE-ACID SEQUESTRANTS (↓ LDL, ↑ cholesterol synthesis)**—*colesevelam* 1.25–1.875 g PO BID, *cholestyramine* 2–24 g PO daily, *colestipol* 5–30 g PO daily in divided doses. Main side effects include constipation, vitamin K deficiency, and drug interactions (bind to other drugs and prevent absorption)
- **PCSK9 INHIBITOR (↓↓↓ LDL)**—*evolocumab* 140 mg SC q2weeks (or 420 mg SC q4weeks) or *alirocumab* 75–150 mg SC q2weeks (or 300 mg SC q4weeks). Inhibit PCSK9 from binding to LDL receptor on hepatocytes, thus facilitating removal of LDL from circulation

MAJOR TRIGLYCERIDE-LOWERING DRUG CLASSES

- **FIBRATES (↓ LDL ↑ HDL, ↓↓ TGL)**—*fenofibrate nanocrystallized tablet* 145 mg PO daily without regard to meals (best oral absorption), *fenofibrate micronized tablet* 160–200 mg PO with dinner (moderate oral absorption and modestly improved with food), *fenofibrate micronized capsule* 200 mg PO with dinner (poor oral absorption but improved with food), *gemfibrozil* 600 mg PO daily (safe in pregnancy beginning in second trimester). Main side effects include rash, pruritis, GI upset, and gallstones
- **OMEGA-3 FATTY ACIDS (↓ TGL, ↑ LDL)**—*icosapent ethyl* 2 g PO bid with food (an ethyl ester of eicosapentaenoic acid that reduces cardiovascular risk) for patients with ↑ triglyceride plus atherosclerotic cardiovascular disease, or diabetes and ≥1 cardiovascular risk factor. Other omega-3 fatty acids not associated with cardiovascular benefit, but may be considered for triglyceride-lowering (e.g. *eicosapentaenoic acid/docosahexaenoic acid [EPA/DHA]* 3–4 g PO daily) but may be limited by fishy odour

SPECIAL CASES

- **FAMILIAL HYPERCHOLESTEROLEMIA**—lifestyle modification and pharmacologic therapy with potent statin (atorvastatin, rosuvastatin) plus add-on therapy with ezetimibe or bile-acid sequestrant, or both. Consider PCSK9 inhibitor when available. Homozygotes may require LDL apheresis. Consider genetic counseling for affected family members

TREATMENT ISSUES (CONT'D)

- **FAMILIAL COMBINED HYPERLIPEMIA**—lifestyle modification (weight reduction and dietary changes) and pharmacologic therapy with statin plus add-on therapy with ezetimibe or fibrate
- **DYSBETALIPOPROTEINEMIA**—identify and treat comorbidities (diabetes, obesity, hypothyroidism). Pharmacologic therapy often unnecessary, but when needed, consider statin or fibrates. Consider genetic counseling (for apoE2 gene) for affected family members
- **CHYLOMICRONEMIA SYNDROME**—dietary modification (total fat restriction initially until TG <11.3 mmol/L [1,000 mg/dL] then fat-limited diet), alcohol abstinence, optimize glycemic control, and discontinue offending medications. Pharmacologic therapy with fibrate plus add-on therapy with statin or orlistat

SPECIFIC ENTITIES

METABOLIC SYNDROME (Syndrome X or insulin resistance syndrome)—National Cholesterol Education Program's Adult Treatment Panel (ATP) III report criteria ≥ 3 of the following five features:

- \uparrow **TGL**— ≥ 1.7 mmol/L [≥ 150 mg/dL]
- \downarrow **HDL**— ♀ <1.30 mmol/L [<50 mg/dL], ♂ <1.04 mmol/L [<40 mg/dL]
- **INSULIN RESISTANCE**—fasting glucose ≥ 5.6 mmol/L [≥ 100 mg/dL] (modified; originally defined as fasting glucose ≥ 6.1 mmol/L [≥ 110 mg/dL])
- **WAIST CIRCUMFERENCE**— ♂ >102 cm [>40 in.], ♀ >88 cm [>35 in.]. May consider ethnic-specific cut-offs where appropriate (Europid ♂ ≥ 94 cm [≥ 37 in.], ♀ ≥ 80 cm [≥ 31.5 in.]; South Asian/Chinese: ♂ ≥ 90 cm [≥ 35.5 in.], ♀ ≥ 80 cm [31.5 in.]; Japanese: ♂ ≥ 85 cm [33.5 in.], ♀ ≥ 90 cm [35.5 in.]
- **HYPERTENSION**— $\geq 130/85$ mmHg or on treatment

FAMILIAL DYSLIPIDEMIAS (FREDRICKSON CLASSIFICATION)

Type	Mechanism	Lipid profile	Tendon xanthoma	Palmar xanthoma	Eruptive xanthoma	Xanthelasma	Tuberous xanthoma	Cardiac risk
Type I. Hyperchylomicronemia (LPL deficiency)	LPL deficiency resulting in chylomicron accumulation	$\uparrow\uparrow$ TGL			✓	✓		-
Type IIa. Familial hypercholesterolemia	LDL receptor defect	\uparrow TC (LDL) +/- \uparrow TG +/- \uparrow apoB	✓			✓	✓	++
Type IIb. Familial combined hyperlipidemia	\uparrow hepatic production of VLDL	\uparrow apoB +/- \uparrow TG +/- \uparrow TC (LDL)				✓	(sometimes)	+
Type III. Dysbetalipoproteinemia	ApoE Δ (apoE2/E2); \uparrow clearance of chylomicron and VLDL remnants	\uparrow TGL \uparrow TC (VLDL, IDL)	(sometimes)	✓		✓	✓	+ (and PVD)
Type IV. Hypertriglyceridemia	\uparrow hepatic production of VLDL	\uparrow TC (VLDL) \uparrow TGL \downarrow HDL			✓	✓		+
Type V. Mixed hypertriglyceridemia	\uparrow production and \downarrow clearance of VLDL and chylomicrons	\uparrow TGL \uparrow TC (VLDL)			✓	✓		-

Smoking Issues

See SMOKING ISSUES (p. 490)

Approach to ECG

2009 AHA/ACC/HRS Recommendations
Standardization/Interpretation ECGKligfield et al. *Circulation* 2007;115(10)Wagner et al. *Circulation* 2009;119(10)

TEN STEPS TO ECG

- ID**—name and age, date, technique (12 lead, calibration, paper speed)
- RATE**—normal 60–100 beats/min. 300/150/100/75/60/50 rule
- RHYTHM**—regular/irregular, wide/narrow complex, sinus, atrial, atrioventricular, ventricular
- AXIS**—deviation, rotation
- PR INTERVAL**—normal 120–200 ms; first, second, third degree AV block
- QRS INTERVAL**—normal 80–110 ms, intraventricular conduction delay 110–120 ms, RBBB, LBBB, LAFB, LPFB
- QT INTERVAL**—QT <50% of RR interval; normal QTc 390–480 ms (women), 390–460 ms (men)
- HYPERTROPHY/ENLARGEMENT**—RAE, LAE, RVH, LVH
- ISCHEMIA**—ST elevation/depression, T wave inversion
- INFARCTION**—Q waves
- SPECIAL CONDITIONS**

CHEST LEADS PLACEMENT

- V1**—4th intercostal space, right sternal border
V2—4th intercostal space, left sternal border
V3—halfway between V2 and V4
V4—5th intercostal space, left mid-clavicular line
V5—5th intercostal space, left anterior axillary line
V6—5th intercostal space, left mid-axillary line

RATE AND RHYTHM

SINUS—P before QRS, QRS after P, P upright I + II, P down aVR. Normal (rate 60–100), tachycardia (rate >100), bradycardia (rate <60), arrhythmia (variable)

ATRIAL—rate 60–80 normally, variable P wave, short PR interval

JUNCTIONAL (mid and distal region of AV node)—rate 40–60, no P wave or inverted P wave

VENTRICULAR (His bundle, bundle branches, ventricle)—rate 20–40, no P wave

TACHYCARDIA

REGULAR NARROW COMPLEX TACHYCARDIA—sinus tachycardia, atrial flutter with fixed block, supraventricular tachycardia (atrial tachycardia, AV nodal reentry, orthodromic AVRT [WPW], accelerated junctional tachycardia)

IRREGULAR NARROW COMPLEX TACHYCARDIA—sinus tachycardia/arrhythmia, premature atrial contractions, multifocal atrial tachycardia, ectopic atrial tachyarrhythmia with variable block, atrial flutter with variable block, atrial fibrillation

REGULAR WIDE COMPLEX TACHYCARDIA—ventricular tachycardia, supraventricular tachycardia with aberrant conduction, pacemaker-mediated tachyarrhythmia, antidromic AVRT (WPW), metabolic abnormality (e.g. TCA overdose, hyperkalemia), artifact

IRREGULAR WIDE COMPLEX TACHYCARDIA—monomorphic ventricular tachycardia (during “warm-up phenomenon”), polymorphic ventricular tachycardia, atrial fibrillation with pre-excitation (WPW), irregular supraventricular tachycardia with aberrant conduction, coarse ventricular fibrillation, artifact

DISTINGUISHING FEATURES SUGGESTIVE OF VT RATHER THAN SVT WITH ABERRANT CONDUCTION—older age, history of coronary artery disease (>90% pre-test probability), history of structural heart disease (>90% pre-test probability), AV dissociation (dissociated P waves, fusion beats, capture beats), atypical bundle branch block morphology, concordance of precordial leads, QRS width >160 ms in LBBB or >140 ms in RBBB, extreme LAD (−90° to −180°). Hemodynamic stability (or instability) is not a useful distinguishing feature

BRADYCARDIA AND PROLONGED PR

SINUS—sinus bradycardia, sick sinus syndrome/sinus node dysfunction, sinus exit block, tachycardia-bradycardia syndrome (SSS + AF usually)

AV BLOCK—prolonged PR interval

- FIRST DEGREE**—PR >200 ms constantly
- SECOND DEGREE**

BRADYCARDIA AND PROLONGED PR (CONT'D)

- **MOBITZ TYPE I** (Wenckebach)—PR progressively longer and then dropped QRS
- **MOBITZ TYPE II**—PR constant and then suddenly dropped QRS. When any but not all ventricular beats are dropped, second degree block exists
- **THIRD DEGREE**—complete blockage with independent atrial and escape rhythms (junctional or ventricular escape)

PROLONGED QRS—BUNDLE BRANCH BLOCK AND HEMIBLOCK

ANATOMY—SA node (RCA 59%, LAD 38%, both 3%) → AV node (RCA 90%, LCX 10%) → bundle of His (RCA) → right bundle (LAD), left anterior fascicle (LAD, RCA), and left posterior fascicle (RCA, LAD)

RBBB—QRS ≥ 120 ms, slurred S wave in I and V6 and rSR' in V1–3 with R' taller than r. May also see QR' complex in V1 (suggestive of old or new infarct). QRS polarity positive in V1–2. Causes include LAD involvement/anterior infarction, may be benign in young people

LBBB—QRS ≥ 120 ms, broad notched or slurred R in I, aVL, V5, and V6, with no Q waves; broad monomorphic S in V1, may have small r wave. QRS polarity negative in V1–2. Causes include hypertension, CAD, dilated cardiomyopathy, rheumatic heart disease, infiltrative diseases, benign or idiopathic

LEFT ANTERIOR FASCICULAR BLOCK—QRS < 120 ms, left axis deviation –45° to –90°, qR in aVL, R-peak time in aVL of 45 ms or more. May be benign, LAD involvement/anterior infarction. Shortcut to diagnosis—I up, II down, aVF down

LEFT POSTERIOR FASCICULAR BLOCK—right axis deviation 90–180°, QRS < 120 ms, rS in I and aVL, and qR in III and aVF

PROLONGED QT

NORMAL—QTc = square root (QT in seconds/RR interval in seconds); QT < 50% of RR interval; normal QTc 390–480 ms (women), 390–460 ms (men)

CAUSES—**genetic**, **metabolic** (hypokalemia, hypomagnesemia, hypocalcemia), **antiarrhythmics** (quinidine, procainamide, amiodarone, sotalol), **antibiotics** (macrolide, trimethoprim-sulfamethoxazole, fluoroquinolone), **psychotropics** (TCA, SSRI, haloperidol, risperidone), **analgesics** (methadone), **structural heart disease** (HF, LVH, acute ischemia), **others** (HIV, anorexia nervosa, stroke, brain injury)

PROGRESSION—may result in torsades de pointes, VT, and sudden death (amiodarone less likely)

PROLONGED QT (CONT'D)

TREATMENTS—remove offending agent(s), overdrive pacing, isoproterenol infusion, magnesium

HYPERTROPHY CRITERIA

RAE—tall peaked P in II and aVF (>2.5 mm high); large initial component of biphasic P in V1 (p pulmonale)

LAE—wide notched P in II (>2.5 mm long); biphasic P in V1 with broad negative phase; (p mitrale)

LVH—tall R in aVL (>11 mm); R in V5 or V6 (whichever is taller) plus S in V1 >35 mm (Sokolow-Lyon criteria); R in V5 or R in V6 > 27 mm; poor R wave progression in precordial leads; ST depression and T wave inversion in lateral leads (I, aVL, V5–6) suggestive of ventricular strain; R in aVL plus S in V3 >28 mm in male or >20 mm in female (Cornell criteria). Diagnosis difficult with LBBB, consider LVH if S in V1 + R in V5 >45 mm (Klein criteria)

RVH—right axis deviation (>110°); R > S wave in V1 and R > 7 mm; persistent S waves V5–6; ST depression and T wave inversion V1–3

DIFFERENTIAL DIAGNOSIS FOR DOMINANT R WAVE IN V1—RV hypertrophy, right bundle branch block, posterior myocardial infarction, pre-excitation (Wolff-Parkinson-White), dextrocardia, Duchenne muscular dystrophy, hypertrophic cardiomyopathy, normal variant, incorrect lead placement, juvenile pattern

ISCHEMIA/INFARCT MORPHOLOGY

HYPERACUTE T WAVES—starts in seconds

ST ELEVATION—transmural injury, starts in minutes

ST DEPRESSION—subendocardial infarction. Consider posterior infarct if in V1/V2

T WAVE INVERSION—starts in hours, stays for weeks, and flips back in months

Q WAVES—starts in 8 h. If no reperfusion, stays forever. Considered significant if >1 block wide and height >1/3 of QRS

ACCELERATED IDIOVENTRICULAR RHYTHM—suggests reperfusion post-infarction (HR < 100, intermittent)

VOLTAGE CRITERIA

NORMAL—QRS >5 mm high in limb leads, QRS >10 mm high in precordial leads

LOW—thick chest wall, COPD, pericarditis, pleural effusion, amyloidosis, myxedema, hemochromatosis

DIFFERENTIAL DIAGNOSIS OF ST ELEVATION

NORMAL MALE PATTERN—1–3 mm elevation, concave, most marked in V2

ST ELEVATION OF NORMAL VARIANT—seen in V4–5, short QT, high QRS voltage

BENIGN EARLY REPOLARIZATION—most marked in V4 with notching at J point, upright T waves. Reciprocal ST depression in aVR, not in aVL, when limb leads are involved

ACUTE MI—ST segment with a plateau of shoulder or upsloping, reciprocal changes can be seen in opposite leads

PRINZMETAL ANGINA—same as MI but transient

ACUTE PERICARDITIS—diffuse ST elevation, ST depression in aVR. Elevation seldom >5 mm, PR segment depression (best seen in II)

ACUTE MYOCARDITIS—diffuse ST elevation, may simulate acute MI/pericarditis

AORTIC DISSECTION—obstruction of right coronary artery by dissection flap

LV ANEURYSM—persistent ST elevation after MI

DIFFERENTIAL DIAGNOSIS OF ST ELEVATION (CONT'D)

PULMONARY EMBOLISM—changes simulating MI seen often in both inferior and anteroseptal leads

STRESS (TAKOTSUBO) CARDIOMYOPATHY—transient apical and/or mid LV systolic dysfunction that mimics myocardial infarction, in the absence of obstructive CAD

LBBB—concave, ST segment deviation discordant from QRS. In the presence of LBBB, features suggestive of infarction include concordant ST segment changes (ST elevation ≥ 1 mm in leads with positive QRS complex and ST depression ≥ 1 mm in V1–3), discordant ST-segment changes (ST elevation ≥ 5 mm in leads with negative QRS complex) (Sgarbossa criteria)

LVH—concave, other features of LVH

HYPERKALEMIA—see below

HYPOTHERMIA—Osborne waves may be seen
Wang et al. *NEJM* 2003;349(22)

INFARCTION ZONES

Territory	Leads	Artery	Comment
Inferior	II, III, aVF ^a	RCA, LCX ^b	RV, SA, AV nodes
Lateral	I, aVL, V5, V6	LCX, RCA	
Posterior	V1i, V2i, V8, V9 ^c	RCA	
Anterior	V1–V4 ^d	LAD	May be massive LV
RV	R leads (V1), V4R	RCA	Preload

^aEvidence of inferior MI should trigger one to automatically check V4R for RV infarction, which occurs in up to 40% of patients with inferior MI. May see increased JVP and clear lung fields clinically. ST elevation in V4R is diagnostic and prognostic

^bInferior infarcts may be related to either RCA (ST elevation in III > II and ST depression in I, aVL, or both >1 mm) or LCX (ST elevation in I, aVL, V5–6 and ST depression in V1–3)

^ci = inverted. ST depression in V1–V2 in a regular ECG should trigger one to automatically request for posterior leads to check for posterior MI. Posterior infarct may be associated with inferior and lateral infarct as these territories are all supplied by RCA

^dV1–V2 = septal, V3–V4 = anterior

SPECIAL CONDITIONS

HYPERTHYROIDISM—tachycardia, non-specific ST-T changes, biphasic T in V2–V6

DIGITALIS EFFECT—slowing SA, AV. Gradual downward sloping/scooping of ST. ST depression in I, II, aVF, V2–V6

DIGITALIS TOXICITY—unifocal or multifocal PVCs, first degree heart block, ventricular bigeminy, paroxysmal atrial tachycardia (often with 2:1 AV conduction), bidirectional VT, atrial

SPECIAL CONDITIONS (CONT'D)

fibrillation with complete heart block (regular escape rhythm)

HYPERKALEMIA—tall, peaked T wave (especially precordial leads. Definitions of “tall T wave” include a height >5 mm in limb lead or 10 mm in precordial lead or a T wave height >50% of the entire QRS excursion in same lead), widened QRS, wide and flat P wave

SPECIAL CONDITIONS (CONT'D)

HYPOKALEMIA—flattened T wave/inversion, U wave

COPD—RAD, ↓ amplitude, multifocal atrial tachycardia

HYPERCALCEMIA—short QT

HYPOCALCEMIA—prolonged QT

WOLFF-PARKINSON-WHITE SYNDROME—short PR (<120 ms), delta wave, prolonged QRS (>120 ms), symptomatic tachycardia. Pharmacological treatments include amiodarone and procainamide. **AV nodal blocking drugs**

SPECIAL CONDITIONS (CONT'D)

(adenosine, β -blockers, verapamil/diltiazem, digoxin) are contraindicated in patients with WPW and AF as they may precipitate VF. Consider catheter ablation if symptomatic arrhythmias, AF, or atrial flutter. If failed, consider surgical ablation

BRUGADA SYNDROME—type 1: high take-off and cove-shaped ST-segment elevation (≥ 2 mm) in V1–V2. Type 2: saddle-back ST-T pattern in V1–V2



Acute Renal Failure: Pre-renal

DIFFERENTIAL DIAGNOSIS

TRUE INTRAVASCULAR FLUID LOSS

- HEMORRHAGE
- GI LOSS—diarrhea, vomiting
- RENAL LOSS—diuretic, osmotic
- SKIN LOSS—increased insensible losses, sweating, burns

DECREASED EFFECTIVE CIRCULATING FLUID

- HEART FAILURE
- HYPOALBUMINEMIA—protein-losing enteropathy, nephrotic, cirrhosis, malnutrition
- THIRD SPACING
- SEPSIS

ALTERED RENAL HEMODYNAMICS

- AFFERENT—renal artery stenosis (RAS), fibromuscular dysplasia, ASA, NSAIDs, cyclosporin, tacrolimus, cocaine, hypercalcemia (vasospasm)
- EFFERENT—ACE inhibitors, ARB, renal vein thrombosis

PATHOPHYSIOLOGY

RISK FACTORS—patients with advanced age, hypertension, chronic kidney disease, renal artery stenosis, or on medications (NSAIDs, ACE inhibitors, ARBs) are particularly susceptible to ischemic insults due to impaired auto-regulation

Related Topic

Renal Artery Stenosis (p. 74)

INVESTIGATIONS

BASIC

- LABS—CBC, lytes, urea, Cr, Ca, urinalysis, urine lytes, urine Cr
- MICROBIOLOGY—blood C&S, urine C&S

INVESTIGATIONS (CONT'D)

SPECIAL

- RENAL ARTERY STENOSIS WORKUP—renal Doppler, CT/MR renal angiogram (use with caution in renal failure), captopril renogram (used less frequently due to lower sensitivity and specificity)

DIAGNOSTIC ISSUES

CHRONIC KIDNEY DISEASE EPIDEMIOLOGY COLLABORATION (CKD-EPI)

- ESTIMATED GFR = $141 \times \min(\text{serum creatinine in mg/dL} / \text{kappa}, 1)^{\text{alpha}} \times \max(\text{serum creatinine in mg/dL} / \text{kappa}, 1)^{-1.209} \times 0.993^{\text{age}} \times \text{sex} \times \text{race}$
- For males, sex=1, alpha=-0.411, kappa=0.7; for females, sex=1.018, alpha=-0.329, kappa=0.7. Race=1.159 if patient is Black
- NOTE—only valid in steady state creatinine and not valid for extremes of weight

COCKCROFT-GAULT FORMULA (less often used nowadays)

- CREATININE CLEARANCE (SI UNITS)— $\text{CrCl} = (140 - \text{age}) \times (\text{weight in kg}) / (\text{Cr in } \mu\text{mol/L})$, multiply by 1.2 if male
- CREATININE CLEARANCE (US UNITS)— $\text{CrCl} = (140 - \text{age}) \times (\text{weight in lbs} \times 0.37) / (\text{Cr in mg/dL} \times 88.4)$, multiply by 1.2 if male
- NOTE—creatinine is used to estimate GFR, but 5% of creatinine is secreted and thus overestimates GFR. At low GFR, proportion of creatinine secreted becomes higher, so overestimates even more

FEATURES SUGGESTING PRE-RENAL CAUSES

- UREA:CR RATIO—(urea in mmol/L $\times 10$) > Cr in $\mu\text{mol/L}$ (or in US units: [urea in mg/dL/20] > Cr in mg/dL). Urea reabsorption increases during pre-renal failure, resulting in a disproportionately high serum urea level
- 10–20–30 RULE—urine $\text{Na}^+ 30 \text{ mmol/L}$
- FeNA— $(U_{\text{Na}}/P_{\text{Na}})/(U_{\text{Cr}}/P_{\text{Cr}}) \times 100\%$, <1%

DIAGNOSTIC ISSUES (CONT'D)

- **URINALYSIS**—bland, high specific gravity

DISTINGUISHING FEATURES BETWEEN PRE-RENAL FAILURE AND ATN

	Pre-renal	ATN
Urea:Cr ratio (SI)	Urea \times 10) $>$ Cr	(Urea \times 20) $<$ Cr
Urea:Cr ratio (US)	Urea $>$ (Cr \times 20)	Urea $<$ (Cr \times 10)
Increase in Cr	Variable	$<$ 44 μ mol/L/day [$<$ 0.5 mg/dL/day]
Urinalysis	Normal	Heme granular casts
Urine Na	$<$ 20 mmol/L	$>$ 30 mmol/L
FE _{Na}	$<$ 1%	$>$ 2%
Urine osmo	$>$ 500 mOsm/kg	$<$ 350 mOsm/kg

MANAGEMENT

TREAT UNDERLYING CAUSE—fluid resuscitation (consider 0.5–1 L IV bolus over 2–4 h, then 100–200 mL/h with frequent volume reassessments; buffered crystalloid should be used preferentially if there are no contraindications since this has been shown to reduce AKI risk)

RENAL REPLACEMENT—dialysis (peritoneal, hemodialysis). If needed, usually temporary

TREATMENT ISSUES**ACUTE INDICATIONS FOR DIALYSIS****★AEIOU★**

- **ACIDOSIS**—persistent despite medical treatment
- **ELECTROLYTES**—persistent severe hyperkalemia despite medical treatment
- **INTOXICATION**—ASA, Li, methanol, ethylene glycol, or other dialyzable toxins
- **OVERLOAD**—persistent fluid overload despite medical treatment
- **UREMIA**—pericarditis, encephalopathy

Acute Renal Failure: Renal**DIFFERENTIAL DIAGNOSIS****VASCULAR**

- **EMBOLI**—atherothrombotic, cholesterol
- **MICROANGIOPATHIC HEMOLYTIC ANEMIA**—TTP, HUS, scleroderma, malignant hypertension
- **VASCULITIS**—PAN, Takayasu syndrome
- **HYPERTENSION**—hypertensive emergency

TUBULAR

- **ACUTE TUBULAR NECROSIS (ATN)**—ischemia, sepsis, contrast dye, aminoglycosides, amphotericin, acyclovir, myoglobin, hemoglobin, uric acid
- **INTRA-TUBULAR OBSTRUCTION**—uric acid, indinavir, calcium oxalate, acyclovir, methotrexate, light chains (myeloma)

INTERSTITIAL (ACUTE INTERSTITIAL NEPHRITIS, AIN)

- **IATROGENIC**—proton pump inhibitors, penicillins, cephalosporins, sulfonamides, rifampin, NSAIDs, diuretics
- **INFECTIONS**—pyelonephritis
- **INFILTRATE**—Sjögren syndrome, sarcoidosis
- **IDIOPATHIC**

DIFFERENTIAL DIAGNOSIS (CONT'D)**GLOMERULAR**

- **NEPHROTIC**—MCD, MGN, FSGS, MPGN (rarely if ever cause acute renal failure on their own)
- **NEPHRITIC**—IgA, MPGN, mesangial proliferative GN, RPGN
 - **ANTI-GBM ANTIBODY**—Goodpasture syndrome, anti-GBM antibody nephritis
 - **IMMUNE COMPLEX**—SLE, HBV, HCV, endocarditis, post-strep/infectious GN, IgA, cryoglobulinemia, shunt nephritis
 - **PAUCI-IMMUNE**—granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyarteritis (MPA)

CLINICAL FEATURES

HISTORY—duration (previous Cr), N&V, diarrhea, blood loss, obstructive urinary symptoms (frequency, urgency, hesitancy, slow stream, incontinence), hemoptysis, hematuria, edema, contrast dye, nephrotoxins, past medical history

CLINICAL FEATURES (CONT'D)

(recent infections, HBV, HCV, HF, diabetes, hypertension, malignancy, connective tissue disease), medications (ACE inhibitors, ARB, NSAIDs, ASA, cyclosporine, penicillins, cephalosporins, acyclovir, amphotericin, chemotherapy)

PHYSICAL—orthostatic vitals especially heart rate and blood pressure, respiratory and cardiac examination (JVP, heart failure), abdominal examination (masses, renal bruit), ankle edema, cholesterol emboli

Related Topic

Glomerulonephritis (p. 87)

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, urinalysis, urine lytes, urine Cr
- **ETIOLOGY WORKUP**—ANA, anti-dsDNA, ENA, p-anca, c-anca, anti-GBM antibody, C3, C4, CK, uric acid, ASO-titer, HBV/HCV serology, RF, cryoglobulin, quantitative Ig, serum protein electrophoresis, urinary protein electrophoresis, urinary eosinophil (of questionable clinical value because it is neither sensitive nor specific for AIN)
- **MICROBIOLOGY**—blood C&S, urine C&S if suspect infection
- **IMAGING**—US renal

SPECIAL

- **IMAGING**—CXR, echocardiogram
- **SPECIAL**—renal biopsy

INVESTIGATION ISSUES

DISTINGUISHING FEATURES BETWEEN VARIOUS RENAL ETIOLOGIES

	Urinalysis findings	Further tests
Vascular	Bland Urinary eosinophils (cholesterol emboli)	Peripheral smear (TTP) Anti-MPO (p-ANCA) ANA (lupus), ENA
Tubular	Muddy brown casts (ATN)	CK (rhabdomyolysis) Uric acid (gout)
Interstitial	WBC casts, urinary eosinophil	Systemic eosinophilia

INVESTIGATION ISSUES (CONT'D)

	Urinalysis findings	Further tests
Glomerular	RBC casts Acanthocyte (dysmorphic RBC) Oval fat body Fatty cast	Anti-PR3 (c-ANCA) Anti-MPO (p-ANCA) Eosinophilia (EGPA, AIN) Anti-GBM (Goodpasture syndrome) ANA, anti-dsDNA (SLE) ASO titer (PSGN) Blood C&S, echo (infectious endocarditis) HBV/HCV serology, SPE, UPE (multiple myeloma) Cryoglobulins, rheumatoid factor (cryoglobulinemia)

MANAGEMENT

PREVENTION—avoid contrast dye, nephrotoxins if possible

TREAT UNDERLYING CAUSE—nephrotic syndrome (low-salt diet and furosemide for volume regulation if needed; statin if needed to correct hyperlipidemia)

RENAL REPLACEMENT—dialysis (peritoneal, hemodialysis)

SPECIFIC ENTITIES

PSEUDO-RENAL FAILURE—cimetidine and trimethoprim may reduce tubular secretion of creatinine causing a small but significant increase in serum creatinine in the absence of ↓ GFR

MULTIPLE MYELOMA AND RENAL FAILURE

- **PRE-RENAL**—N&V, renal vein thrombosis, calcium-induced vasospasm, nephrogenic diabetes insipidus (secondary to hypercalcemia)
- **RENAL**—secondary amyloidosis (λ), light chain cast nephropathy (myeloma kidney), monoclonal immunoglobulin deposition disease (MIDD) including light chain deposition disease (κ) and heavy chain deposition disease, plasma cell infiltration, cryoglobulinemia, pyelonephritis, sepsis
- **POST-RENAL**—renal stones (hypercalcemia), neurogenic bladder

SPECIFIC ENTITIES (CONT'D)**NSAID-INDUCED RENAL FAILURE**

- **PRE-RENAL**—inhibition of prostaglandin synthesis leading to afferent vasoconstriction, hypertensive nephropathy
- **RENAL**—acute interstitial nephritis, nephrotic syndrome (minimal change disease, membranous)

ACUTE TUBULAR NECROSIS (ATN)

- **PATHOPHYSIOLOGY**—tubular damage from either ischemia or toxins → decreased reabsorption of Na → vasoconstriction → decreased GFR. Also may be related to tubular blockage from damaged epithelial cells. Risk factors include elderly (GFR ↓ by 1 mL/min/year after age 40), pre-existing renal dysfunction, decreased cardiac function, diabetes, dehydration, and multiple nephrotoxins
- **TREATMENTS**—after the insults are stopped, may start to recover in 3–5 days. Generally takes 7–21 days (some up to 8 weeks) for full recovery

CONTRAST NEPHROPATHY

- **PATHOPHYSIOLOGY**—contrast-induced vasospasm, hyperosmolar load, oxygen free radical generation or direct tubular toxicity → acute

SPECIFIC ENTITIES (CONT'D)

tubular injury → ↑ Cr or ↓ GFR by 25%. Usually develops immediately after exposure to contrast, peaks in 48–72 h. Risk factors and recovery time course same as ATN. Key differential diagnosis is renal atheroemboli after arterial catheterization (usually delayed onset of renal failure and may see other signs of arterial ischemia)

- **RISK FACTORS**—patient risk factors (pre-existent renal failure, multiple myeloma, diabetes mellitus, hypertension, volume contraction [diuretics], HF, exposure to nephrotoxins such as NSAIDs or aminoglycosides, recent acute coronary syndrome), procedural risk factors (increased dye load, increased osmolar dye load)
- **PREVENTION**—avoid contrast dye, nephrotoxins/diuretics, and volume depletion if possible. If contrast absolutely required, use low (iohexol) or iso-osmolar (iodixanol) non-ionic agents. Hydration options include (1) IV 1/2 NS at 1 mL/kg/h starting 12 h before until 12 h after contrast exposure; (2) IV NS 154 mmol/L at 3 mL/kg/h starting 1 h before until 6 h after contrast exposure (note: NS and NaHCO₃ are felt to be equivalent)

Acute Renal Failure: Post-renal**DIFFERENTIAL DIAGNOSIS**

URETHRA—stricture, stenosis

PROSTATE—BPH, prostatitis, cancer

BLADDER—cancer, stones, clots, neurogenic

URETERS (esp. bilateral involvement)

- **INTRALUMINAL**—cancer, stones, clots, papillary necrosis
- **EXTRALUMINAL**—cancer, retroperitoneal fibrosis, pregnancy

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, Cr/urea, urinalysis
- **IMAGING**—US abd/pelvis

SPECIAL

- **POST-RESIDUAL VOLUME**—>200 mL suggests obstruction

INVESTIGATIONS (CONT'D)

- **CT ABD/KUB/IVP**—if suspect stones or tumors
- **DIURESIS RENOGRAPHY OR UROGRAPHY**

DIAGNOSTIC ISSUES

RENAL US—hydronephrosis suggests post-renal causes. However, retroperitoneal fibrosis and acute post-renal obstruction may not show hydronephrosis

MANAGEMENT

TREAT UNDERLYING CAUSE—Foley catheter. For BPH (*tamsulosin* 0.4 mg PO daily or TURP)

RENAL REPLACEMENT—**dialysis** (peritoneal, hemodialysis)

Glomerulopathies

PATHOPHYSIOLOGY OF GLOMERULOPATHIES

AUTOIMMUNE PHENOMENON—antibodies binding to structural components of glomeruli (more glomerular basement membrane and podocytes involvement in nephrotic syndrome, more mesangium and endothelium involvement in nephritic syndrome), circulating antigen–antibody complexes, and/or cell-mediated immunity → further immune activation and damage to glomeruli

PATHOLOGY TERMS—**focal** = 50% of glomeruli, **segmental** = segment of glomerulus, **global** = entire glomerulus

CLINICAL FEATURES

CLINICAL MANIFESTATIONS OF GLOMERULAR DISEASES

Clinical

manifestation	Examples
Asymptomatic proteinuria	FSGS, mesangial proliferative GN, diabetic nephropathy
Nephrotic syndrome	MCD, FSGS, MGN, MPGN, amyloidosis, light chain deposition disease, diabetic nephropathy
Asymptomatic hematuria	Thin basement membrane disease, IgA nephropathy, Alport syndrome
Recurrent gross hematuria	Thin basement membrane disease, IgA nephropathy, Alport syndrome
Acute nephritis	Post-infectious GN, IgA nephropathy, lupus nephritis, MPGN
Rapidly progressive glomerular nephritis (RPGN)	See text
Pulmonary-renal syndrome	Antiglomerular basement membrane antibody disease, immune complex vasculitis, pauci-immune (ANCA) vasculitis
Chronic renal failure	Sclerosed glomerular disease

CLINICAL FEATURES (CONT'D)

DISTINGUISHING FEATURES BETWEEN NEPHROTIC AND NEPHRITIC SYNDROMES

	Nephrotic	Nephritic
Onset	Slower	Faster
Edema	++++	++
Blood pressure	N/↓/↑	↑
Volume/ JVP	N/↓/↑	↑
Proteinuria	>3 g/day	May be <3 g/day
Hematuria	May occur	+++
Urine sediment	Hyaline casts, lipid droplets (oval fat body)	Dysmorphic RBC, WBC, RBC casts, granular casts
Albumin	↓↓↓	N/mild ↓
Creatinine	N/↑	Usually ↑
Serum Na	May be ↓↓	N/mild ↓

NOTE—nephrotic syndrome ≠ nephritic range proteinuria, which is defined as proteinuria >3 g/day without other symptoms and signs

NEPHROTIC SYNDROME

DIFFERENTIAL DIAGNOSIS—minimal change disease, membranous GN, focal segmental glomerulosclerosis, MPGN, diabetes, amyloidosis, IgA nephropathy, HIV, drug-associated (NSAIDs, gold, pamidronate)

CLINICAL FEATURES—proteinuria (>3 g/day), edema, hypoalbuminemia, hyperlipidemia, lipi-duria, hypercoagulability

INVESTIGATIONS—CBC, lytes, urea, Cr, 24-h urine for protein and Cr, spot urine protein/Cr ratio, albumin/Cr ratio, renal biopsy (simplification/effacement of visceral podocyte foot processes, classically non-inflammatory), lipid profile

POOR PROGNOSTIC FACTORS—male, age >50, ↑ creatinine, proteinuria >10 g/day, proteinuria >6 months, hypertension

TREATMENTS—Na restriction, blood pressure control, ACE inhibitor/ARB, treatment of dyslipidemia, treatment of underlying glomerular disease, anticoagulate if high risk

COMPLICATIONS—AKI/hypovolemia, malnutrition, hyperlipidemia, infections (especially encapsulated bacteria), arterial/venous thrombosis (30–40%), renal vein thrombosis, edema

NEPHRITIC SYNDROME

DIFFERENTIAL DIAGNOSIS—MPGN, rapidly progressive/crescentic GN (anti-GBM, immune, pauci-immune), IgA nephropathy

CLINICAL FEATURES—hematuria, proteinuria, hypertension, azotemia

INVESTIGATIONS—CBC, lytes, urea, Cr, ANA, anti-dsDNA, ENA, anti-MPO (p-anca), anti-PR3 (c-anca), anti-GBM, C3, C4 (complements low except for IgA nephropathy), CK, uric acid, ASO titer, HBV serology, HCV serology, cryoglobulin, quantitative Ig, serum protein electrophoresis, renal biopsy

TREATMENTS—steroid, cyclophosphamide, mycophenolate mofetil, rituximab

SPECIFIC ENTITIES**MINIMAL CHANGE DISEASE (MCD)**

- **PATHOPHYSIOLOGY**—T-cell abnormality → ↑ glomerular permeability
- **CAUSES**—primary, secondary (NSAIDs, Li, interferon, NHL, Hodgkin lymphoma, leukemia, HIV, mononucleosis)
- **CLINICAL FEATURES**—pure nephrotic (minimal hematuria, no RBC casts, creatinine not elevated)
- **PATHOLOGY**—light microscopy (normal), immunofluorescence (no immune complexes), electron microscopy (effacement of podocyte foot processes)
- **TREATMENTS**—steroid, cyclophosphamide, cyclosporine
- **PROGNOSIS**—90% steroid responsive, 10% steroid resistant, end-stage renal disease rare

MEMBRANOUS GN (MGN)

- **CAUSES**—primary, secondary (gold, penicillamine, captopril, solid tumors [breast, colon, and lung], Hodgkin lymphoma, SLE, rheumatoid arthritis, autoimmune thyroiditis, syphilis, HBV, HCV, chronic transplant rejection)
- **CLINICAL FEATURES**—pure nephrotic (minimal hematuria, no RBC casts)
- **PATHOLOGY**—light microscopy (basement membrane thickening, spikes), immunofluorescence (immune complexes IgG, and complements in subepithelial space), electron microscopy (same as immunofluorescence)
- **TREATMENTS**—steroid, cyclophosphamide, cyclosporine or tacrolimus, rituximab

SPECIFIC ENTITIES (CONT'D)

- **PROGNOSIS**—40% remission, 30% stable, 30% end-stage renal disease over 10–20 years

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

- **CAUSES**—primary, secondary (Li, heroin, lymphomas, HIV. May also be associated with sickle cell disease, hypertension, and obesity)
- **CLINICAL FEATURES**—pure nephrotic (minimal hematuria, no RBC casts)
- **PATHOLOGY**—light microscopy (segmental areas of sclerosis), immunofluorescence (no immune complexes), electron microscopy (effacement of podocyte foot processes)
- **TREATMENTS**—steroid, cyclosporine or tacrolimus, mycophenolate mofetil, rituximab
- **PROGNOSIS**—large percentage with end-stage renal disease over 15–20 years

MEMBRANOPROLIFERATIVE GN (MPGN)

- **PATHOPHYSIOLOGY**—(1) immune complex-mediated due to the deposition of immunoglobulins in the kidney and subsequent complement activation, or (2) complement-mediated (known as C3GN) due to either hereditary or acquired abnormalities of the complement system such as C3 nephritic factor and individual complement gene mutations
- **CAUSES**—primary, secondary (HCV, HBV, endocarditis, abscess, infected shunts, CLL, lymphomas, SLE, cryoglobulinemia, partial lipodystrophy, sickle cell, complement deficiency, complement system abnormalities [hereditary or acquired])
- **CLINICAL FEATURES**—50% nephrotic, 20% asymptomatic proteinuria/hematuria, 30% acute nephritic
- **PATHOLOGY**—light microscopy (basement membrane thickening, mesangial cell hypercellularity), immunofluorescence (complements along capillary walls), electron microscopy, immune complex mediated will have staining of immunoglobulins and complement, complement mediated will have staining of complement with minimal or no immunoglobulins.
- **TREATMENTS**—steroid, mycophenolate mofetil, cyclophosphamide, cyclosporine, complement system inhibitors (e.g. eculizumab for C3GN)
- **PROGNOSIS**—40–75% end-stage renal disease over 10–15 years

SPECIFIC ENTITIES (CONT'D)**RAPIDLY PROGRESSIVE GN (RPGN)—ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY DISEASE**

- **PATHOPHYSIOLOGY**—antibody against $\alpha 3$ chain of type IV collagen
- **CAUSES**—Goodpasture syndrome, anti-GBM antibody nephritis
- **CLINICAL FEATURES**—nephritic (hematuria, proteinuria, AKI). Goodpasture syndrome also has lung involvement whereas anti-GBM antibody nephritis affects kidney alone
- **PATHOLOGY**—immunofluorescence (linear staining)
- **TREATMENTS**—plasmapheresis with IV pulse steroids followed by PO steroids with PO cyclophosphamide

RAPIDLY PROGRESSIVE GN (RPGN)—IMMUNE COMPLEX

- **PATHOPHYSIOLOGY**—deposition of circulating immune complex in glomeruli, usually in sub-endothelial location
- **CAUSES**—SLE, HBV, HCV, endocarditis, post-strep GN, post-infectious GN, IgA nephropathy, cryoglobulinemia, shunt nephritis
- **CLINICAL FEATURES**—nephritic (hematuria, proteinuria, AKI)
- **PATHOLOGY**—immunofluorescence (granular staining)
- **TREATMENTS**—treat any underlying conditions if present (e.g. infections). Specific treatment of primary diseases will depend on the underlying glomerular disease. Treatments may include IV pulse steroids followed by PO steroids with IV/PO cyclophosphamide, rituximab

RAPIDLY PROGRESSIVE GN (RPGN)—PAUCI-IMMUNE COMPLEX

- **CAUSES**—granulomatosis with polyangiitis (anti-PR3 [c-anca]), microscopic polyangiitis (anti-MPO [p-anca]), eosinophilic granulomatosis with polyangiitis (EGPA)
- **CLINICAL FEATURES**—nephritic (hematuria, proteinuria, AKI). May have lung involvement

SPECIFIC ENTITIES (CONT'D)

- **PATHOLOGY**—immunofluorescence (no staining)
- **TREATMENTS**—IV pulse steroids followed by PO steroids with PO cyclophosphamide, rituximab

IGA NEPHROPATHY

- **PATHOPHYSIOLOGY**—abnormal regulation of production or structure of IgA in response to environmental antigens → illness triggers production of IgA and/or IgA immune complex → deposit in mesangium
- **CAUSES**—primary, secondary (IgA vasculitis, celiac disease, dermatitis herpetiformis, cirrhosis, HIV, malignancies, seronegative spondyloarthropathies)
- **CLINICAL FEATURES**—50% recurrent macroscopic hematuria with URTI, 30–40% persistent microhematuria and proteinuria, 10% rapidly progressive renal failure, <10% nephrotic syndrome
- **PATHOLOGY**—light microscopy (focal or diffuse mesangial hypercellularity and matrix expansion), immunofluorescence (extensive IgA deposition in mesangium and capillary walls), electron microscopy (mesangial deposits). Patients presenting with nephrotic syndrome may also have nephrotic histologic picture. Note: most of the time IgA nephropathy is a clinical diagnosis. No biopsy unless AKI or severe symptoms
- **TREATMENTS**—ACE inhibitors for greater than 300 mg/day of albumin. Steroids, cytotoxic agents for those not controlled by ACE inhibitors
- **PROGNOSIS**—20–40% end-stage renal disease over 20 years. Risk depends on amount of proteinuria

Related Topics

Acute Renal Failure (p. 83)

Chronic Kidney Disease (p. 89)

Chronic Kidney Disease**DIFFERENTIAL DIAGNOSIS**

CAUSES OF ACUTE RENAL FAILURE—pre-renal, renal, post-renal (see ACUTE RENAL FAILURE p. 83)

CHRONIC KIDNEY DISEASES

- **RENOVASCULAR DISEASE**—atherosclerosis, hypertensive nephropathy, glomerulosclerosis (with age)

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **DIABETES**—proteinuria
- **GLOMERULONEPHRITIS**
- **POLYCYSTIC KIDNEY DISEASE**
- **MULTIPLE MYELOMA**
- **NEPHROTOXINS**—NSAIDs

PATHOPHYSIOLOGY

DEFINITION OF CHRONIC KIDNEY DISEASE—>3 months of abnormal renal function, suggests irreversible component

STAGING OF CHRONIC KIDNEY DISEASE GLOMERULAR STAGE

- **STAGE GI** (GFR ≥ 90 mL/min/1.73 m², proteinuria)—observe, consider ACE inhibitor if albuminuria >30 mg/mmol or diabetes
- **STAGE GII** (GFR 60–89 mL/min/1.73 m²)—consider ACE inhibitor if albuminuria >30 mg/mmol or diabetes
- **STAGE GIIIa** (GFR 45–59 mL/min/1.73 m²)—consider statin if more than 50 years old or high risk (e.g. diabetes), see below for ACE indications
- **STAGE GIIIb** (GFR 30–44 mL/min/1.73 m²)—consider statin if more than 50 years old or high risk (e.g. diabetes), see below for ACE indications
- **STAGE GIV** (GFR 15–29 mL/min/1.73 m²)—consider statin if older than 50 years old or high risk of diabetes, see below for ACE indications
- **STAGE GV** (GFR <15 mL/min/1.73 m²)—dialysis (if indications for hemodialysis. Most do not start above GFR of 5–10 mL/min/1.73 m² although there is no strict GFR cutoff), transplantation, or palliation

ALBUMINURIA STAGE

- **STAGE AI** (albumin-to-creatinine ratio [ACR] <3 mg/mmol)
- **STAGE AII** (ACR 3–30 mg/mmol)—ACE inhibitor for diabetes, consider statin
- **STAGE AIII** (ACR >30 mg/mmol)—ACE inhibitor for all, SGLT2 inhibitor for diabetes, consider statin

RISK FACTORS FOR CHRONIC KIDNEY DISEASE DEVELOPMENT AND PROGRESSION—old age, hypertension, proteinuria (not just a surrogate marker), high-protein diet, dyslipidemia, smoking

CLINICAL FEATURES**SIGNS AND SYMPTOMS OF CHRONIC KIDNEY DISEASE**

- **VOLUME OVERLOAD**
- **ELECTROLYTE/ACID-BASE BALANCE**—hyperkalemia
- **METABOLIC ACIDOSIS**
- **NORMOCYTIC ANEMIA**
- **CALCIUM/PHOSPHATE BALANCE**—↓ 1,25(OH)₂ vitamin D₃ synthesis in kidney, ↑ PO₄ due to

CLINICAL FEATURES (CONT'D)

decreased filtration → ↓ Ca → ↑ PTH → chronic kidney disease—mineral bone disease (pathological descriptions include **osteitis fibrosa** with increased bone resorption from secondary hyperparathyroidism; **osteomalacia** with decreased bone resorption and unmineralized bone due to aluminum binder use [now uncommon]; **adynamic bone disease** with decreased bone resorption due to oversuppression of PTH; **mixed uremic osteodystrophy** either high or low bone turnover with abnormal mineralization)

• UREMIC SYMPTOMS

- **CONSTITUTIONAL**—fatigue, generalized weakness
- **NEUROLOGIC**—decreased memory and concentration, slow and slurred speech, myotonic jerks, seizures, altered smell and taste, peripheral neuropathy, sleep disturbances, restless leg syndrome
- **GASTROINTESTINAL**—anorexia, nausea and vomiting, gastritis
- **HEMATOLOGIC**—anemia, platelet dysfunction, and bleeding
- **MUSCULOSKELETAL**—bone disorders, arthropathy, muscle cramps
- **DERMATOLOGIC**—pruritus, uremic frost, sallow
- **SEXUAL**—amenorrhea, sexual dysfunction, infertility

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, HbA1C, Ca, PO₄, Mg, PTH, albumin, fasting lipid profile, urinalysis, 24-h urinary albumin collection, 24-h urinary protein collection

SPECIAL

- **MYELOMA WORKUP**—serum protein electrophoresis, urinary protein electrophoresis, consider serum free light chains

DIAGNOSTIC ISSUES

DISTINGUISHING FEATURES BETWEEN CHRONIC AND ACUTE KIDNEY INJURY—previous creatinine (>3 months of elevated creatinine suggests CKD), anemia, small kidneys from renal US (except diabetes, amyloidosis, acromegaly, renal vein thrombosis, HIV nephropathy), renal osteodystrophy consistent with CKD. Renal biopsy is also helpful

MANAGEMENT**SLOW PROGRESSION**

- **LIMIT PROTEIN INTAKE**—0.8–1 g/kg/day
- **ACE INHIBITION**—blood pressure and proteinuria control (*ramipril* 1.25–10 mg PO daily), renoprotective (see below) indicated for patients with diabetes or patients with chronic kidney disease with albuminuria greater than 300 mg/day or 500 mg/day or total proteinuria
- **LIPID CONTROL**
- **AVOID NEPHROTOXINS**
- **SMOKING CESSATION**
- **DIABETES MELLITUS**—SGLT2 inhibitors for patients with GFR >30 mL/min/1.73 m² and >300 mg/day of albuminuria (stage A3).
- **TREAT HYPERTENSION**—see Hypertension: Acute and Long-term Management (p. 70)

TREAT COMPLICATIONS

- **VOLUME OVERLOAD**—low-sodium diet, diuretics
- **HYPERKALEMIA** (K >5.5 mmol/L)—low-potassium diet, *hydrochlorothiazide* 12.5 mg PO daily (if GFR >30 mL/min/1.73 m²), *furosemide* 20 mg PO daily (if GFR less than 30 mL/min/1.73 m²), *kayexalate* 30 g PO daily, decrease ACE inhibitor, consider newer novel potassium binders (sodium zirconium cyclosilicate, patiromer)
- **METABOLIC ACIDOSIS**—consider NaHCO₃ if low pH or HCO₃
- **ANEMIA** (Hb <95 g/L [Hb <9.5 g/dL])—*epoetin alfa* 50–200 U/kg/week SC/IV div 2–3 ×/week, *darbepoetin alfa* 0.45 µg/kg SC every week, *ferrous fumarate* 600 mg PO nightly, goal to keep Hb 95–115 g/L [9.5–11.5 g/dL]. Ensure that iron stores are adequate before starting erythropoietin
- **CALCIUM/PHOSPHATE BALANCE**—keep Ca normal, PO₄ <1.5 mmol/L [<4.6 mg/dL], PTH <2–3 × normal, dietary phosphate restriction, phosphate binder *CaCO₃* 500 mg PO TID, *calcitriol* 0.25–1 µg PO daily, parathyroidectomy

RENAL REPLACEMENT—dialysis (peritoneal, hemodialysis at home and/or in-center), **renal transplant**

TREATMENT ISSUES

CRITERIA FOR DIALYSIS IN CHRONIC KIDNEY DISEASE—uremic symptoms, any acute indications, GFR <6 mL/min/1.73 m²

ACE INHIBITORS IN RENAL FAILURE—ACE inhibition leads to vasodilation of efferent arterioles → ↓ intraglomerular pressure → ↓ long-term remodeling/stress → slow progression of chronic kidney disease. Other positive effects of ACE inhibition include ↓ blood pressure, ↓ proteinuria, and ↓ mediators of glomerular tubule hypertrophy and fibrosis. Should start in all patients with chronic kidney disease ± hypertension ± proteinuria. If <30% rise in creatinine after starting ACE inhibitor, should continue as long-term benefit important. Expect GFR to return to pre-ACE inhibitor baseline after 3–4 months due to remodeling

SPECIFIC ENTITIES**DIABETIC NEPHROPATHY**

- **STAGE AI ALBUMINURIA** (<30 mg/day)—lasts 8–10 years, treatment with glycemic/blood pressure/lipid control, smoking cessation
- **STAGE AII ALBUMINURIA** (30–300 mg/day)—lasts 5–10 years, same treatment as above plus ACE inhibitor, protein restriction
- **STAGE AIII ALBUMINURIA** (>300 mg/day)—CrCl declines by 2–20 mL/min/year, same treatment as above, add SGLT2 inhibitor
- **PERCENTAGES**—25–40% of type 1 or 2 diabetics develop nephropathy: 99% of type 1 diabetics with chronic kidney disease are related to diabetes, while this is true only for 30% of type 2 diabetics

Related Topics

Acute Renal Failure (p. 83)
 Diabetes Mellitus (p. 365)
 Glomerulonephritis (p. 87)
 Hypertension (p. 70)
 Multiple Myeloma (p. 199)
 Polycystic Kidney Disease (p. 93)

Proteinuria**DIFFERENTIAL DIAGNOSIS**

FUNCTIONAL OR TRANSIENT (<1 g/day)—infection, fever, exercise, orthostatic
TUBULAR (0.5–1 g/day)—interstitial nephritis, ATN, proximal tubular dysfunction (Fanconi syndrome)

DIFFERENTIAL DIAGNOSIS (CONT'D)

GLOMERULAR (1–3 g/day, usually >3 g/day)—nephrotic syndrome, nephritic syndrome, early diabetes
OVERFLOW (any amount but usually >1 g/day)—multiple myeloma

PATHOPHYSIOLOGY

DEFINITION OF PROTEINURIA—>150 mg/day of protein in urine. Physiologically, <150 mg of protein is secreted per day (Tamm-Horsfall mucoprotein mainly, with <30 mg albumin)

PROTEIN FILTRATION—based on size and charge. Large proteins such as albumin are usually retained by glomerular basement membrane (affected in glomerular proteinuria), while small proteins such as β_2 microglobulin filter through but are reabsorbed at proximal tubules (affected in tubular proteinuria)

CLINICAL FEATURES

HISTORY—ankle swelling, fever, strenuous exercise, urinary tract infections (dysuria, frequency), past medical history (myeloma, diabetes, glomerulonephropathies, lupus), medications (antibiotics, NSAIDs)

PHYSICAL—vitals particularly blood pressure, abdominal examination (cystic kidney), ankle edema, periorbital edema

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, HbA1C, fasting glucose, albumin
- **URINALYSIS**—inaccurate and dependent on urine volume, detects mainly negative charged proteins such as albumin and less so light chains

INVESTIGATIONS (CONT'D)

- **SULFOSALICYLIC ACID TEST**—detects all proteins
- **SPOT PROTEIN /CR RATIO** (SI units)—to estimate daily protein excretion in mg
 - $\delta = \text{ratio} \times 0.14\text{--}0.16 \text{ mg/kg/day} \times \text{weight in kg}$
 - $\varphi = \text{ratio} \times 0.18\text{--}0.20 \text{ mg/kg/day} \times \text{weight in kg}$
- **24-H URINARY PROTEIN**—most accurate but cumbersome method to quantify urinary protein

SPECIAL

- **MYELOMA WORKUP**—urinary protein electrophoresis, serum protein electrophoresis
- **KIDNEY BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE—observe if <1 g/day, urine benign and creatinine normal. Consider biopsy otherwise.

SLOW PROGRESSION—ACE inhibitors, SGLT2 inhibitors (if type 2 diabetes and ACR >30 mg/mmol)

SPECIFIC ENTITIES

ORTHOSTATIC/POSTURAL PROTEINURIA—mainly in healthy young people. Split upright and recumbent urine collections could reveal protein loss mainly with upright position. Usually disappears with time and is of no clinical significance

Hematuria**DIFFERENTIAL DIAGNOSIS**

PIGMENTS—beets, myoglobinuria, hemoglobinuria, porphyrin, rifampin, food coloring

TRANSIENT—menstruation, urinary tract infections, fever, exercise (march hematuria), trauma, endometriosis, renal vein thrombosis

GLOMERULAR

- **NEPHRITIC SYNDROME**—MPGN, RPGN, IgA nephropathy (see GLOMERULOPATHIES p. 87)
- **HEREDITARY DISORDERS**—Alport syndrome, thin basement membrane disease, loin pain hematuria syndrome

EXTRA-GLOMERULAR

- **TUMORS**—kidneys, ureters, bladder, urethra
- **STONES**
- **CYSTIC KIDNEY DISEASE**—polycystic kidney disease, medullary cystic kidney disease, medullary sponge kidney

PATHOPHYSIOLOGY

DEFINITION OF HEMATURIA—>1–2 RBC/high-power field

CLINICAL FEATURES

HISTORY—blood clots, other sources of bleeding (GI, hemoptysis, epistaxis), beets, fever, strenuous exercise, urinary tract infections (dysuria, frequency), last menstrual period, past medical history (tumors, renal stones, cystic kidney disease, lupus, Alport syndrome), medications (ASA, NSAIDs, anticoagulants), ANCA (sinus, hemoptysis, neuropathy, hearing problems, asthma)

PHYSICAL—vitals (particularly blood pressure), check hearing, abdominal examination (cystic kidney)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, INR, PTT, urinalysis, urine C&S, urine cytology, GN serology (if you suspect GN)
- **IMAGING**—KUB, US abd, IVP, CT abd

SPECIAL

- **CYSTOSCOPY**—if suspect extra-glomerular bleed
- **KIDNEY BIOPSY**—if suspect glomerular pathology
- **URINE TESTS**—24-h urine calcium, oxalate, citrate, phosphate, sodium and urate (if stones suspected)

DIAGNOSTIC ISSUES**DIFFERENTIATING FEATURES FOR SOURCE OF BLEEDING**

- **GLOMERULAR**—cola urine, proteinuria, dysmorphic RBC (acanthocytes), RBC casts, no clot
- **EXTRA-GLOMERULAR**—bright red urine, no proteinuria, no dysmorphic RBC, clots, no RBC casts

MANAGEMENT**TREAT UNDERLYING CAUSE****SPECIFIC ENTITIES**

ISOLATED PERSISTENT HEMATURIA—predisposition to stones, IgA nephropathy, Alport syndrome, thin basement membrane disease, loin pain-hematuria syndrome

ALPORT SYNDROME

- **PATHOPHYSIOLOGY**—X-linked defect in $\alpha 5$ chain of type IV collagen
- **CLINICAL FEATURES**—hematuria without proteinuria, may have hearing loss. End-stage renal disease by age 30–45 in males. Persistent microhematuria but rarely renal failure in female carriers

THIN BASEMENT DISEASE

- **PATHOPHYSIOLOGY**—autosomal dominant; defect of type IV collagen (usually $\alpha 3$ or $\alpha 4$ chain)
- **CLINICAL FEATURES**—hematuria without proteinuria. Normal GFR

Related topics

Glomerulonephritis (p. 87)

Polycystic Kidney Disease (p. 93)

Cystic Kidney Diseases**CAUSES**

SIMPLE CYST

MALIGNANT CYST

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

MEDULLARY SPONGE KIDNEY

AUTOSOMAL DOMINANT TUBULOINTERSTITIAL KIDNEY DISEASE (previously known as MEDULLARY CYSTIC KIDNEY DISEASE)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, Cr/urea, urinalysis
- **IMAGING**—US renal, IVP (medullary sponge kidney)

MANAGEMENT

TREAT COMPLICATIONS—infections, stones, dialysis if end-stage renal disease

SPECIFIC ENTITIES

AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

★THE RULE OF 60'S★

- **PATHOPHYSIOLOGY**—autosomal dominant, affecting 1/400–1/1000 persons. 85% PKD1 (polycystin) mutation and 15% PKD2 mutation → multiple cysts formation in kidneys, liver, pancreas, ovaries, and spleen → cysts in renal cortex and medulla enlarge in size over years, cysts are prone to bleeding and infections. Risk factors for progression include younger age at diagnosis, male, Black, hypertension, and PKD1
- **CLINICAL FEATURES**—symptoms may include abdominal pain/fullness, microscopic hematuria (gross hematuria if cyst hemorrhages), hypertension, renal stone disease, recurrent UTI (cyst infections). Extrarenal involvements include cysts in other organs (liver **60%**),

SPECIFIC ENTITIES (CONT'D)

- abdominal wall hernias (45%), colonic diverticuli, mitral valve prolapse (25%), and intracranial aneurysms (5–10%). Progression to end-stage renal disease <2% by age 40, 25% by age 50, 50% by age 60, and 75% by age 70
- **DIAGNOSIS**—radiologic based on multiple cyst in kidneys (age 2 cysts; age 30–60, 2 cysts in each kidney; age >60, ≥4 cysts in each kidney) in patients with a family history of PKD. No radiologic criteria exist for patients without a family history.
 - **TREATMENTS**—tolvaptan (vasopressin 2 receptor antagonist, indicated for patients with a high risk of progression), blood pressure control, ACE inhibitors, dialysis if end-stage renal disease

AUTOSOMAL DOMINANT TUBULOINTERSTITIAL KIDNEY DISEASE (previously known as MEDULLARY CYSTIC KIDNEY DISEASE)

- **PATHOPHYSIOLOGY**—genetic abnormality with diffuse tubulointerstitial cysts at corticomedullary border; cysts may be absent altogether
- **CLINICAL FEATURES**—symptoms include precocious gout, family history of CKD
- Frequently progress to end-stage renal disease by age 20–50
- **TREATMENTS**—dialysis if end-stage renal disease

MEDULLARY SPONGE KIDNEY

- **PATHOPHYSIOLOGY**—malformation of terminal collecting ducts bilaterally
- **CLINICAL FEATURES**—usually asymptomatic, but may see kidney stones, microscopic hematuria, or infections. Renal failure not likely. May see “brush-like” appearance of calyces in IVP
- **TREATMENTS**—treatment of stones and infections as needed

SIMPLE CYSTS

- **PATHOPHYSIOLOGY**—30% of men, 15% of women by age 70
- **CLINICAL FEATURES**—cortex affected. May be single or multiple. Usually round, well demarcated, smooth walls, no echoes within cyst, strong posterior wall echo. Asymptomatic and renal failure unlikely

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—US renal every 6–12 months to help distinguish from cystic malignancy based on US appearance of worrisome cysts

MALIGNANT RENAL CYSTS

- **PATHOPHYSIOLOGY**—3–5% of all malignancies
- **CLINICAL FEATURES**—>50% incidentally found, classic triad (flank pain, hematuria and fever), hypercalcemia, erythrocytosis, Stauffer syndrome (features of cholestasis without kidney stone unrelated to metastasis)
- **DIAGNOSIS**—US or CT. MR typically used to further characterize cysts
- **BOSNIAK CLASSIFICATION**
 - **BOSNIAK I**—simple cyst (thin walled, no septae, no calcification, low density, no solid component and does not enhance). No further imaging required
 - **BOSNIAK II**—thick septae, mild calcification, or uniformly attenuated lesion less than 3cm. Consider CT scan to characterize lesion
 - **BOSNIAK IIF**—well marginated, multiple septae or minimal smooth thickening, thick or nodular calcification, total enhancement in lesions >3cm. Consider CT scan to characterize lesion. Risk of malignancy is higher and monitoring in 6–12 months is advised
 - **BOSNIAK III**—thickened or irregular smooth walls and measurable enhancement. Risk of malignancy is 40–60%. High risk. Needs referral for assessment by urology
 - **BOSNIAK IV**—findings of Bosniak III with soft tissue component. Risk of malignancy is 85–100%. Referral to urology
- **MANAGEMENT**—rule out genetic syndromes (von Hippel Lindau, tuberous sclerosis). Surgical management via partial or radical nephrectomy is mainstay for non-metastatic cancers. Ablative therapies are possible for localized disease. Biopsy is not pursued unless ablative therapy or for chemotherapy in metastatic disease due to risk of seeding peritoneum. Adjuvant chemotherapy is considered for higher risk cancers or metastatic lesions (see KIDNEY CANCER p. 227)

Metabolic Acidosis

DIFFERENTIAL DIAGNOSIS

HIGH ANION GAP (NORMOCHLOREMIC)

★ MUDPILE CATS ★

- METHANOL
- UREMIA
- DKA
- PARALDEHYDE
- ISONIAZID AND IRON
- LACTIC ACIDOSIS
- ETHYLENE GLYCOL
- CYANIDE
- ARSENIC/ACETAMINOPHEN
- TOLUENE
- SALICYLATES

★ KULT ★

- KETONES
- UREMIA
- LACTIC ACIDOSIS
- TOXINS

NORMAL-ANION GAP (HYPERCHLOREMIC)

- HCL GAIN—drinking HCl
- HCO₃ LOSS—renal (proximal RTA, acetazolamide), GI (diarrhea, ostomy loss)
- ↓ HCO₃ PRODUCTION—distal RTA, aldosterone deficiency/resistance

★ HARD POPS ★

- HYPERALIMENTATION (resulting from amino acid load in TPN)
- AMPHOTERICIN, ACETAZOLAMIDE
- RENAL FAILURE, RTA (type I, II, IV)
- DIARRHEA
- PANCREATITIS, PANCREATIC FISTULA
- OBSTRUCTIVE UROPATHY (RTA IV)
- PEE (ureteroenteric drain/ileal conduit)
- SALINE

INVESTIGATIONS

BASIC

- LABS—CBC, lytes, urea, Cr, glucose, lactate, ketone, serum alcohol/methanol, serum osmolality, urinalysis, urine lytes
- ABG

SPECIAL

- URINE OXALATE CRYSTALS—if suspect ethylene glycol ingestion

Related Topics

- Osmolar Gap (p. 123)
- Overdose (p. 120)
- Respiratory Acidosis (p. 24)
- Respiratory Alkalosis (p. 25)

DIAGNOSTIC ISSUES

APPROACH TO ARTERIAL BLOOD GAS (ABG)

1. **Check accuracy of data.** $H^+ = 24 \times PCO_2/HCO_3$ (modified Henderson–Hasselbalch formula). Recollect ABG and lytes if discrepancy found
2. **Identify primary acid/base disturbance**
 - **Acidemia**—pH < 7.35
 - **Alkalemia**—pH > 7.45
 - **Acidosis/alkalosis**—disturbance in PCO₂ or HCO₃, irrespective of pH, that may result in acidemia/alkalemia, respectively
 - **Metabolic**—initiated by change in HCO₃
 - **Respiratory**—initiated by change in PCO₂
3. **Check compensation**

	Primary change HCO ₃	Compensation pCO ₂
MAc	↓ 10	↓ 10–13
MAIk	↑ 10	↑ 5–7
	pCO ₂	HCO ₃
RAIk	↓ 10	↓ 5 (chronic) 2 (acute)
RAC	↑ 10	↑ 3 (chronic) 1 (acute)

Normal pCO₂ = 40 mmHg, HCO₃ = 24 mmol/L

4. **Calculate anion gap** (↑ anion gap in MAc, ↓ anion gap may be due to hypoalbuminemia [10:2.5 ratio], paraproteinemia [e.g. myeloma], halide ingestion [e.g. lithium] or laboratory error)

ANION GAP = Na – Cl – HCO₃; normal is between 8 and 12 mmol/L

4a. **If anion gap metabolic acidosis, calculate osmolar gap** to differentiate between causes **OSMOLAR GAP** = (Glucose + Urea + Na⁺ × 2) – observed osmolality

★ **GUN2** ★ (see p. 123 for more details)

4b. **Calculate “delta ratio”** (also known as “delta-delta”) to check for any superimposed metabolic disorder
 $\Delta AG/\Delta HCO_3 = (AG - 10)/(24 - HCO_3)$
5. **Any superimposed respiratory disorder?** After adjusting pCO₂ to account for HCO₃ changes (see compensation table above), is there evidence of hypoventilation (↑ pCO₂) or hyperventilation (↓ pCO₂)?

ΔAG/ΔHCO₃ Interpretation

< 0.4	Combined ↑ AG MAc + non-AG MAc (i.e. ↓ HCO ₃ >> ↑ AG)
0.4–0.8	Possible ↑ AG MAc + non-AG MAc; typical for renal failure

DIAGNOSTIC ISSUES (CONT'D)

Δ AG/ Δ HCO ₃	Interpretation
1.0–2.0	Isolated ↑ AG MAC Lactic acidosis usually 1.6 DKA usually 1.0
>2.0	Combined ↑ AG MAC + MAlk, or Pre-existing compensated RAc (i.e. ↑ AG >> ↓ HCO ₃)

NOTE—be wary of over interpretation, use clinical judgment

MANAGEMENT

ACUTE—ABC, O₂, IV, intubation, NaHCO₃ 1–2 amp IV bolus if pH <7.0

TREAT UNDERLYING CAUSE**SPECIFIC ENTITIES****LYTES AND URINE LYTES**

- **ANION GAP METABOLIC ACIDOSIS**—serum chloride normal
- **URINE NET CHARGE** (UNC, also known as urine anion gap)—urine Na + K – Cl. In the presence of acidosis and normal renal ammonium secretion, UNC would be negative because NH₄⁺ is excreted as the unmeasured cation (i.e. type II RTA, not type I RTA); remember to look for GI losses (neGUTive)

RENAL TUBULAR ACIDOSIS - TYPE I (distal)

- **PATHOPHYSIOLOGY**—inability of intercalated cells to make/secretate NH₄⁺ in distal tubule. Causes include **H⁺/ATPase mutation** (associated with hypokalemia), **back leakage of hydrogen ions due to increased luminal membrane permeability** (amphotericin B), **non-functional H⁺/ATPase** (Sjögren syn-

SPECIFIC ENTITIES (CONT'D)

drome, rheumatoid arthritis), cirrhosis; urine pH elevated because of ↓ H⁺ in urine. Serum K ↓ in most cases

- **DIAGNOSIS**—positive UNC, urine pH inappropriately high despite metabolic acidosis
- **TREATMENTS**—treat underlying cause. HCO₃ and K supplement, or potassium citrate

RENAL TUBULAR ACIDOSIS - TYPE II (proximal)

- **PATHOPHYSIOLOGY**—inability to reabsorb HCO₃ at the proximal tubule. Causes include **Fanconi syndrome** (multiple myeloma, carbonic anhydrase inhibitor, ifosfamide), **genetic disorders** (Wilson disease, cystinosis), **vitamin D deficiency**, and **renal transplant**
- **DIAGNOSIS**—low serum K, negative urine net charge. Confirmation is done by HCO₃ challenge → check urine pH every 2 h → measure serum HCO₃ level when urine pH >7 (expect relatively “low” serum HCO₃ in type II RTA). Urinary pH initially ↑ due to HCO₃ loss, but then ↓ as serum HCO₃ becomes low
- **TREATMENTS**—usually self-limiting in adults. HCO₃ supplement has limited utility due to HCO₃ wasting and may even lead to hypokalemia

RENAL TUBULAR ACIDOSIS - TYPE IV

- **PATHOPHYSIOLOGY**—causes include **hyporeninemic hypaldosteronism** (renal failure, frequently diabetic nephropathy and sometimes acute glomerulonephritis, ACE inhibitors, NSAIDs), **primary aldosterone deficiency** (Addison disease, congenital adrenal hyperplasia), **aldosterone resistance** (amiloride, spironolactone, tubulointerstitial disease), sickle cell disease
- **DIAGNOSIS**—high serum K
- **TREATMENTS**—K restriction in diet, diuretics. Fludrocortisone may be used with caution

DISTINGUISHING FEATURES FOR RENAL TUBULAR ACIDOSIS

	Type I	Type II	Type IV
Pathology	Distal	Proximal	Ald deficiency/resistance
Serum K	↓	↓	↑
Serum HCO ₃	Variable	10–20	>17
Urine Ph	>5.3	Variable	<5.3
UNC	Positive	Negative	Variable/usually positive

Metabolic Alkalosis

DIFFERENTIAL DIAGNOSIS

HCO₃ GAIN—HCO₃ administration (IV/PO), citrate (transfusion), acetate (TPN)

H⁺ LOSS

- **GI Loss**—vomiting, NG suction
- **PHYSIOLOGIC ALDOSTERONE-MEDIATED RENAL LOSS** (volume sensitive)
 - ↓ **FLUID INTAKE**
 - **RENAL LOSS**—diuretics, Bartter syndrome, Gitelman syndrome, hypomagnesemia
 - **GI Loss**—vomiting, ileus, villous adenoma, stool Cl loss
 - **SKIN LOSS**—sweat, burn
 - **INTRACELLULAR ACIDOSIS**—hypokalemia
- **PATHOLOGICAL ALDOSTERONE-MEDIATED RENAL LOSS** (volume insensitive)
 - ↑ **RENIN**—renal artery stenosis, tumor
 - ↑ **ALDOSTERONE**—Conn syndrome
 - ↑ **ALDOSTERONE-LIKE**—Cushing syndrome

★ CLEVER PD ★

- **CONTRACTION**
- **LICORICE**
- **ENDOCRINE**—Conn syndrome, Cushing syndrome, Bartter syndrome
- **VOMITING**
- **EXCESS ALKALI**
- **REFEEDING ALKALOSIS**
- **POST-HYPERCAPNIA**
- **DIURETICS**

PATHOPHYSIOLOGY

FACTORS THAT POTENTIATE METABOLIC ALKALOSIS—↓effective circulating fluid volume, hypokalemia, hyperaldosteronism, chloride deficiency

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, serum osmolality, urinalysis, urine lytes, magnesium, urine osmolality
- **ABG**

INVESTIGATIONS (CONT'D)

SPECIAL

- **SERUM ALDOSTERONE AND RENIN**

DIAGNOSTIC ISSUES

LYTES AND URINE LYTES

	U-Na	U-K	U-Cl	BP
Vomit HCl loss	↑	↑	↓	↓
Burn NaCl loss	↓	↑	↓	↓
Physiologic renal loss	↑	↑	↑	↓
Pathologic renal loss	↓	↑	↓	↑

URINE CHLORIDE

- **INCREASED** (>20 mmol/L, “Cl resistant”)—diuretic use (decreased Cl reabsorption), Bartter and Gitelman syndrome (decreased Cl reabsorption), mineralocorticoid excess (Conn syndrome), Cushing syndrome, licorice, severe hypokalemia (impaired Cl transport), hypomagnesemia, alkali load, idiopathic
- **DECREASED** (<10 mmol/L, “Cl responsive”)—decreased chloride intake, vomiting, NG drainage, post-diuresis, cystic fibrosis, villous adenoma, laxative abuse, persistent post-hypercapnia, RTA (decreased NH₄ excretion)

MANAGEMENT

ACUTE—ABC, O₂, IV

TREAT UNDERLYING CAUSE—**volume sensitive** (fluids, replete K), **volume insensitive** (spironolactone, amiloride)

SPECIFIC ENTITIES

BARTTER SYNDROME—mutation of the Na–K–2Cl transporter in the thick ascending limb of Henle (similar to inhibition by loop diuretics). Characterized by hypercalcemia

GITELMAN SYNDROME—mutation of the Na–Cl transporter in the distal tubule (similar to inhibition by thiazide diuretics). Characterized by hypocalcemia

Hyponatremia

DIFFERENTIAL DIAGNOSIS OF HYPOSMOLAR HYPONATREMIA

HYPVOLEMIC (VOLUME DEPLETION)

- **RENAL LOSS**—diuretics, hypoadrenalism, hypomagnesemia, Bartter

DIFFERENTIAL DIAGNOSIS OF HYPOSMOLAR HYPONATREMIA (CONT'D)

- **GI Loss**—vomiting, diarrhea, third spacing
- **SKIN LOSS**—sweat burns
- **BLOOD LOSS**

DIFFERENTIAL DIAGNOSIS OF HYPOSMOLAR HYPONATREMIA (CONT'D)

EUVOLEMIC

- **NON-SIADH MECHANISMS**
 - **ADRENAL INSUFFICIENCY**
 - **HYPOTHYROIDISM**
 - **PSYCHOGENIC POLYDIPSIA**
 - **LOW-SOLUTE DIET**—beer potomania, tea-and-toast syndrome
- **SIADH MECHANISMS**
 - **PHYSIOLOGIC RESPONSE**—stress, anxiety, pain, nausea
 - **CANCER**—SCLC, pancreatic, duodenum, thymoma, lymphoma
 - **LUNG DISEASE**—TB, abscess, empyema, pneumonia, viral pneumonitis
 - **CNS PROBLEMS**—skull fracture, subarachnoid hemorrhage, subdural hemorrhage, cerebral atrophy, encephalitis, meningitis, Guillain-Barré syndrome, lupus, acute intermittent porphyria
 - **DRUGS**—morphine, carbamazepine, TCA, chlorpropamide, vincristine, vinblastine, clofibrate, oxytocin, general anesthesia

HYPERVOLEMIC (edema)—cardiac failure, cirrhosis, GI-losing enteropathy, nephrotic syndrome, malnutrition

PATHOPHYSIOLOGY

DEFINITION OF HYPONATREMIA— $\text{Na} < 135$ mmol/L. The serum osmolality should be less than 275 mmol/L for hyposmolar hyponatremia

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, Cr, glucose, TSH, cortisol, urine lytes, urine Cr, serum and urine osmolality (e.g. to rule out pseudohyponatremia)

DIAGNOSTIC ISSUES

VOLUME STATUS—the patient's volume status (hypovolemia, euvolemic, hypervolemia) helps to narrow the differential diagnosis and dictates the appropriate workup

SIADH CRITERIA—diagnosis of SIADH requires the following: cause available, clinically euvolemic, hyponatremic, increased urine osmolality (>100 mmol/L and usually >300 mmol/L), specific gravity (>1.003), increased urine Na (>30 mmol/L), and low uric acid. Also need to rule out hypothyroidism, adrenal insufficiency, diuretic use, and psychogenic polydipsia.

DIAGNOSTIC ISSUES (CONT'D)

CALCULATING CORRECTION RATE

- **CHANGE IN SERUM Na**
- $= (\text{Na}_{\text{infusate}} - \text{Na}_{\text{serum}}) / (\text{total body water} + 1)$ where total body water $\approx 0.5 \times$ body weight (kg) in women and $0.6 \times$ body weight (kg) in men
- **VOLUME OF INFUSATE NEEDED** (in liters) = intended change in serum Na over a defined period of time (usually 8 mmol/L over 24 h)/change in serum Na
- In patients with chronic hyponatremia, the **daily limit of increase in serum Na** should be ≤ 8 mmol/L to minimize the risk of osmotic demyelination syndrome (ODS). The initial rate of correction can still be 1–2 mmol/L per hour for several hours in patients with severe symptoms. In patients with acute hyponatremia, the daily limit can be more flexible
- **INFUSATE SODIUM CONTENT**—D5W (5% dextrose in water) 0 mmol/L, $\frac{1}{2}$ NS (0.45% NaCl in water) 77 mmol/L, Ringer lactate 130 mmol/L, NS (0.9% NaCl in water) 154 mmol/L, 3% hypertonic saline 513 mmol/L, 5% hypertonic saline 855 mmol/L

MANAGEMENT

HYPOVOLEMIC—NS infusion. 3 bouillon cubes/L water daily $\times 3$ days. Hypertonic saline or furosemide if severe (be extremely cautious)

EUVOLEMIC—**free water restriction** < 1 L/days. NS or hypertonic saline (3%), plus furosemide if severe. Urea and salt tabs can be considered. Treat underlying cause

HYPERVOLEMIC—**Na and free water restriction** < 1 L/day, bed rest. Treat underlying cause

TREATMENT ISSUES

VAPTANS (“Aquaretics”)—oral V2 receptor antagonists \rightarrow block ADH action \rightarrow water diuresis (for correction of euvolemic and hypervolemic hyponatremia, but requires close monitoring. Generally avoided in acute hyponatremia due to risk of over correction)

INDICATIONS FOR HYPERTONIC SALINE—severe symptoms such as seizures

FUROSEMIDE-INDUCED DIURESIS—furosemide can be used to treat hyponatremia, particularly with the concurrent use of normal saline or hypertonic saline. It works by reducing the interstitial gradient and making the urine more dilute. Careful monitoring to avoid Na overcorrection

SPECIFIC ENTITIES

PSEUDOHYPONATREMIA—severe paraproteinemia or hypertriglyceridemia

HYPEROSMOLAR HYPONATREMIA—hyperglycemia (correct Na by adding 3 mmol/L for every 10 mmol/L increase in glucose), hypertonic 3 mmol/L mannitol

ISOOSMOLAR HYPONATREMIA—glycine or sorbitol flushing solutions during transurethral resection

ACUTE HYPONATREMIA

- **PATHOPHYSIOLOGY**—very different from chronic hyponatremia. Usually develops postop due to ADH release from stress, pain, nausea, meds (morphine, chlorpromazine, carbamazepine), brain natriuretic peptide
- **DIAGNOSIS**—low Na
- **TREATMENTS**—compared to chronic hyponatremia, it is acceptable to correct Na rapidly to ~140 mmol/L with little risk of CPM

OSMOTIC DEMYELINATION SYNDROME

- **PATHOPHYSIOLOGY**—within first day of hyponatremia, brain swells as water shifts into cells to

SPECIFIC ENTITIES (CONT'D)

equilibrate osmotic gradient → brain cells extrude Na, K, and osmolytes to balance the gradient and to minimize cerebral edema → over next 2–3 days, brain volume returns to normal → rapid Na correction can lead to “shrinking” of brain cells or osmotic demyelination, particularly if Na increased by >12 mmol/L per day

- **CLINICAL FEATURES**—typically delayed 2–6 days (may be weeks) after correction and often irreversible. Symptoms include dysarthria, dysphagia, paraparesis, lethargy, coma, and seizures
- **RISK FACTORS**—alcohol use disorder, ♀ on thiazide diuretics, patients with low K^+ , elderly, and burn victims
- **DIAGNOSIS**—CT head, MRI head
- **TREATMENTS**—dismal prognosis with no effective therapy. Careful avoidance of Na overcorrection is key. If overcorrection occurs, re-lowering sodium is warranted and is likely protective

Hypernatremia**DIFFERENTIAL DIAGNOSIS**

HYPVOLEMIC—decreased thirst, decreased water access

EUVOLEMIC (diabetes insipidus)

- **NEUROGENIC**—trauma, tumors, **infections** (TB, meningitis, encephalitis), **infiltrative** (sarcoidosis), vascular, idiopathic
- **NEPHROGENIC**—**renal disorders** (polycystic kidneys, infiltration, infection, ischemia), **hypercalcemia**, **medications** (lithium, demeclocycline, amphotericin B), **genetic** (x-linked), **idiopathic**

HYPEROLEMIC—drink seawater, excessive IV fluid, primary hyperaldosteronism

PATHOPHYSIOLOGY

DEFINITION OF HYPERNATREMIA—Na >145 mmol/L

CLINICAL FEATURES

SYMPTOMS—may include intense thirst, muscle weakness, confusion, and coma. Brain shrinkage could potentially cause vascular rupture, leading to cerebral bleeding, subarachnoid hemorrhage, permanent neurologic deficit, and death

INVESTIGATIONS**BASIC**

- **LABS**—lytes, urea, Cr, glucose, Ca, serum osmolality, urinalysis, urine lytes, urine Cr, urine osmolality

SPECIAL

- **DDAVP TEST**—to distinguish between nephrogenic and neurogenic diabetes insipidus (DI)

DIAGNOSTIC ISSUES**CALCULATING CORRECTION RATE**

- **WATER DEFICIT** (in liters)
= $(Na_{\text{current}}/Na_{\text{goal}} - 1) \times \text{total body water}$
- **CHANGE IN SERUM Na**
= $(Na_{\text{infusate}} - Na_{\text{serum}})/(\text{total body water} + 1)$
where total body water $\approx 0.5 \times \text{body weight}$ in women and $0.6 \times \text{body weight}$ in men
- **VOLUME OF INFUSATE NEEDED** (in liters) = intended change in serum Na over a defined period of time (usually 10 mmol/L over 24 h) divided by change in serum Na + 1.5 L to compensate for obligatory daily water losses
- **INFUSATE SODIUM CONTENT**—D5W (5% dextrose in water) 0 mmol/L, 1/2NS (0.45% NaCl in water) 77 mmol/L, Ringer lactate 130 mmol/L, NS (0.9% NaCl in water) 154 mmol/L. Avoid using

DIAGNOSTIC ISSUES (CONT'D)

NS for correction of hypernatremia unless hemodynamic instability/fluid resuscitation

OSMOLALITY—urine osmolality is usually lower than serum osmolality in diabetes insipidus, whereas urine osmolality is usually higher than serum osmolality in hypovolemic hypernatremia

MANAGEMENT

HYPOVOLEMIC—hypotonic fluid infusion. Treat underlying cause

EUVOLEMIC—ADH if central diabetes insipidus. Free water hydration. Treat underlying cause (see POLYURIA p. 381 (diabetes insipidus))

Hypokalemia**DIFFERENTIAL DIAGNOSIS**

↓ **INTAKE**—rare

SHIFT INTO CELL—metabolic alkalosis, hyperinsulin states, ↑ β-adrenergic states, hypothermia

↑ **OUTPUT**

- **GI LOSS**—diarrhea, vomiting, tube drainage
- **RENAL LOSS**—diuretics, hypomagnesemia, type I or II RTA, hyperaldosteronism, Conn syndrome, renal artery stenosis, genetic (Bartter and Gitelman syndrome)

PATHOPHYSIOLOGY

DEFINITION OF HYPOKALEMIA—K <3.5 mmol/L

PHYSIOLOGY—daily intake of potassium is usually 40–120 mEq/day (banana contains 1 mEq of K every 2.5 cm [1 in.]), which is mostly excreted by the kidneys. In hypokalemia, renal excretion may decrease to 5–25 mEq/day

POTASSIUM DEFICIT—every 1 mmol/L decrease in serum K represents a loss of approximately 150–300 mmol of total body K. Males, younger age, and higher muscle mass may require replacement at the higher end of this range

HYPERALDOSTERONISM DUE TO HYPOVOLEMIA—usually does not lead to hypokalemia as it is counterbalanced by a decreased distal renal flow (which on its own would lead to decreased K excretion)

CLINICAL FEATURES

SYMPTOMS—usually not present unless K <2.5 mmol/L

- **MUSCULAR**—weakness or paralysis (periodic hypokalemia paralysis). May include extrem-

CLINICAL FEATURES (CONT'D)

ities, respiratory and gastrointestinal muscles. Cramps, paresthesia, tetany, muscle tenderness, atrophy, and rhabdomyolysis may develop

- **CARDIAC**—arrhythmia includes sinus bradycardia, paroxysmal atrial or junctional tachycardia, AV block, VT, VF, ST depression, small T waves and U waves
- **RENAL**—impaired urinary concentrating ability (nocturia, polydipsia, polyuria), increased renal bicarbonate reabsorption, increased renal ammonia production due to intracellular acidosis, and hypokalemic nephropathy

INVESTIGATIONS**BASIC**

- **LABS**—lytes, magnesium, urea, Cr, glucose, CK, serum osmo, urinalysis, urine lytes, urine osmo

SPECIAL

- **ECG**
- **HYPERALDOSTERONISM WORKUP**—serum aldosterone and plasma renin activity

MANAGEMENT

ACUTE (K <3.0 mmol/L)—KCl 10 mEq in 100 mL D5W IV bolus × 3. For continuous infusion, maximum KCl concentration is 40 mEq/L

K SUPPLEMENT—KCl 20–120 mEq PO divided over once daily to QID. Oral supplementation is preferred over intravenous in general. Need to replete Mg if low to facilitate correction of K (MgSO₄, 5 g IV over 4 h)

TREAT UNDERLYING CAUSE**Hyperkalemia****DIFFERENTIAL DIAGNOSIS**

PSEUDOHYPERKALEMIA—hemolysed blood sample, leukocytosis, thrombocytosis

↑ **INTAKE**—rare

DIFFERENTIAL DIAGNOSIS (CONT'D)

SHIFT OUT OF CELL—metabolic acidosis, diabetes (insulin deficit), β-blockade

DIFFERENTIAL DIAGNOSIS (CONT'D)

↑ **RELEASE**—rhabdomyolysis, tumor lysis, strenuous exercise, intravascular hemolysis

↓ **OUTPUT**

- ↓ **DISTAL TUBULAR FLOW**—renal failure, ↓ effective circulating fluid volume
- **HYPOALDOSTERONISM**—↓renin, adrenal insufficiency, type IV RTA, ACE inhibitors, ARBs, spironolactone, NSAIDs

PATHOPHYSIOLOGY

DEFINITION OF HYPERKALEMIA—K >5.0 mmol/L

CLINICAL FEATURES**SYMPTOMS**

- **MUSCULAR**—weakness and even paralysis of extremities, but rarely respiratory muscle involvement
- **CARDIAC**—tall, peaked T wave (especially pre-cordial leads), widen QRS, wide and flat P wave, VF

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, CK, serum osmolality, urinalysis, urine lytes, urine osmolality
- **ECG**—consider if K >6.0 mmol/L. May see peaked T waves, PR prolongation, widened or absent P waves, widened QRS, VF, sine wave or PEA arrest

INVESTIGATIONS (CONT'D)**SPECIAL**

- **ABG/VBG**—quick way to get serum K level
- **HYPOALDOSTERONISM WORKUP**—serum aldosterone and plasma renin activity

MANAGEMENT**ACUTE** (K >6.0 mmol/L with ECG changes)

- **STABILIZE MEMBRANE**—*calcium chloride* 10% 10 mL IV push, *calcium gluconate* 10% 10 mL IV push, do NOT give if hyperkalemia related to digoxin (can precipitate VF)
- **SHIFTING K INTO CELLS** (temporizing measure)
 - **INSULIN**—D50 50 mL IV push followed by *Humulin® R* 10 U in 50 mL of D50% IV bolus. Consider dextrose drip or second amp of D50W as hypoglycemia occurs up to 70% of cases when only 1 amp of D50 given
 - **ALKALOSIS**—*NaHCO₃* 45 mEq IV over 5 min, repeat in 30 min PRN for acidosis
 - **β-AGONIST**—*salbutamol* 10–20 mg via NEB, monitor heart rate

REMOVAL OF K—*kayexalate* 30 g PO daily-QID (avoid if HF/Na retention), each dose followed by lactulose 30 mL PO. **Ca resonium** 30–40 g in 50 mL 20% sorbitol. Newer potassium binders patiromer and sodium zirconium cyclosilicate may be used. **Diuretics** (*furosemide* 40 mg IV, doses up to 200 mg may be needed in AKI). **Dialysis TREAT UNDERLYING CAUSE**—**discontinue drugs** (K supplements, ACE inhibitors, ARBs, spironolactone, NSAIDs, trimethoprim)

Hypomagnesemia**DIFFERENTIAL DIAGNOSIS**

↓ **INTAKE**—malnutrition, malabsorption, mal-digestion, PPIs

SHIFT INTO BONE—hungry bone syndrome

↑ **OUTPUT**

- **GI Loss**—diarrhea, small bowel bypass surgery, acute pancreatitis
- **RENAL LOSS**—thiazide, loop diuretics, alcohol, hypercalcemia, tubular dysfunction (alcohol, aminoglycosides, amphotericin B, cisplatin, cyclosporine, acute tubular necrosis in diuretic phase, primary renal magnesium wasting)

PATHOPHYSIOLOGY

DEFINITION OF HYPOMAGNESEMIA—Mg <0.7 mmol/L [<1.4 mEq/L]

CLINICAL FEATURES**SYMPTOMS**

- **LYTES /Ca/PO₄**—↓ K, ↓ Ca, PTH resistance, vitamin D deficiency
- **HEART**—ventricular arrhythmias, widening of the QRS, peaking or diminution (severe) of T waves, prolongation of PR interval, and *torsade de pointes*

INVESTIGATIONS**BASIC**

- **LABS**—lytes, urea, Cr, Ca, Mg, PO₄, serum osmolality, urinalysis, urine Mg, urine Cr

DIAGNOSTIC ISSUES

FeMg = $(U_{Mg}/U_{Cr}) / (0.7 \times P_{Mg}/P_{Cr})$, <3 suggests extrarenal loss

MANAGEMENT

MG SUPPLEMENT— $MgSO_4$ 5 g IV over 5 h, *Mg gluconate* 500 mg PO TID

MANAGEMENT (CONT'D)

TREAT UNDERLYING CAUSE—amiloride may be used to prevent amphotericin B induced hypomagnesemia and hypokalemia

Hypophosphatemia**DIFFERENTIAL DIAGNOSIS**

↓ **INTAKE**—alcoholism, inadequate intake, anitacid

SHIFT INTO CELL—acute respiratory alkalosis (DKA, hyperventilation), hyperinsulin (especially refeeding syndrome), hungry bone syndrome

↑ **OUTPUT**

- **PRIMARY HYPERPARATHYROIDISM**
- **SECONDARY HYPERPARATHYROIDISM** (vitamin D deficiency/resistance)—hereditary hypophosphatemic rickets, oncogenic osteomalacia, Fanconi syndrome, osmotic diuresis, acetazolamide, acute volume expansion, steatorrhea, chronic diarrhea

PATHOPHYSIOLOGY

DEFINITION OF HYPOPHOSPHATEMIA— $PO_4 < 0.8$ mmol/L [< 2.5 mg/dL]

CLINICAL FEATURES**SYMPTOMS**

- **CNS** (intracellular ATP falls)—metabolic encephalopathy
- **MUSCULAR** (intracellular ATP falls)—↓ myocardial contractility, HF, respiratory failure, proximal myopathy, dysphagia, ileus, rhabdomyolysis

CLINICAL FEATURES (CONT'D)

- **HEMATOLOGIC** (RBC 2,3 DPG falls)—hemolysis, ↓ WBC activity, ↓ clot retraction, thrombocytopenia

Related Topics

Hypocalcemia (p. 386)

Vitamin D Deficiency (p. 387)

INVESTIGATIONS**BASIC**

- **LABS**—Ca, Mg, PO_4 , PTH, CK, 24-h urinary PO_4 collection (< 100 mg), urine PO_4 , urine Cr

DIAGNOSTIC ISSUES

$FePO_4 = (U_{PO_4}/U_{Cr}) / (P_{PO_4}/P_{Cr})$, < 5 suggests not due to ↑ output

MANAGEMENT

PO_4 SUPPLEMENT—**potassium phosphate** (22 mmol K^+ , 15 mmol PO_4) in 250 mL NS over 4 h, or **sodium phosphate** (20 mmol Na^+ , 15 mmol PO_4) in 250 mL NS over 4 h, or **sodium phosphate** 1 g PO TID (replaces ~100 mmol/day)

TREAT UNDERLYING CAUSE—**vitamin D deficiency** (*vitamin D* 800 U PO daily)

Ureteral Calculi**CAUSES**

CALCIUM (80%)—calcium oxalate or calcium phosphate, radiodense

URIC ACID (10–15%)—20% of patients also have gout, radiolucent

STRUVITE (10–15%)—urea-splitting bacteria (*Proteus*, *Klebsiella*), infected stone. Staghorn calculi if filled entire renal pelvis, radiodense

CYSTINE (1%)—autosomal recessive disorders of renal tubular absorption of dibasic amino acids, radiodense

DRUGS—protease inhibitors (indinavir, atazanavir)

PATHOPHYSIOLOGY**STONE FORMATION**

- **PROMOTERS**—low urine volumes, urine cystine, pH (distal RTA), uric acid, Ca/oxalate/ PO_4 , anatomic defects (medullary sponge kidney)
- **INHIBITORS**—high urine volumes, urine citrate, Mg, Tamm-Horsfall proteins, nephrocalcin, uropontin, orthophosphates
- **COMPLICATIONS**—obstruction, renal failure, infection, urosepsis, ureteral stricture

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, Ca, PO₄, PTH, uric acid, urinalysis (artifact most times)
- **IMAGING**—unenhanced CT abd/pelvis (sens 96%, spc 100%), KUB (consider EWSL if see stone on film), US abd, IVP

SPECIAL

- **URINE TEST**—24-h urinary Ca/PO₄, oxalate, urate, Mg, citrate, and Na
- **CYSTOSCOPY**

DIAGNOSTIC ISSUES

RADIODENSE STONES—★**COLAS**★ Calcium, Cystine, Ornithine, Lysine, Arginine, Struvite

RADIOLUCENT STONES—uric acid, matrix (organic substances associated with urea-producing bacteria), indinavir (radiolucent on X-ray and CT)

MANAGEMENT

ACUTE—**pain control** (*ketorolac* 30–60 mg IV/IM, then 15 mg IV/IM q6h or 10 mg PO q6h, *diclofenac* 50 mg PO BID–TID, or *morphine* 5 mg SC q4h). **N&V** (*dimenhydrinate* 25–50 mg PO/IV/SC q4h PRN, *metoclopramide* 10 mg PO/IV q4h PRN).

MANAGEMENT (CONT'D)

Urology consult (if stone does not pass spontaneously or >5 mm, consider shock wave lithotripsy, ureteroscopy, percutaneous nephrolithotomy. If obstructed, infected upper urinary tract, impending renal deterioration, intractable pain/N&V, anuria or high-grade obstruction of solitary kidney, nephrostomy or insert stent). **Infection** (*ciprofloxacin* 500 mg PO q12h, or *ampicillin* and *gentamicin*; urosepsis from obstructing nephrolithiasis requires emergent decompression)

PREVENTION—↑ **daily fluid intake** (>2 L of urine/day, or water plus 125 mL lemon juice/day).

Hypercalciuria (dietary Na and protein restriction, do not restrict calcium intake, *hydrochlorothiazide* 25 mg PO daily-BID). **Hyperoxaluria** (diet oxalate restriction with ↓ spinach, chocolate, cocoa, beets, nuts, *Ca citrate* 1 g PO TID with meals). **Hypocitraturia** (*K citrate* 25 mEq PO BID or *Ca citrate* 1 g PO TID; avoid Na citrate). Evidence suggests citrate likely works even in patients with normal urine citrate levels **Hyperuricosuria** (dietary uric acid restrictions, *allopurinol* 100 mg PO daily, alkalinization of urine with K citrate or NaHCO₃). **Hypomagnesuria** (*Mg gluconate* 500 mg PO TID)

Hypertension

See HYPERTENSION (p. 70)

Approach to Dialysis**HEMODIALYSIS**

PRINCIPLES OF CLEARANCE—**fluid removal** (ultrafiltration ± osmotic gradient), **solute removal** (small toxins, middle molecules, electrolytes; dialysis by osmotic gradient). Urea is a surrogate marker and is not toxic itself

FACTORS AFFECTING EFFICIENCY—counter-current exchange, blood pump speed, dialysate speed (500 mL/min), size of membrane, time (4–6 h 3 × week)

VASCULAR ACCESS—temporary (double lumen internal jugular/femoral. Avoid subclavian placement if possible to minimize risk of central vein stenosis), intermediate (permacath internal jugular), permanent (AV graft, AV fistula)

ORDERS

- **GOAL WEIGHT DETERMINATION**—symptoms, clinical fluid status, blood pressure

HEMODIALYSIS (CONT'D)

- **FILTER**—low efficiency for new patients, high-flux, high-efficiency filters for most other patients
- **BLOOD PUMP SPEED**—usually 400–450 mL/min for end-stage renal disease. May start at 200–250 mL/min for new patients
- **DIALYSATE FLOW**—500 mL/min
- **DURATION**—usually 4 h. May start at 2.5 h for new patients
- **FLUID REMOVAL**—net weight gain + fluid given during dialysis. Try to attain dry weight
- **Na⁺**—ramp, step or intermittent may be used with prescribed sodium of 150–140 mmol/L or 150–135 mmol/L to keep intravascular osmolality high at beginning of run to maintain blood pressure. Otherwise, may simply set Na at 137 mmol/L or 140 mmol/L

HEMODIALYSIS (CONT'D)

throughout the run. If hyponatremia, set Na at 132–135 mmol/L

- **K⁺**—as a general rule, [dialysate K] = 7 mmol/L – [serum K]. Careful with 1 K⁺ bath
- **HCO₃⁻**—25–40 mmol/L (usually 35 mmol/L)
- **Ca²⁺**—1.25–1.75 mmol/L [5–7 mg/dL]
- **TEMPERATURE**—35.5 °C [95.9 °F]
- **HEPARIN**—needed if system clotting. 500 U bolus then 500 U/h if first time. Otherwise, 1000 U bolus then 500 U/h. If high risk (active bleed, HIT, anticoagulated), consider no heparin. Citrate is an alternative if HIT. Low molecular weight heparin (tinzaparin) can also be used when dosed for renal function

ADEQUACY—goal KT/V 1.4/session (for 3 ×/week)

COMPLICATIONS OF INTERMITTENT HEMODIALYSIS

- **DIALYSIS DISEQUILIBRIUM SYNDROME**—high osmolar state in new patients just starting dialysis. With rapid removal of osmolality by dialysis intravascularly, can lead to shifting of fluid intracellularly and cerebral edema. Patients become confused and ↓ level of consciousness. See dialysis orders above for preventative measures
- **↓ BLOOD PRESSURE DURING RUN**—too rapid removal of fluid, also see SHOCK p. 116 for other causes. Treatments include Trendelenburg position, stopping ultrafiltration, fluid bolus NS 100 mL, and consider ramping Na next time
- **MUSCLE CRAMPS**—usually due to rapid fluid removal. Give fluid bolus NS 100 mL, re-assess target weight and consider ramping Na next time
- **ITCHING**—unknown cause. *Diphenhydramine* 50 mg × 1 dose or *hydroxyzine* 10–25 mg × 1 dose

CONTINUOUS RENAL REPLACEMENT THERAPY

TYPES—continuous arterial–venous hemofiltration (CAVHD) obsolete, continuous venous–venous hemofiltration (CVVHD), CVVHD + diffusion component

INDICATIONS TO STOP CONTINUOUS RENAL REPLACEMENT—urine output increased, hemodynamically stable (consider switching to intermittent hemodialysis)

CONTINUOUS RENAL REPLACEMENT THERAPY (CONT'D)

ADVANTAGES OF CONTINUOUS RENAL REPLACEMENT THERAPY (CRRT) COMPARED TO INTERMITTENT HEMODIALYSIS—use in hemodynamically unstable patients (less likely sudden blood pressure drop), better in keeping metabolites low and stable, better in removing middle and larger molecules (especially in septic patients), better nutrition for patient can be provided. CRRT has not been shown to provide any survival advantage compared to intermittent HD

DISADVANTAGES OF CONTINUOUS RENAL REPLACEMENT—requires anticoagulation (heparin, citrate, NS flush q30 min), removes more solute, and requires more filter replacement

PERITONEAL DIALYSIS (PD)

ADVANTAGES OF PERITONEAL DIALYSIS COMPARED TO INTERMITTENT HEMODIALYSIS—better middle molecular clearance, better control of fluid and blood pressure, preserves residual renal function better, cheaper, increased patient autonomy

METHODS OF CLEARANCE—**continuous ambulatory peritoneal dialysis** (4 × 2 L exchanges/day for 30–40 min during the day, with one indwelling exchange overnight), **continuous cyclic peritoneal dialysis** (reverse timing of CAPD)

FACTORS AFFECTING EFFICIENCY—volume of exchanges, time of exchange, efficiency of peritoneal membrane (high average transporter vs. low average transporter)

DIALYSATE—**Dianeal** (standard with Na 132 mmol/L, Cl 95 mmol/L, Mg 0.25 mmol/L [5 mEq/L], osmolality 395 mmol/kg, pH 5.2, dextrose 0.5%, 1.5%, 2.5%, or 4.25%), **Extraneal**® (icodextrin 7.5%), **Nutrineal**® (1.1% amino acid solution. Good nutrition). Concentration of glucose affect fluid removal

ADEQUACY—goal KT/V 1.7/week and creatinine clearance 60 L/week

COMPLICATIONS OF PERITONEAL DIALYSIS

- **PERITONITIS**—triad of abdominal pain, cloudy dialysate, and >100 WBC/mm³ (>50% PMN). Treat with intraperitoneal antibiotics that cover Gram-negative and Gram-positive bacteria such as ceftazidime, aminoglycoside, or fluoroquinolones and vancomycin empirically until

PERITONEAL DIALYSIS (PD) (CONT'D)

cultures available (add anti-fungal therapy if Gram stain shows yeast). Local resistance patterns should drive initial empiric therapy

- **MECHANICAL**—blockage (causes include constipation, omental wrap, tube in wrong position), leak, pleural effusion

PERITONEAL DIALYSIS (PD) (CONT'D)

- **METABOLIC**—hypokalemia, hyperglycemia (glucose in dialysate)
- **MEMBRANE**—lasts 6–8 years as glucose toxic to peritoneal membrane



Intensive Care Issues

ICU ADMISSION CRITERIA

NEED FOR FREQUENT OR CONTINUOUS MONITORING—post-high-risk surgery, high risk for clinical deterioration, need for frequent laboratory investigations or monitoring (e.g. ABGs) that cannot be performed in lower acuity setting

HIGH INTENSITY OF NURSING CARE

LIFE SUPPORT THERAPY—mechanical ventilation, vasoactive drugs, continuous renal replacement, artificial liver support, extracorporeal life support

PREVENTATIVE STRATEGIES

VENTILATOR-ASSOCIATED PNEUMONIA—remove endotracheal tube as soon as possible, orotracheal intubation unless contraindicated, strict hand hygiene, oral and dental hygiene, semi-recumbent positioning (head of bed at 30–45°), subglottic suctioning, drainage of condensate from ventilator circuits, initiate enteral nutrition within 24–48h ICU admission, minimize gastric acid suppression therapy (proton pump inhibitors) when possible

GASTROINTESTINAL STRESS ULCERATION—risk factors include mechanical ventilation, coagulopathy. Prophylaxis with H₂ blockers (e.g. *ranitidine* 50 mg IV q8h or 150 mg PO/NG q12h) preferred unless high risk as use of proton pump inhibitors is associated with increased risk of ventilator-associated pneumonia

VENOUS THROMBOEMBOLISM—particularly in patients with trauma and prolonged bed rest. Prophylaxis includes unfractionated heparin SC, LMWH, fondaparinux, or pneumatic compression stockings

SEDATION, ANALGESIA, PARALYSIS IN THE ICU

SEDATION/AMNESIA—*propofol* 5 mcg/kg/min initial infusion, titrate by 5–10 mcg/kg/min, typical infusion range 5–50 mcg/kg/min. Rapid

SEDATION, ANALGESIA, PARALYSIS IN THE ICU (CONT'D)

onset, short duration: appropriate for short-term sedation, monitor for acidosis and increased CK with prolonged use. *Midazolam* 0.03 mg/kg loading dose, then 0.02–0.1 mg/kg/h IV infusion, typical infusion range 0–10 mg/h, rapid onset, short duration; *lorazepam* 0.5–10 mg IV q2–4 h PRN, load with 0.5–2 mg q15min, avoid continuous infusion as propylene glycol solvent may accumulate. Use for intermediate to prolonged sedation, longer duration than midazolam, most potent amnestic

ANALGESIA—*fentanyl* 50–100 mcg q5min IV load to effect, then 1–4 mcg/kg/h by continuous IV infusion, typical infusion range 50–300 mcg/h, 100× more potent than morphine. Used in patients with hemodynamic instability, rapid onset, short duration (but highly lipophilic; may accumulate with prolonged infusion); *morphine* 0.05 mg/kg IV load, then 4–15 mg/h. May cause hypotension due to histamine release; *hydromorphone* 0.5 mg IV initially, then 1–2 mg q1h or 0.5–2 mg/h infusion, 5× more potent than morphine

NEUROMUSCULAR BLOCKAGE—*rocuronium* 0.5 mg/kg IV PRN, onset 1 min, duration 30 min; *pancuronium* 0.06–0.15 mg/kg IV PRN, onset 2–3 min, duration 60–120 min, may run continuous infusion 0.01–0.05 mg/kg/h, vagolytic effect may cause tachycardia; *cisatracurium* 0.15–0.2 mg/kg IV PRN, onset 2–3 min, duration 30 min, may run continuous infusion 3 µg/kg/min; *succinylcholine* 0.5–1.5 mg/kg IV, onset 1 min, duration ~10 min, metabolized by pseudocholinesterase, many contraindications (personal/family history malignant hyperthermia, neuromuscular disease with denervating injury, muscular dystrophy, rhabdomyolysis, burns, stroke, hyperkalemia)

DIFFERENTIAL DIAGNOSIS FOR WEAKNESS IN THE ICU

ENCEPHALOPATHY—hypoxic/ischemic, septic, hepatic, uremic, hypoglycemic, iatrogenic (drugs)

MYELOPATHY—hypoxic/ischemic, traumatic

NEUROPATHY—critical illness polyneuropathy, Guillain-Barré syndrome, motor neuron disease, compression, hypophosphatemia

NEUROMUSCULAR JUNCTION—blocking agents, Lambert-Eaton, myasthenia gravis, hypomagnesemia, hypocalcemia, organophosphates, botulism

MYOPATHY—critical illness myopathy, acute necrotizing myopathy, hypokalemia, hypophosphatemia, hypocalcemia, hypomagnesemia, steroid, muscular dystrophy, polymyositis

PROCEDURES

RADIAL ARTERIAL LINE INSERTION

Ailon et al. *NEJM* 2014;371(E21)

- **LANDMARK**—palpate radial artery immediately proximal to scaphoid or use US to localize. Insert 20-gauge catheter at 30°

FEMORAL ARTERIAL LINE INSERTION

- **LANDMARK**—identify femoral artery midway between ASIS and pubic symphysis, ideally with US. Puncture and insert catheter over the wire, *never dilate an artery!*

FEMORAL CENTRAL VENOUS CATHETER

Tsui et al. *NEJM* 2008;358(E30)

- **LANDMARK**—femoral artery is midway between ASIS and pubic symphysis. Femoral vein is medial to artery. Ideally use ultrasound for localization. Insert introducer needle through skin at 45° toward umbilicus, about 1 cm below the inguinal ligament, then use Seldinger technique to place catheter
- **COMPLICATIONS**—arterial puncture (9–15%), hematoma (4%), infection (6–20%)

INTERNAL JUGULAR CENTRAL VENOUS CATHETER

Ortega et al. *NEJM* 2010;362(E57)

- **LANDMARK**—locate carotid pulse. Internal jugular is immediately lateral to carotid. Ideally use US to localize and guide placement. Insert introducer needle through skin at 20° toward ipsilateral nipple, slightly superior to the apex of the triangle
- **KEY POINTS**—place patient in Trendelenburg position, avoid significant contralateral rotation as it may increase incidence of artery/vein overlap and decrease venous return, occlude hubs at all times to prevent air embolism

PROCEDURES (CONT'D)

- **COMPLICATIONS**—arterial puncture (6.3–9.4%), hematoma (<2.2%), pneumothorax (<0.2%), infections (0.45%)
- **REMOVAL**—place patient in Trendelenburg position and ask him/her to perform a Valsalva maneuver, or time with inspiration if mechanically ventilated and sedated, when removing the catheter to prevent air embolism

SUBCLAVIAN CENTRAL VENOUS CATHETER

Schulman et al. *NEJM* 2018;379(E1)

- **LANDMARK**—subclavian vein is directly underneath clavicle. Ideally use US to localize and guide placement. Insert introducer needle through skin at 20° 2 cm lateral and 2 cm caudal to the middle third of clavicle aiming toward sternal angle. When needle hits clavicle, apply downward pressure (so needle is parallel to clavicle) and slide it under inferior surface to puncture subclavian vein
- **KEY POINTS**—place patient in Trendelenburg position and occlude hubs at all times to avoid air embolism
- **COMPLICATIONS**—arterial puncture (6.3–9.4%), hematoma (<2.2%), pneumothorax (<0.2%), infection (0.12%)
- **REMOVAL**—place patient in Trendelenburg position and ask him/her to perform a Valsalva maneuver, or time with inspiration if mechanically ventilated and sedated, when removing the catheter to prevent air embolism

CENTRAL VENOUS OXYGEN SATURATION

ARTERIAL OXYGEN CONTENT (C_aO_2)

- $C_aO_2 = O_2$ carried by hemoglobin + O_2 dissolved in blood
- $C_aO_2 = 1.36 \times Hb \times S_aO_2 + 0.003 \times P_aO_2$ where S_aO_2 = arterial Hb saturation

VENOUS OXYGEN CONTENT (C_vO_2)

- $C_vO_2 = O_2$ carried by hemoglobin + O_2 dissolved in blood
- $C_vO_2 = 1.36 \times Hb \times S_vO_2 + 0.003 \times P_vO_2$ where S_vO_2 = mixed venous Hb saturation ($S_{c,v}O_2$ if using central venous saturation)

OXYGEN FLUX (DO_2)

- DO_2 = amount of oxygen delivered to tissues/min
- $DO_2 = CO \times C_aO_2$, where $C_aO_2 \sim 1.36 \times Hb \times S_aO_2$ since $0.003 \times P_aO_2$ is negligible

OXYGEN CONSUMPTION (VO_2)

- VO_2 = the arteriovenous oxygen content difference multiplied by cardiac output
- $VO_2 = CO \times (C_aO_2 - C_vO_2) \approx$ constant (the body normally extracts ~25% of the delivered oxygen)

CENTRAL VENOUS OXYGEN SATURATION (CONT'D)

gen except in fever, sepsis, hyperthyroidism, i.e. $VO_2/DO_2 = 0.25$

INTERPRETATION

- As $CO \times (C_vO_2 - C_aO_2) \approx \text{constant}$, $\downarrow C_vO_2$ suggests $\downarrow CO$ or $\downarrow O_2$ consumption from end-stage shock
- S_vO_2 is about 70–75% saturated. A mixed venous saturation of $<50\%$ is alarming, $<25\%$ is usually unsustainable

PROGNOSTIC ISSUES

ACUTE PHYSIOLOGIC AND CHRONIC HEALTH EVALUATION (APACHE) IV SCORE—predicts hospital mortality, web-based programs are available

- **CLINICAL**—age, GCS, organ failure (biopsy-proven cirrhosis, NYHA class IV, severe COPD, chronic hemodialysis, immunocompromise), procedure (non-surgical, elective, emergency operation)
- **VITALS**—HR, RR, MAP, temp
- **ABG**—pH, A-a gradient or PaO_2
- **CBC**—Hct, WBC
- **CHEMISTRY**—Na, K, Cr

SEQUENTIAL (SEPSIS-RELATED) ORGAN FAILURE ASSESSMENT (SOFA)—sequential

assessment of organ dysfunction severity in critically ill sepsis patients, points assigned based on degree of dysfunction of six organ systems. Calculate score at admission and q24 hours

- **CLINICAL**—GCS
- **VITALS**—MAP/administration of vasoactive agent
- **ABG**— PaO_2 , FiO_2
- **CBC**—platelet count
- **CHEMISTRY**—bilirubin, creatinine

VENTILATION—95% of patients with acute respiratory failure can be weaned within 7 days of intubation. 5% are unable to be weaned from the ventilator and require tracheostomy and longer-term ventilatory support

CARDIOPULMONARY RESUSCITATION

CONDITIONS ASSOCIATED WITH NEGLIGIBLE CHANCE OF SURVIVING CPR—decompensated diseases (cancer, sepsis, pre-arrest hypotension or hypoxia, anemia, chronic renal failure), **poor baseline function** (dependent on ADLs), **scene of CPR** (>10 min of CPR without the return of at least a single vital sign, unwitnessed arrest)

CARDIOPULMONARY RESUSCITATION (CONT'D)

PROGNOSIS—respiratory arrest better than cardiac arrest. VT/VF/bradycardia better than asystole/PEA (patients with VF/VT witnessed arrest and response within 5 min of resuscitation have the highest probability of survival to discharge). Outcomes most favorable if resuscitated promptly; however, many have neurologic impairment, particularly if out-of-hospital arrest

COMA AND BRAIN DEATH

EXAMINATION OF THE UNRESPONSIVE PATIENT

- **VITALS**—including GCS
- **5 N**—neurological, noggin (raccoon eyes, Battle sign), neck (C-spine), nose, needle (tracks for recreational drug use)
- **EYES**—fundoscopy, pupillary reflex, corneal reflex, oculocephalic reflex, oculovestibular reflex
- **OTHERS**—gag reflex, cough reflex, tone, limb reflexes, Babinski

GLASGOW COMA SCALE

- **EYES OPENING**—1 = none, 2 = to pain, 3 = to voice, 4 = voluntary
- **LANGUAGE**—1 = none, 2 = sounds, 3 = words, 4 = disorganized sentences, 5 = organized sentences/oriented
- **MOTOR**—1 = none, 2 = extension to pain (decerebrate), 3 = flexion to pain (decorticate), 4 = withdraws, 5 = localizes to pain; 6 = obeys commands
- **CONSIDER INTUBATION**—if GCS <8 , unable to protect airway

OCULOCEPHALIC REFLEX

- **DOLL'S EYES RESPONSE**—avoid this test in patients with suspected cervical spine injury. Move the patient's head from side to side. Conjugate eye movement in the opposite direction to head movement is expected in the comatose patient, while it may be absent/asymmetric if the patient has brain stem injury or if psychogenic

OCULOVESTIBULAR REFLEX

- **CALORIC TESTING**—instillation of ice-cold water into the ear canal on one side (ensure tympanic membrane intact prior to performing). Conjugate eye movement to the irrigated side is expected in the comatose patient (without nystagmus), while it may be absent or asymmetric if brain stem injury. In a conscious patient, nystagmus will be seen with the slow phase toward irrigated side and the fast phase

BRAIN DEATH (CONT'D)

toward the opposite side. Warm water instillation produces the opposite effect (★**COWS**★). In conscious patient instilled with **C**old water, nystagmus fast phase moves toward **O**pposite side; with **W**arm water, nystagmus fast phase moves toward **S**ame side)

ANOXIC BRAIN INJURY SPECTRUM

1. Good recovery (mild disability)
2. Moderate disability (independent with ADLs)
3. Severe disability (dependent for ADLs)
4. Persistent vegetative state (unawareness but awake at times)
5. Persistent coma (unawareness at all times but potentially reversible)
6. Brain death (unawareness at all times and irreversible)

DEFINITION OF BRAIN DEATH

- **HISTORY**—documentation of cause and irreversibility, absence of drug intoxication or poisoning, absence of hypothermia or metabolic causes for encephalopathy
- **PHYSICAL**—core temperature $\geq 34^\circ\text{C}$ [$\geq 93.2^\circ\text{F}$], absence of motor response to painful stimulus, absence of brain stem reflexes (pupillary, corneal, gag, cough, doll's eyes, calorics), apnea testing

BRAIN DEATH (CONT'D)

- **IMAGING**—perfusion scan (most sensitive test), cerebral angiogram, EEG, transcranial doppler US, somatosensory evoked potentials (SSEPs)
- **CRITERIA**—need history, physical features and apnea testing to confirm brain death clinically. If apnea testing cannot be performed or indeterminate, ancillary testing required (cerebral blood flow most reliable 'stand alone' test)
- **BRAIN DEATH MIMICS**—locked-in syndrome (focal injury to pons), hypothermia (light reflex lost $28\text{--}32^\circ\text{C}$ [$82.4\text{--}89.6^\circ\text{F}$], other brain stem reflexes lost $<28^\circ\text{C}$ [82.4°F]), drug intoxication, Guillain-Barré syndrome

APNEA TESTING

1. Pre-oxygenate and obtain ABG just prior to test
2. Pulse oximetry on, ventilator off, 100% oxygen 6 L/min into trachea or place patient on bagger
3. Observe for respiratory movements. Obtain ABG after 10 min. Reconnect ventilator immediately and draw ABG if SBP <100 mmHg, $\text{SpO}_2 <85\%$, or arrhythmia
4. Apnea present if respiratory movements are absent, $\text{PaCO}_2 \geq 60$ mmHg or increased ≥ 20 mmHg above baseline

Hypoxemia**DIFFERENTIAL DIAGNOSIS**

R TO L SHUNT (unresponsive to supplemental O_2 , $V/Q <1$)—ARDS, heart failure, pneumonia, alveolar hemorrhage, atelectasis, pulmonary arteriovenous malformation, intracardiac shunt (ASD, VSD, PFO)

V/Q MISMATCH ($V/Q >1$)—asthma, COPD, fibrosis, pulmonary embolism, tumor-filled alveoli, atelectasis, heart failure, pneumonia, ARDS

DIFFUSION DEFECTS—interstitial lung disease, PJP, atypical pneumonia

HYPOVENTILATION (A-a normal)

- **CNS**—sedating drugs, tumor, stroke, sleep apnea
- **NEUROMUSCULAR**—botulism, Guillain-Barré syndrome, ALS, myxedema
- **UPPER AIRWAY OBSTRUCTION**—epiglottitis, laryngospasm
- **LOWER AIRWAY OBSTRUCTION**—COPD, asthma
- **DEAD SPACE VENTILATION**—COPD

LOW O_2 PARTIAL PRESSURE (A-a normal)—high altitude

PATHOPHYSIOLOGY

DEFINITION OF HYPOXEMIA— $\text{P}_a\text{O}_2 < 60$ mmHg. Note that hypoxia refers specifically to decreased oxygen supply to tissues and organs

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, troponin/CK, lactate
- **IMAGING**—CXR, CT chest
- **ABG**
- **ECG**

OTHER

- BNP, D-dimer, echocardiogram, respiratory pathogen panel, sputum culture

DIAGNOSTIC ISSUES**OXIMETRY**

- **NORMAL**— $>90\%$ is normal. Dyspnea may occur $\sim 85\%$. Pulmonary hypertension may develop from chronic alveolar hypoxia if saturations $<80\%$

DIAGNOSTIC ISSUES (CONT'D)

- **ACCURACY**—between 70% and 100% saturation error is $\pm 2\%$. Saturation values $< 70\%$ may not be valid. Most reliable when applied to well-perfused, warm, and motionless extremities. Nail polish, darkly pigmented skin, carboxyhemoglobin, methemoglobin may all affect readings. Co-oximetry required for accurate results (run ABG). Continuous oximetry is better than spot measurements
- **CORRELATION**— S_pO_2 50% = P_aO_2 27 mmHg, 75% = 40 mmHg, 90% = 60 mmHg, 92% = 80 mmHg, 95% = 90 mmHg. ABG is the gold standard for diagnosing hypoxemia

OVERALL APPROACH TO DETERMINING THE CAUSE OF HYPOXEMIA

1. Confirm ABG shows low P_aO_2
2. Exclude diffusion defects and low partial pressure of O_2
3. Check $PaCO_2$. If normal or low, then hypoventilation is excluded. This leaves either shunt or V/Q mismatch, which can be distinguished with response to O_2 (absence of response suggests shunt. V/Q mismatch should respond to O_2)
4. If high $PaCO_2$, then hypoventilation is present. Check A-a gradient to determine if co-existing shunt or V/Q mismatch (presence of A-a gradient suggests yes and should check response to O_2 to distinguish between these two possibilities)

ALVEOLAR-ARTERIAL (A-a) O_2 GRADIENT

- **NORMAL**—A-a gradient $< \text{age}/4 + 4$, or $< 0.4 \times \text{age}$. Usually < 15 mmHg in young, up to ~ 30 mmHg in elderly
- **CALCULATION**—A-a gradient = $P_aO_2 - P_aO_2 = [(P_B - 47) \times 0.21 - PaCO_2/0.8] - P_aO_2$, where P_B = barometric pressure ≈ 760 mmHg if at sea level

DIAGNOSTIC ISSUES (CONT'D)

- **INTERPRETATION**—calculation used when FiO_2 is 21% (room air). Normal range changes with supplemental oxygen. If A-a gradient normal, consider hypoventilation or low inspired O_2 as causes of hypoxemia. If A-a gradient high, consider V/Q mismatch, R to L shunt, and/or diffusion defects

P_aO_2/P_aO_2 RATIO—when $FiO_2 > 21\%$ (i.e. on supplemental O_2 therapy), P_aO_2/P_aO_2 ratio should be used instead of A-a gradient

- **NORMAL**— $P_aO_2/P_aO_2 \geq 0.99 - (0.003 \times \text{age})$, usually > 0.82
- **INTERPRETATION**—unlike A-a gradient, P_aO_2/P_aO_2 ratio decreases in the presence of V/Q mismatch, R to L shunt, or diffusion defects

MANAGEMENT

ACUTE—ABC, O_2 , IV, **mechanical ventilation if severe respiratory failure** (invasive or non-invasive)

TREAT UNDERLYING CAUSE**TREATMENT ISSUES**

AVOID OVER-CORRECTING O_2 SATURATION IN HYPOVENTILATION— O_2 displaces CO_2 from Hb, causing elevated CO_2 in blood. In addition, O_2 may change V/Q relationship and may decrease hypoxic drive. For patients with chronic hypoventilation ($\uparrow HCO_3^-$), O_2 to keep saturation between 88 and 92% only

SPECIFIC ENTITIES

HYPOXEMIC RESPIRATORY FAILURE ($P_aO_2 < 60$ mmHg)—failure to oxygenate, see DIFFERENTIAL DIAGNOSIS OF HYPOXEMIA

HYPERCARBIC RESPIRATORY FAILURE (P_aCO_2 greater than baseline with concomitant acidosis)—failure to ventilate, see hypoventilation under DIFFERENTIAL DIAGNOSIS OF HYPOXEMIA

Acute Respiratory Distress Syndrome**DIFFERENTIAL DIAGNOSIS****PULMONARY EDEMA**

- **CARDIOGENIC**—ischemic cardiomyopathy, valvular disease
- **NON-CARDIOGENIC**—ARDS, toxic inhalation, drug reaction, aspiration, fat embolism

INFECTION—bacterial, viral, mycobacterial, fungal

DIFFERENTIAL DIAGNOSIS (CONT'D)

HEMORRHAGE—pulmonary embolism, pulmonary contusion, bleeding diathesis, DIC, anticoagulation, vasculitis (granulomatosis with polyangiitis, Goodpasture syndrome, SLE)

PATHOPHYSIOLOGY

DEFINITION OF ARDS

Ranieri et al. *JAMA* 2012;307:23

- **ACUTE ONSET**—new (or worsening) respiratory symptoms <1 week
- **BILATERAL ALVEOLAR INFILTRATES**—often asymmetric/patchy, peripheral > central
- **MODERATE TO SEVERE HYPOXEMIA (WITH PEEP OR CPAP ≥ 5 CM H₂O)**—mild: PaO₂/FiO₂ > 200 mmHg but ≤ 300 mmHg; moderate: PaO₂/FiO₂ > 100 but ≤ 200 mmHg; severe: PaO₂/FiO₂ ≤ 100 mmHg
- **ABSENCE OF CARDIAC FAILURE OR FLUID OVERLOAD**—objective assessment to exclude hydrostatic pulmonary edema (e.g. echocardiography) required if no risk factors for ARDS present

INFLAMMATION IN ARDS—ARDS is a clinical syndrome of severe lung injury due to systemic inflammation. Cytokine release results in capillary membrane permeability and protein-rich fluid exudation into the alveolar space, impairing oxygenation. Ongoing inflammation may lead to extensive fibrosis

PHASES OF ARDS—<10 days = exudative phase, 10–14 days = fibroproliferative-fibrotic phase

HYPOXEMIA IN ARDS—caused mainly by right to left shunt, thus the P_aO₂/F_iO₂ ratio is low. V/Q mismatch and hypoventilation may also contribute

CAUSES—over 80% of ARDS caused by infection, aspiration, and trauma

- **PULMONARY**—pneumonia (bacterial, viral, fungal including PJP, mycobacterial), aspiration, drowning, inhalation injury (O₂, smoke, NO₂), reperfusion injury (post-lung transplant or cardiopulmonary bypass)
- **GI**—acute pancreatitis
- **CNS**—neurogenic (intracerebral hemorrhage)
- **SYSTEMIC**—sepsis, transfusion reaction, major trauma, drugs (heroin, cocaine, aspirin, chemotherapy)

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, troponin/CK, urinalysis, lactate, BNP, lipase if abdominal symptoms
- **MICROBIOLOGY**—blood C&S, respiratory pathogen panel (NP swab and lower resp specimen if intubated), sputum Gram stain/C&S/AFB, urine C&S

INVESTIGATIONS (CONT'D)

- **IMAGING**—CXR, CT chest, echocardiogram
- **ABG**
- **ECG**

DIAGNOSTIC AND PROGNOSTIC ISSUES

PROGNOSIS OF ARDS—overall mortality rate ~45%. Mortality increases with additional organ failure (>99% if three system failures)

MANAGEMENT

ABC—O₂ to keep S_vO₂ 88–95%, IV access

MECHANICAL VENTILATION

Hoo *NEJM* 2013;368(23)

- **LUNG-PROTECTIVE VENTILATION** (low tidal volumes to minimize ventilation-induced lung injury)—set tidal volume ~4–8 mL/kg, based on ideal body weight, maintain plateau pressure ≤ 30 cmH₂O
- **PEEP**—should be employed to keep FiO₂ in non-toxic range (<0.60). Increase PEEP by increments of 3–5 cmH₂O (maximum = 24 cmH₂O) to \uparrow mean airway pressure, recruit alveoli (preventing alveolar collapse and ventilator-induced lung injury) and \uparrow functional residual capacity (may be harmful)
- **RECRUITMENT**—recruitment maneuvers may be used to keep alveoli open; e.g. 40 cmH₂O PEEP for 40 seconds
- **PERMISSIVE HYPERCAPNIA**—generally tolerate pH >7.25, may need to run HCO₃ infusion to maintain pH
- **SALVAGE/ALTERNATE MODES OF VENTILATION**—APRV (airway pressure release ventilation), prone positioning (only salvage technique with mortality benefit), extracorporeal life support

MEDICATIONS—no effective pharmacologic therapy for ARDS. There is limited evidence regarding steroid use for treatment of ARDS and no evidence for prophylaxis. Some clinicians use in non-resolving cases (start 7–14 days after onset. *Methylprednisolone* 2 mg/kg load, then 2 mg/kg/day from days 1 to 14, then taper by 50%/week to 0.125 mg/kg/day, monitor for infection). Inhaled *nitric oxide* or *epoprostenol* selectively dilate pulmonary vessels of ventilated alveoli, improving V/Q matching and oxygenation (but no effect on mortality or ventilation days)

TREAT UNDERLYING CAUSE

OXYGEN DELIVERY AND VENTILATION ISSUES**OXYGEN DELIVERY DEVICES**

Device	Flow rates	FiO ₂ (%)
Nasal cannula	1 L/min	21–24
	2 L/min	25–28
	3 L/min	29–32
	4 L/min	33–36
	5 L/min	37–40
	6 L/min	41–44
Simple oxygen face mask	6–10 L/min	35–60
Face mask with oxygen reservoir (non-rebreather mask)	6 L/min	60

OXYGEN DELIVERY AND VENTILATION ISSUES (CONT'D)

Device	Flow rates	FiO ₂ (%)
	7 L/min	70
	8 L/min	80
	9 L/min	90
	10–15 L/min	95+
Venturi mask	4–8 L/min	24–40
	10–12 L/min	41–50
High flow nasal cannula	Up to 60 L/min	21–100

NOTE—delivered O₂ (FiO₂) is approximate

Ventilation Issues**MECHANICAL VENTILATION****INDICATIONS FOR MECHANICAL VENTILATION**

- **DECREASED COMPLIANCE** (stiff lungs)—pulmonary fibrosis, pulmonary edema, ARDS
- **INCREASED RESISTANCE** (narrowed airways, air trapping)—status asthmaticus, COPD exacerbations, bronchial tumor, excessive secretions
- **MECHANICAL FAILURE**—spinal cord injury, Guillain-Barré and other neuromuscular diseases
- **LACK OF RESPIRATORY DRIVE**—neurologic disease, drug overdose

NON-INVASIVE MECHANICAL VENTILATION (NIMV)

- **CONDITIONS IN WHICH NIMV IS USED**—COPD, HF, asthma, postoperative respiratory failure, postextubation in select situations. If no improvement after 30 min–1 h, should intubate
- **INDICATIONS**—pH 7.2–7.3, RR >25, use of accessory muscles, and cooperative
- **CONTRAINDICATIONS**—↓ level of consciousness (but can consider use if ↓ LOC due to ↑ PCO₂), respiratory arrest, facial trauma/surgery/burn, upper airway obstruction, copious secretions, aspiration risk, GI bleeding, gastroesophageal surgery, esophageal rupture, hemodynamic instability, co-existent organ failure, morbid obesity, extreme anxiety

MECHANICAL VENTILATION (CONT'D)

- **MASK TYPES**—full face, nose and mouth, nasal only
- **VENTILATORY MODES**—CPAP or BIPAP. CPAP is mainly used for obstructive sleep apnea; however, can be used in isolated hypoxemia (ventilation adequate). BIPAP is used to assist with oxygenation and ventilation

INVASIVE MECHANICAL VENTILATION

- **INDICATIONS**—severe hypoxemia, acute hypercapnia, need for airway protection (GCS ≤8), impending airway occlusion, therapeutic hyperventilation. In general, intubate if BIPAP contraindicated or failed, or clinical status severe and likely to require longer term ventilation
- **TUBES**—endotracheal tube, tracheostomy tube (see ARTIFICIAL AIRWAYS p. 114)

TERMINOLOGY

- **RESISTANCE**—restriction that inhibits flow of gas in airways. May result in increased P_{peak} or decreased minute volume (V_E)
- **COMPLIANCE**—ease with which lungs expand. Normal ~50 mL/cm H₂O
- **TIDAL VOLUME (VT)**—amount of air delivered per breath. Normal ~8 mL/kg (500 mL)
- **MINUTE VOLUME (V_E)**—amount of air delivered per minute. V_E (mL/min) = VT × RR
- **POSITIVE END-EXPIRATORY PRESSURE (PEEP)**—maintenance of positive pressure throughout

MECHANICAL VENTILATION (CONT'D)

exhalation. PEEP improves P_aO_2 mainly by augmenting mean airway pressure. Other potential mechanisms include recruitment of collapsed alveoli, increased functional residual capacity, and improvement in V/Q matching. Usually set at 5–15 cmH₂O

- **PEAK AIRWAY PRESSURE** (P_{peak})—maximal inspiratory pressure to distend alveoli and to overcome airway resistance. P_{peak} is dependent on inflation volume, airways resistance, and lung/chest wall compliance. Occurs about halfway through inspiration phase
- **PLATEAU PRESSURE** (P_{plat})—pressure to prevent lungs from deflating at end inspiration. Related to lung/chest wall compliance. Limit to ≤ 30 cmH₂O in ARDS
- **RAPID SHALLOW BREATHING INDEX** (RSBI)—index used for weaning/liberation from mechanical ventilation. $RSBI = RR/\text{tidal volume}$ (measured in liters). The lower the better (<70 is excellent, <100 is good).

ASSESSMENT OF AIRWAY

PRIOR TO INTUBATION—assess airway to anticipate difficulty of procedure, establish IV access (for blood pressure control and medication administration), position patient (sniffing position), remove false teeth/dentures, suction and endotracheal tube ready

SUBJECTIVE SIGNS OF DIFFICULT AIRWAY—prominent upper incisors, short/thick neck, large tongue, micrognathia

OBJECTIVE SIGNS OF DIFFICULT AIRWAY

- **NECK EXTENSION**—atlanto-occipital extension $\leq 35^\circ$
- **THYROMENTAL DISTANCE**— <6 cm [<2.4 in] (3 finger breaths)
- **MOUTH OPENING**— <4 cm [<1.6 in] (2–3 finger breaths)
- **MANDIBULAR LENGTH**— <9 cm [3.5 in]
- **MALLAMPATI SCORE**—III/IV may indicate difficult airway for intubation
 - I = visualization of the soft palate, fauces, uvula, anterior and posterior pillars
 - II = visualization of the soft palate, fauces, and uvula
 - III = visualization of the soft palate and the base of the uvula
 - IV = soft palate is not visible at all

ARTIFICIAL AIRWAYS

ORAL AIRWAYS—used in unconscious patients without a gag reflex to prevent airway collapse/obstruction. Also allow access for suctioning and stimulation of cough. Sizes 8, 9, 10 cm in length

ARTIFICIAL AIRWAYS (CONT'D)

(Guedel sizes 3, 4, 5). Insert backward along the hard palate and rotate into position. If improperly placed, may push tongue posteriorly and obstruct the airway. Can induce vomiting or laryngospasm if placed in an awake or semiconscious patient

ENDOTRACHEAL TUBES (Kabrhel et al. *NEJM* 2007 356:e15)—inserted nasally or orally, with aid of laryngoscope, bronchoscope, or glidescope. Sizes 6.0–9.0 mm in diameter. Cuff occludes airway surrounding endotracheal tube (cuff pressure <25 mmHg ideally; inflate cuff only to the point when leak disappears, i.e. use minimal occlusion pressure to avoid iatrogenic airway ischemia)

TRACHEOSTOMY TUBES

- **INDICATIONS**—long-term ventilation (>10 –14 days intubation), to facilitate weaning, or to bypass an upper airway obstruction
- **TYPES**—Portex[®], Shiley[™] (fenestrated)
- **COMPONENTS**—fenestrations (openings in tracheostomy tube allowing weaker patients to tolerate plugging trials easier), disposable inner cannula (seal fenestration, allows easier exchange of tracheostomy tube if plugged), cuff (balloon that occludes airway surrounding tracheostomy tube)
- **PLUGGING PROCEDURE**—provide alternate source of O₂ (via upper airway), suction of upper and lower airways, deflate cuff completely, remove inner cannula if present, insert plug and lock it in place, assess patient for airway patency, increased work of breathing and stridor
- **DECANNULATION CRITERIA**—breathing spontaneously without ventilator assistance, consistent cough and ability to expectorate secretions, airway protected, on minimal F₂O₂ ($<40\%$ or <5 –6 L/min), no evidence of upper airway obstruction

TRACHEOSTOMY BUTTONS—to maintain stoma during weaning. Less resistance than plugged tracheostomy tube. Usually left in for <24 h

VENTILATORY SETTINGS

RATE—minimal respiratory rate. Normal = 8–16
TIDAL VOLUME—range 5–8 mL/kg of ideal body weight. Normal = 400–600 mL. In volume cycled modes only

PEAK FLOW—determines how fast a positive pressure breath is delivered. In volume cycled modes only

PRESSURE SUPPORT—ranges from 6 cm H₂O (almost no support) to 30 cm H₂O (max support). Normal = 14–16 cm H₂O. In pressure limited modes only

VENTILATORY SETTINGS (CONT'D)

INSPIRATORY TIME—determines duration over which the pressure is delivered. In pressure limited modes only

F_iO₂—range 0.21–1.0. Normal=0.4 or to keep S_pO₂ ≥92%

SENSITIVITY—determines the degree of patient effort required to trigger a positive pressure breath

PEEP/EPAP—generally start at 5 cm H₂O, usual max 15–20 cm H₂O (can go higher in ARDS)

VENTILATORY MODES

- **ASSIST CONTROL (AC)**—mandatory ventilator controlled breaths at set rate. Patient may breathe spontaneously (i.e. trigger the ventilator, “assist” breaths) but ventilator augments breath to reach fixed volume or pressure (VC or PC)
- **VOLUME CONTROL (VC)**—set tidal volume, machine-initiated inspiration
- **PRESSURE CONTROL (PC)**—set pressure, machine-initiated inspiration
- **VOLUME SUPPORT (VS)**—set tidal volume, patient-initiated inspiration (no backup rate, ventilator only boosts airflow to pre-determined volume)
- **PRESSURE SUPPORT (PS)**—set pressure, patient-initiated inspiration (no backup rate, ventilator only boosts airflow to pre-determined pressure)
- **SYNCHRONIZED INTERMITTENT MANDATORY VENTILATION (SIMV)**—mandatory positive pressure breaths delivered at a preset rate and breath type (either volume cycled or pressure limited). Any other breaths patient takes are normal spontaneous breaths with or without additional pressure/volume support (i.e. patient determines size of breath)
- **PRESSURE-REGULATED VOLUME CONTROL (PRVC)**—similar to volume control ventilation, with the ventilator monitoring all respiratory parameters (e.g. pressure) to continually maintain the set tidal volume
- **AIRWAY PRESSURE RELEASE VENTILATION (APRV)**—a form of inverse ratio ventilation using two levels of CPAP (P_{high} and P_{low}). This mode attempts to maximize mean airway pressure and thus alveolar recruitment at P_{high}, while dropping briefly to P_{low} for CO₂ elimination. Used in refractory hypoxemia due to ARDS or massive atelectasis
- **HIGH FREQUENCY OSCILLATORY VENTILATION (HFOV)**—employs very high respiratory rates and very small tidal volumes. Goal is to maximize alveolar recruitment and to minimize ventilator induced lung injury. Has fallen out of

VENTILATORY SETTINGS (CONT'D)

favor for refractory hypoxemia due to ARDS (lack of benefit and potential harm)

- **CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)**—allows a spontaneously breathing patient to breathe at an elevated baseline airway pressure, permitting improved ventilation, decreased work of breathing, reduced atelectasis, and improved gas exchange. May be used as NIMV (more common) or in intubated patients (generally referred to as PEEP with invasive ventilation)
- **BILEVEL POSITIVE AIRWAY PRESSURE (BIPAP)**—consists of inspiratory positive airway pressure phase (IPAP, start at 12 cmH₂O, up to 20 cmH₂O) and expiratory positive airway pressure phase (EPAP, start at 6 cmH₂O, up to 10 cmH₂O). IPAP leads to ↑ airflow which ↑ V_E and helps to ↓ PCO₂, whereas EPAP leads to ↑ FRC and mainly ↑ PO₂. Commonly used form of NIMV

VENTILATOR WEANING AND LIBERATION**CRITERIA FOR LIBERATION FROM VENTILATOR**

- **REVERSAL OF INITIAL DISEASE PROCESS**—complete reversal not necessary. Ideally, stable chest wall and good pain control. Minimal secretions (or strong cough; able to clear secretions), minimal sedation, no metabolic acidosis, adequate hemoglobin, adequate nutrition
- **F_iO₂**—effective oxygenation at F_iO₂ ≤0.5
- **PEEP**—effective gas exchange at PEEP ≤7.5 cmH₂O (unless required for triggering to match auto-PEEP e.g. in advanced COPD)
- **MINUTE VENTILATION**—maintain normal pH at V_E 10–12 Lpm or less
- **SPONTANEOUS PARAMETERS**—while off ventilator, able to generate own parameters. VT >5–7 mL/kg, V_e <10 L, VC = 12–15 mL/kg, NIF (negative inspiratory force) >–20 cmH₂O, RSBI <105 (even better if <70), cuff leak present

PROCESS FOR WEANING VENTILATED PATIENTS

- **MEASURES**—PSV trial builds endurance. Cold nebulizer trial builds strength. The less time the patient is on ventilator, the more normal their lung function, the simpler and shorter the weaning process. Daily spontaneous breathing trials significantly shorten the weaning process
- **QUICK**—switch directly to CPAP, cold neb, or bagger trial. Extubate soon after
- **SLOW**—slowly decrease PSV to low levels, intermittent trials of PSV, CPAP, or cold neb allowing patient to rest on increased or full support

VENTILATOR-ASSOCIATED PNEUMONIA**PATHOPHYSIOLOGY**

- **DEFINITION**—pneumonia in patient mechanically ventilated ≥ 48 h
- **RISK FACTORS**—prolonged mechanical ventilation, need for reintubation, aspiration of gastric contents, acid suppression therapy, supine positioning, poor oral/dental hygiene
- **MICROBIOLOGY**—predominantly *Staphylococcus aureus* (including MRSA), Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter spp*), *Pseudomonas aeruginosa*. Other common microorganisms include *Stenotrophomonas*, *Acinetobacter*

DIAGNOSIS—diagnosis can be difficult. Look for new lung infiltrate, new onset fever, purulent sputum, leukocytosis, decline in oxygenation

VENTILATOR-ASSOCIATED PNEUMONIA (CONT'D)**TREATMENTS**

- **EMPIRIC THERAPY**—treatment should be informed by local resistance patterns and patient risk factors for MDR pathogens. In general, treat with anti-pseudomonal carbapenem or β -lactam/ β -lactamase inhibitor. Add second agent with GN activity if MDR risk factors: aminoglycoside, respiratory fluoroquinolone or polymyxin. Add vancomycin or linezolid if high rates of MRSA. De-escalate therapy as soon as possible when culture results known
- **DURATION OF THERAPY**—short course therapy (7 days) irrespective of etiology

2016 IDSA/ATS Hospital-Acquired VAP Guidelines

Shock**DIFFERENTIAL DIAGNOSIS****★SHOCK★**

DISTRIBUTIVE—septic (pneumonia, bacteremia/line infection, UTI, intraabdominal infection, meningitis, necrotizing fasciitis), drugs, anaphylaxis, hepatic failure, adrenal insufficiency, neurogenic

HYPOVOLEMIC/HEMORRHAGIC—blood loss (trauma, GI bleed, retroperitoneal hemorrhage), GI losses, renal losses, burns

OBSTRUCTIVE—pulmonary embolism, tension pneumothorax, cardiac tamponade

CARDIOGENIC—ischemic, hypertensive, valvular, arrhythmia, peripartum, toxic, infiltrative, idiopathic, familial, autoimmune, myxedema

PATHOPHYSIOLOGY

DEFINITION—hypotension leading to cellular hypoperfusion, hypoxia, lactic acidosis, and subsequent organ failure (oliguria, hepatic and GI dysfunction, altered mental status)

IT'S SIMPLE MATH

- **BP** = $CO \times SVR = (SV \times HR) \times SVR$, where CO = cardiac output and HR = heart rate
- **STROKE VOLUME (SV)**—decreases in cardiogenic, hypovolemic, and obstructive shock
- **SYSTEMIC VASCULAR RESISTANCE (SVR)**—decreases in distributive shock (septic, anaphylactic, neurogenic, hepatic)

CLINICAL FEATURES

HISTORY—risk factors for sepsis, blood loss, MI, or pulmonary embolism; past medical history; medications

CLINICAL FEATURES (CONT'D)

PHYSICAL—vitals, warm vs. cool peripheral extremities (warm in distributive shock, cool in hypovolemic, obstructive, cardiogenic shock). Assess volume status, cardiac and respiratory function. Look for evidence of end-organ dysfunction

ASSESSMENT OF VOLUME STATUS

- **VITALS**—heart rate and blood pressure (postural if possible)
- **SKIN**—skin turgor (inner aspect of thigh, sternum), oral mucosa
- **CARDIOPULMONARY**—JVP or CVP, crackles, S₃
- **URINE**—urine output
- **EXTREMITIES**—peripheral pulses, skin temperature, capillary refill

FEET EXAMINATION

- **WARM FEET**—vasodilation → distributive shock → give fluids and consider vasopressors
- **COLD FEET**—vasoconstriction → cardiogenic vs. hypovolemic/obstructive vs. late septic shock → give fluids and consider inotropes especially if suspect cardiogenic cause. Also check troponin and consider echocardiogram

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, INR, PTT, AST, ALT, ALP, bilirubin, Ca, Mg, PO₄, TSH, D-dimer, lactate, CK, troponin, urinalysis, random cortisol
- **MICROBIOLOGY**—blood C&S, sputum C&S, urine C&S

INVESTIGATIONS (CONT'D)

- **IMAGING**—depends on suspected source; CXR, AXR, echocardiogram, CT where appropriate (e.g. CT abdomen if intra-abdominal source suspected)
- **ECG**
- **ABG**

DIAGNOSTIC ISSUES**PULMONARY ARTERY CATHETERIZATION**

- **INDICATIONS**—diagnosis (shock states, pulmonary artery hypertension, acute valvular disease, intracardiac shunts, cardiac tamponade, pulmonary embolus), hemodynamic monitoring (complicated acute MI, multi-organ system failure, post-cardiac surgery), treatment (aspiration of air emboli). No mortality benefit with use of PA catheter in critically ill patients
- **CONTRAINDICATIONS**—presence of right ventricular assist device, tricuspid or pulmonary mechanical valve, tricuspid or pulmonary valve endocarditis, right heart mass (thrombus and/or tumor)
- **SITES OF ENTRY** (relative preference)—right internal jugular vein (has shortest and straightest path to the heart) > left subclavian vein > right subclavian vein > left internal jugular vein > femoral veins
- **NORMAL VALUES**
 - **CENTRAL VENOUS PRESSURE (CVP)** = 5–8 mmHg, may accept higher values in patients ventilated with high PEEP or high baseline LVEDP (e.g. chronic hypertension)
 - **RIGHT ATRIAL PRESSURE (RAP)** = 5–8 mmHg
 - **RIGHT VENTRICULAR PRESSURE (RVP)** = 20–30/2–8 mmHg
 - **PULMONARY ARTERY PRESSURE (PAP)** = 20–30/5–15 mmHg, mean 10–22 mmHg
 - **PULMONARY CAPILLARY WEDGE PRESSURE (PCWP)** = pulmonary artery occlusion pressure (PAOP) ~ LA pressure = 8–12 mmHg (PCWP >18 mmHg suggests interstitial edema, PCWP >24 mmHg suggests alveolar edema)
 - **LEFT VENTRICULAR PRESSURE (LVP)** = 120/8 mmHg
 - **AORTIC PRESSURE** = 120/80 mmHg, MAP 70–110 mmHg
 - **SYSTEMIC VASCULAR RESISTANCE INDEX (SVRI)** = 1970–2390 dynes-sec/cm⁵/m²
 - **CARDIAC INDEX** = 2.4–4.2 L/min/m², CO = 4–7 L/min
 - **DO₂** = 400–650 mL/min/m²
 - **VO₂** = 125–175 mL/min/m²

DIAGNOSTIC ISSUES (CONT'D)

- **COMPLICATIONS**—arterial puncture, hemothorax, pneumothorax, venous or air embolus, sustained ventricular tachycardia, ventricular fibrillation, heart block (most commonly RBBB, or complete heart block in the setting of pre-existing LBBB), infection, pulmonary artery thrombosis/embolism/infarction/rupture, knotting of catheter (requires fluoroscopic removal), pulmonary or tricuspid valve insufficiency

DISTINGUISHING FEATURES BETWEEN SHOCK STATES

	CO	CVP	PCWP	SVR
Distributive	↑	↓/N	↓/N	↓
Hypovolemic	↓	↓	↓	↑
Cardiogenic	↓	↑	↑	↑
Isolated RHF	↓	↑	↓	↑
Isolated LHF	↓	↓/N	↑	↑
Tamponade ^a	↓	↑	↑	↑

^aIn tamponade or tension pneumothorax, observe equalization of pressures, i.e. CVP = RA = RV = EDP = PCWP; cardiogenic shock gives heart failure picture on CXR, whereas tamponade usually has clear CXR with cardiomegaly only

Related Topics

Anaphylaxis (p. 413)
Myocardial Infarction (p. 30)
Sepsis (p. 118)
Tamponade (p. 38)

MANAGEMENT

ACUTE—ABC, O₂, continuous cardiac and oximetry monitoring, **IV fluid resuscitation** (1–5 L), **ICU consult**, consider intubation/mechanical ventilation, **inotropes or vasopressors** (*norepinephrine* 0.01–0.3 mcg/kg/min IV, up to 1.5 mcg/kg/min in refractory shock; *vasopressin* 0.01–0.04 U/min IV; *epinephrine* 0.01–0.7 mcg/kg/min IV; *ephedrine* 5–25 mg IV q5–10 min until blood pressure stable; *phenylephrine* 20–200 µg/min IV; *dobutamine* 2.5–20 mcg/kg/min IV; *milrinone* 0.375–0.75 mcg/kg/min IV; *dopamine* start 1–4 mcg/kg/min IV, titrate to maximum 20 mcg/kg/min; *midodrine* 5–10 mg PO TID). **Correct coagulopathy** (transfuse PRBC, FFP, cryoprecipitate)

TREAT UNDERLYING CAUSE

TREATMENT ISSUES

INOTROPES/VASOPRESSORS

- **PHYSIOLOGY**— $\alpha 1$ = peripheral vasoconstriction = \uparrow systemic vascular resistance = treatment for sepsis; $\beta 1$ = inotropic and

TREATMENT ISSUES (CONT'D)

chronotropic effect = \uparrow cardiac output = treatment for heart failure; $\beta 2$ = peripheral vasodilation = counter $\alpha 1$ effect

Agent	Mechanism of action	Special note
Norepinephrine	$\alpha 1$ mainly, $\beta 1 \rightarrow \uparrow$ SVR, \uparrow CO	First line for septic shock
Vasopressin	V1, V2 \rightarrow dilates renal, pulmonary, cerebral, coronary arteries and constricts others	Second line for sepsis; AE: gut ischemia, skin necrosis
Epinephrine	$\beta 1, \beta 2, \alpha 1 \rightarrow \uparrow$ CO, \uparrow SVR	Salvage for sepsis, first line for anaphylaxis; AE: ischemia
Phenylephrine	$\alpha 1 \rightarrow \uparrow$ SVR	Sepsis, counteract spinal/epidural anesthesia
Ephedrine	$\beta 1, \beta 2, \alpha 1 \rightarrow \uparrow$ CO, \uparrow SVR	Bolus therapy pending CVC placement for continuous vasopressor therapy
Dobutamine	$\beta 1, \beta 2, \rightarrow \uparrow$ CO, \downarrow SVR	First line for cardiogenic shock
Milrinone	Phosphodiesterase inhibitor $\rightarrow \uparrow$ CO, \downarrow SVR	First line for cardiogenic shock with pulmonary HTN
Dopamine 1–2 $\mu\text{g}/\text{kg}/\text{min}$	DA \rightarrow dilates renal, mesenteric, cerebral arteries and airways	\uparrow renal perfusion/GFR (controversial)
Dopamine 5–10 $\mu\text{g}/\text{kg}/\text{min}$	DA, $\beta 1 \rightarrow \uparrow$ CO	HF/sepsis; AE: tachycardia
Dopamine >10 $\mu\text{g}/\text{kg}/\text{min}$	$\alpha 1 \rightarrow \uparrow$ SVR	Sepsis/HF; AE: tachycardia
Midodrine	$\alpha 1 \rightarrow \uparrow$ SVR	Sepsis; oral

where AE adverse effects, CO cardiac output, CVC central venous catheter, DA dopamine, HF heart failure, HTN hypertension, SVR systemic vascular resistance

Sepsis and Septic Shock

PATHOPHYSIOLOGY

SEPSIS-3 DEFINITIONS (Singer et al. JAMA 2016 315:8)

- **SEPSIS**—life-threatening organ dysfunction caused by a dysregulated host response to infection
- **SEPTIC SHOCK**—sepsis-induced hypotension defined as vasopressor dependence in those with sepsis, despite adequate fluid resuscitation, to maintain MAP ≥ 65 mmHg and having a lactate > 2 mmol/L; characterized by circulatory, cellular and metabolic abnormalities that are associated with high mortality
- **SIRS**—no longer part of sepsis definition as present in many hospitalized patients who never develop infection (poor specificity), poor sensitivity, and is often adaptive/appropriate response to infection

PATHOPHYSIOLOGY (CONT'D)

SIMPLIFIED MECHANISM OF INJURY—infection \rightarrow proinflammatory mediators \rightarrow malignant intravascular inflammation \rightarrow complement activation, \downarrow fibrinolysis \rightarrow endothelial dysfunction, microvascular coagulopathy and thrombosis \rightarrow tissue ischemia \rightarrow organ failure

BAND CELLS—neutrophils with unsegmented nuclei, a developmental stage immediately preceding the mature segmented form

- **LEFT SHIFT**—band cell count $> 0.7 \times 10^9/\text{L}$, commonly seen in infections
- **"SEVERE" LEFT SHIFT**—cells as immature as metamyelocytes may be seen in left shift in response to infection, but unusual to see more immature cells (myelocytes, promyelocytes, blasts). When present, suggestive of myeloproliferative disorder (chronic myelog-

PATHOPHYSIOLOGY (CONT'D)

enous leukemia, agnogenic myeloid metaplasia, or one of the various forms of acute leukemia)

INVESTIGATIONS**BASIC**

- **LABS**—CBC (with differential for left shift), lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, albumin, troponin, CK, INR, PTT, lactate, urinalysis, random cortisol
- **MICROBIOLOGY**—based on clinical syndrome (e.g. sputum, pleural, peritoneal, cerebrospinal fluid cultures); however, all septic patients should have blood and urine cultures
- **IMAGING**—CXR, consider CT based on clinical syndrome (e.g. rule out abdominal pathology such as cholecystitis, intra-abdominal abscess, obstructing renal calculus)

ABG**SPECIAL**

- **LUMBAR PUNCTURE**—if altered level of consciousness
- **THORACENTESIS**—if significant pleural effusion
- **PARACENTESIS**—if ascites

MANAGEMENT

ACUTE—ABC, O₂, IV, consider intubation/mechanical ventilation

RESUSCITATION—fluids (rapid large volume infusions of 500–1000 mL at a time with crystalloids such as Ringer lactate, most patients require 3–10 L IV, albumin is safe but has no mortality benefit, avoid hydroxyethyl starches) and **vasopressors/inotropes** (*norepinephrine* 0.01–0.3 mcg/kg/min but may increase up to 1.5 mcg/kg/min in refractory shock, *vasopressin* 0.01–0.04 U/min IV, *dobutamine* 2.5–20 mcg/kg/min IV) to maintain MAP \geq 65 mmHg or SBP $>$ 90 mmHg, urine output \geq 0.5 mL/kg/h. In addition,

MANAGEMENT (CONT'D)

monitor HR, RR, skin color/temperature, pulse oximetry, mental status, lactate

ANTIMICROBIALS—early **empiric antimicrobials should be administered ASAP, order STAT**. If suspect pulmonary source, macrolide plus β -lactam for community-acquired pneumonia, anti-pseudomonal \pm aminoglycoside or fluoroquinolone (if MDR risk factors) \pm vancomycin (if high-level MRSA endemicity) for nosocomial pneumonia. If suspect urinary source, third-generation cephalosporin or aminoglycoside or carbapenem if high rates of MDR-Gram negatives (such as extended spectrum β -lactamase producers). If suspect intra-abdominal source, β -lactam/ β -lactamase inhibitor or carbapenem. **Tailor antimicrobials** once organism(s) identified and depending on local epidemiology/resistance patterns

SOURCE CONTROL—absolutely imperative. Must drain abscesses and debride devitalized tissues to achieve source control ASAP

GLYCEMIC CONTROL—insulin infusion to keep serum glucose 6–10 mmol/L [110–180 mg/dL], maintaining euglycemia may improve outcomes; however, **must avoid hypoglycemia**

STEROIDS—controversial as no reduction in mortality but hasten time to shock reversal, administer **hydrocortisone** 50 mg IV q6h in patients with moderate-dose vasopressor-dependent shock

BLOOD PRODUCTS—in septic shock patients transfusion may improve oxygen carrying capacity and hypoxia. In stable patients, the threshold for transfusion should be hemoglobin $<$ 70 g/L, with a target of 70–90 g/L

PROPHYLAXIS—DVT (unfractionated heparin SC, LMWH, fondaparinux, pneumatic stockings), **stress ulcer** (PPI or H₂ receptor antagonist)

SPECIFICS—ARDS (lung-protective ventilation), **acute kidney injury** (avoid nephrotoxins, supportive renal replacement therapy), **early enteral feeding**

Lactic Acidosis**DIFFERENTIAL DIAGNOSIS**

TYPE A (occurs with poor tissue perfusion or oxygenation)

- **TISSUE HYPOXIA**—shock, reduced cardiac output or cardiac arrest, hypoxemia, anemia, carbon monoxide poisoning, methemoglobinemia
- **INCREASED OXYGEN DEMAND**—sepsis, seizures, exercise

DIFFERENTIAL DIAGNOSIS (CONT'D)

TYPE B (when evidence of poor tissue perfusion or oxygenation is absent)

- **B1** (systemic diseases)—renal and hepatic failure, diabetes mellitus, and malignancy (lymphoma, leukemia, small cell carcinoma)
- **B2** (drugs/toxins)—metformin, alcohols (ethanol, methanol, ethylene glycol, paraldehyde), cyanide, nitroprusside, isoniazid, epinephrine

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **B3** (inborn errors of metabolism)—defects of pyruvate metabolism, defects of NADH oxidation, disorders of gluconeogenesis (type 1 glycogen storage disease), fatty acid oxidation defects, defects of organic acid metabolism

PATHOPHYSIOLOGY

DEFINITION—>4 mmol/L [>36 mg/dL] (normal ~1 mmol/L [9 mg/dL]) + metabolic acidosis

LACTIC ACID PRODUCTION—part of the glycolytic pathway as pyruvate is converted to lactate to generate NAD from NADH. As anaerobic metabolism increases (↓ O₂ delivery, ↑ metabolic rate), lactate accumulates and causes metabolic acidosis

LACTIC ACID METABOLISM—lactate is metabolized by the liver. Alteration of hepatic function could cause some degree of lactate accumulation. In practice, many cases of chronic lactic acidosis are due to a combined imbalance between increased production and decreased metabolism

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, glucose, urea, Cr, AST, ALT, ALP, bilirubin, serum osmolality and osmolar gap, toxic alcohol levels, troponin, CK, INR, PTT
 - **MICROBIOLOGY**—routine blood and urine C&S, consider culturing other bodily fluids as appropriate (e.g. sputum, pleural, CSF, pericardial, peritoneal)
 - **IMAGING**—AXR ± CT abdomen (if suspect bowel ischemia)
 - **ABG**
- SPECIAL**
- **INBORN ERROR OF METABOLISM** (mitochondrial disorder)—if suspected, consider LP for CSF lactate level ± muscle biopsy

MANAGEMENT

ACUTE—ABC, O₂ to keep S_pO₂ ≥92%, IV, HCO₃ bolus (1–2 amps), or infusion if extremely low pH (<7.2)

TREAT UNDERLYING CAUSE**Toxicology****APPROACH TO OVERDOSE**

HISTORY (brief)—collateral information important, inquire about depression

PHYSICAL (brief)—pupils, lungs, heart, GI, skin

INVESTIGATIONS**BASIC**

- **BLOOD TESTS**—CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, Ca, Mg, PO₄, β-hCG, alcohol level, methanol, ethylene glycol, salicylates, acetaminophen, other drug levels (especially patient's own medications such as digoxin, iron, theophylline, lithium), serum osmolality and osmolar gap
- **URINE TESTS**—urine pregnancy test (if female <50), urine drug screen (as appropriate and may not affect initial management; e.g. opioids, benzodiazepines, cocaine, amphetamines, cannabinoids)
- **IMAGING**—CXR, CT head
- **ECG**
- **ABG**

GENERAL APPROACH TO THE MANAGEMENT OF OVERDOSES

1. **ACUTE**—ABC, O₂, IV, monitor vitals (HR, RR, BP, temp, O₂ sat, blood sugar, GCS), **universal antidote** (glucose 25–50 g IV if capillary glucose measurement not immediately available, naloxone 0.4–2 mg IV, thiamine 50–100 mg IV). Supportive care for airway protection (intubation if GCS ≤8, severe hypoxemia/hypercapnia and/or hemodynamic instability), blood pressure (fluids, vasoactive drugs), arrhythmias, agitation, and seizures
2. **DECONTAMINATION**—**activated charcoal** 50–100 g PO with 60 mL sorbitol (within 1 h ingestion of most drugs except those that are rapidly absorbed). Avoid if bowel obstruction, perforation, or endoscopy is contemplated. **Gastric lavage** with 2–3 mL/kg aliquots if within 60 min of ingestion (should be tried even after 60 min if delayed gastric emptying, e.g. TCA overdose) and if charcoal not indicated (e.g. iron, lithium, cyanide). **Whole bowel irrigation** (polyethylene glycol 2 L/h, up to 10 L). **Skin** (remove clothing, cleanse). Ipecac not recommended

GENERAL APPROACH TO THE MANAGEMENT OF OVERDOSES (CONT'D)

3. **ALKALINIZATION AND/OR HEMOPERFUSION/HEMODIALYSIS—forced alkaline diuresis** will accelerate excretion of acids (aspirin, barbiturates). Give 3 amps of NaHCO_3 in 1 L D5W at 250 mL/h. Monitor urine output and for volume overload, alkalosis and hypokalemia. Goal pH for urine is 7.5–8 and for serum is 7.5–7.6. Consider **hemodialysis** if the patient is toxic with barbiturate, bromides, chloral hydrate, alcohols (isopropanol, acetone, methanol, ethylene glycol), lithium, procainamide, theophylline, salicylates, heavy metals, trichloroethanol, atenolol, sotalol, acebutolol or nadolol
4. **SPECIFIC ANTIDOTES—acetaminophen** (*N-acetylcysteine* 150 mg/kg (~60 mL) in 200 mL D5W IV over 1 h, then 50 mg/kg (~20 mL) in 500 mL D5W IV over 4 h, then 100 mg/kg (~40 mL) in 1 L D5W IV over 16 h. Alternatively, *N-acetylcysteine* 140 mg/kg PO/NG, followed by 70 mg/kg q4h for 17 doses). **Opioids** (*naloxone* 0.4–2 mg IV, repeat PRN). **Benzodiazepines** (*flumazenil* 0.2 mg over 30 s, then 0.5 mg q1min PRN. Maximum total dose 3 mg). **Methanol/ethylene glycol** (*Fomepizole* 15 mg/kg IV, followed by 10 mg/kg q12h until ethylene glycol level <3.2 mmol/L [<20 mg/dL]). If fomepizole not available, 10% *ethanol* in D5W 10 mL/kg IV over 30 min, then 1.5 mL/kg/h, goal EtOH level 22–28 mmol/L [100–128 mg/dL]). **Digitalis** (*Digibind*® 10–20 vials IV if life-threatening arrhythmia). **Calcium channel blockers** (CaCl_2 1 g over 5 min, repeat if lifethreatening disease). **β -blockers** (*glucagon* initial dose 0.05–0.15 mg/kg up to a max dose of 10 mg over 2 min, then infusion 0.07 mg/kg). **Isoniazid** (*pyridoxine* given gram-to-gram of INH ingested). **Tricyclic antidepressant** (NaHCO_3 1–2 mmol/kg IV if cardiac arrhythmia). **Anticholinergics** (*lorazepam* 2–10 mg IV q5min, physostigmine). **Iron** (*deferoxamine* 1 g IM or IV, then 500 mg q4h \times 2, then 500 mg q4–12 h PRN. Maximum total dose 6 g/day). **Cholinergics** (*atropine* 0.5–2 mg IV, repeat q5–30 min PRN)
5. **ANTICIPATE COMPLICATIONS**—delirium, aspiration pneumonia, respiratory failure, electrolyte imbalances, arrhythmias, hypotension, seizures, and others. Consider ICU/CCU consultation where appropriate
6. **PSYCHIATRY CONSULT WHEN STABLE**

ANTICHOLINERGIC SYNDROMES

CAUSES—TCAs, antihistamines, antipsychotics, anti-Parkinson medications, amantadine, antispasmodics, mydriatics, skeletal muscle relaxants

CLINICAL FEATURES—common (fever, tachycardia, hypertension, *dry/flushed skin*, delirium, hallucinations, mydriasis, urinary retention, decreased bowel sounds), **serious** (seizures, coma, respiratory failure, arrhythmias, cardiovascular collapse). ECG findings may include sinus tachycardia, prolonged PR, QRS, and QT intervals, RBBB and ST elevation in leads V1–V3

TREATMENTS—supportive measures, **charcoal**, HCO_3^- if cardiac arrhythmia, sedation with benzodiazepines PRN

SYMPATHOMIMETIC SYNDROMES

CAUSES—cocaine, amphetamines/methamphetamines, LSD, PCP, phenylpropranolamine, ephedrine, pseudoephedrine, methylphenidate, nicotine, theophylline

CLINICAL FEATURES—common (fever, tachycardia, hypertension, *diaphoresis*, delusions, paranoia, mydriasis, hyperreflexia), **serious** (seizures, coma, arrhythmias, cardiovascular collapse)

TREATMENTS—supportive measures, **sedation** with benzodiazepines. Treat severe hypertension (nitroprusside, phentolamine). Avoid β -blockers (unopposed α effect). Control hyperthermia (cooling blanket, may require **paralysis** to limit muscular activity)

CHOLINERGIC SYNDROMES

CAUSES—organophosphate and carbamate insecticides, pilocarpine, physostigmine, edrophonium, some mushrooms

CLINICAL FEATURES—common (delirium, salivation, lacrimation, miosis, diaphoresis, emesis, urinary and fecal incontinence), **serious** (pulmonary edema, seizures, coma)

TREATMENTS—supportive measures, **atropine**

METHANOL AND ETHYLENE GLYCOL OVERDOSE

See METHANOL and ETHYLENE GLYCOL OVERDOSE p. 480

ACETAMINOPHEN OVERDOSE

PATHOPHYSIOLOGY—5% of acetaminophen is metabolized to *N-acetyl-p-benzoquinoneimine* (NAPQI), which is highly toxic to liver, but is normally rapidly inactivated by conjugation with glutathione. With acetaminophen overdose, NAPQI accumulates due to depletion of glutathione

ACETAMINOPHEN OVERDOSE (CONT'D)

stores, causing hepatic necrosis and acute kidney injury. *N*-acetylcysteine, the antidote, regenerates hepatic glutathione stores leading to enhanced conjugation and clearance of NAPQI. A single dose of 10–15 g acetaminophen (twenty 500 mg tablets) can produce liver injury. Fulminant hepatic failure (FHF) usually associated with >25 g

★**The rule of 140s**★ toxic dose = 140 mg/kg, Rumack-Matthew nomogram blood level vs. time (>140 µg/mL 4 h after ingestion → >5 µg/mL 24 h after ingestion). First dose of *N*-acetylcysteine 140 mg/kg PO (IV infusion may also be used: 150 mg/kg in 200 mL D5W over 15 min, then 50 mg/kg in 500 mL D5W over 4 h, then 100 mg/kg in 1 L D5W over 16 h; may continue third stage until liver enzyme normalization in FHF)

CLINICAL FEATURES—first few hours, nausea and vomiting, RUQ pain, diarrhea. Symptoms disappear 24 h after ingestion. Liver failure (↑ INR, bilirubin, transaminases, and encephalopathy) may start at 24–72 h with or without AKI or cardiotoxicity

POOR PROGNOSTIC SIGNS—coagulopathy (most important), acidosis, acute kidney injury, hypophosphatemia, encephalopathy

TREATMENTS—supportive, *N*-acetylcysteine (duration of therapy controversial; if evidence of hepatic injury, continue NAC until transaminases decreasing, INR ≤2, and serum acetaminophen concentration undetectable)

KING'S COLLEGE CRITERIA FOR LIVER TRANSPLANTATION IN TYLENOL OVERDOSE ★**The rule of 3's**★—either pH <7.3 or grade III/IV encephalopathy plus Cr >300 µmol/L [>3.3 mg/dL] plus INR >6.5 (or PT >100 s) (~5% survival with medical therapy alone)

SALICYLATE OVERDOSE

CAUSES (★**The rule of 3's**★)—a single dose of 10–30 g (30 tablets of 325 mg) can be fatal. Symptoms may occur with salicylate >3.0 mmol/L [>40 mg/mL]

CLINICAL FEATURES—**common** (tinnitus, vertigo, N&V, diarrhea, tachypnea, metabolic acidosis, respiratory alkalosis), **serious** (hyperthermia, pulmonary edema, delirium, seizure, coma)

DIAGNOSIS—salicylate level (every 2 h until decreased level), ABG (every 2 h until stable)

TREATMENTS—**supportive** measures (avoid intubation if possible). Consider gastric lavage. **Glucose** 100 mL of D50W IV if altered mental status regardless of serum glucose level. **Activated charcoal** (50–100 g PO/NG q4h × 3doses).

SALICYLATE OVERDOSE (CONT'D)

Alkalinize serum and urine; maintain urine pH 8–8.5 (**NaHCO₃** 1–3 amps IV push, then 3 amps of NaHCO₃ in 1 L D5W at 250 mL/h). Consider **hemodialysis** if altered mentation, cerebral edema, fluid overload, pulmonary edema, severe renal failure, salicylate >7.2 mmol/L [>100 mg/mL] in acute ingestion or >5 mmol/L [>70 mg/mL] in chronic toxicity, rising levels or clinical deterioration

MORTALITY RATE—acute ~1–2% (usually suicidal attempt in young patient), chronic ~25% (often elderly patient, delayed diagnosis due to low index of suspicion)

OPIOID, SEDATIVE OR ETHANOL INTOXICATION SYNDROMES

CAUSES—opioids, barbiturates, benzodiazepines, ethanol, clonidine

CLINICAL FEATURES—**common** (decrease in all vitals, hypothermia, stupor, miosis, dry skin, urinary retention, decreased bowel sounds, hyporeflexia), **serious** (seizures, coma, respiratory depression). Note vitals may be relatively normal, particularly for benzodiazepine overdose

TREATMENTS—**supportive** measures, **naloxone** (if opioids), **flumazenil** (if benzodiazepines), **urinary alkalization** (if barbiturates)

β-BLOCKER OVERDOSE

CLINICAL FEATURES—**common** (hypotension, bradycardia, bronchospasm, hypoglycemia), **serious** (shock, asystole, seizure, coma)

TREATMENTS—**supportive** measures, **fluid** resuscitation, **glucagon** (initial dose 0.05–0.15 mg/kg up to a max dose of 10 mg over 2 min, then infusion 0.07 mg/kg), **IV calcium**, **phosphodiesterase inhibitor** (milrinone or amrinone), **epinephrine**, **dialysis** (for atenolol, sotalol, acebutolol or nadolol), high dose **insulin/glucose infusions**, **intravenous lipid emulsion therapy**. **Atropine** or **pacing** not usually effective. Consider intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) in severely poisoned

CALCIUM CHANNEL BLOCKERS OVERDOSE

CAUSES—dihydropyridine calcium channel blockers (nifedipine, amlodipine, isradipine) affect mainly vascular tone and may cause hypotension with reflex tachycardia. Non-dihydropyridine calcium channel blockers (diltiazem, verapamil) usually lead to SA/AV slowing and negative inotropy

CALCIUM CHANNEL BLOCKERS OVERDOSE (CONT'D)

CLINICAL FEATURES—**common** (hypotension, arrhythmias, delirium, hypokalemia, lactic acidosis, hyperglycemia)

TREATMENTS—**supportive** measures. **Fluid** resuscitation, catecholamines, **IV calcium** (*calcium gluconate* 10% 50 mL or *calcium chloride* 10% 20 mL), **glucagon**, **high dose insulin/glucose infusions**, **intravenous lipid emulsion therapy**. **Hemodialysis not effective**. Consider IABP or ECMO in severely poisoned

LITHIUM TOXICITY

CAUSES—usually related to chronic drug accumulation, although acute overdose may occur. Commonly precipitated by renal failure and dehydration. Therapeutic Li levels 0.6–1.2 mEq/L, mild toxicity = 1.5 to <2.5 mEq/L, moderate toxicity = 2.5–3.5 mEq/L, severe toxicity >3.5 mEq/L

CLINICAL FEATURES—**acute toxicities** include CNS (confusion, ataxia, seizures, coma), neuromuscular (tremors, fasciculations, rigidity, weakness), and others (sinus bradycardia, hypotension, ARDS, acute renal failure, nausea and vomiting, diarrhea, leukocytosis, hypercalcemia). **Chronic toxicities** include nephrogenic diabetes insipidus, leukocytosis, and goiter

TREATMENTS—**supportive** measures, gastric lavage if within 60 min of ingestion, fluid resuscitation with NS followed by **hypotonic solution** infusion if nephrogenic diabetes insipidus, Kayexalate® (binds lithium), whole bowel irrigation, **hemodialysis** (if Li >3.5 mEq/L in acute ingestion or >2.5 mEq/L in chronic ingestion **and** significant symptoms, or persistently high Li levels, beware of rebound effect after hemodialysis due to redistribution)

DIAGNOSTIC ISSUES FOR OVERDOSE

OSMOLAR GAP—measured osmolality – calculated osmolality

- **Osmo_{calc}** = (Glucose in mmol/L) + (Urea in mmol/L) + 2 × (Na mmol/L) ★ **GUN2★**
- US units: **Osmo_{calc}** = (Glucose in mg/dL)/18 + (Urea in mg/dL)/2.8 + 2 × (Na mEq/L)
- **NORMAL OSMOLAR GAP**—typically 2 to +6 mOsm/kg
- **INCREASED OSMOLAR GAP AND ANION GAP**—elevated if >10 mOsm/kg: ethylene glycol, methanol, diabetic or alcoholic ketoacidosis, lactic acidosis, chronic renal failure (other small solutes), severe lactic acidosis (“idiogenic osmole”), sepsis (some inflammatory mediators are believed to be osmotically active)
- **INCREASED OSMOLAR GAP BUT NORMAL ANION GAP**—ethanol, isopropyl alcohol, diethyl ether, sorbitol, mannitol, severe hyperproteinemia, severe hyperlipidemia

ANION GAP (AG)—Na – Cl – HCO₃. AG >12 mEq/L is abnormal and can be caused by methanol, ethylene glycol, uremia, ketoacidosis, paraldehyde, INH, iron, lactic acidosis, cyanide, arsenic, toluene, salicylates (see **METABOLIC ACIDOSIS** p. 94). Decreased anion gap can be caused by excessive cations such as in Li toxicity. Remember to adjust AG in hypoalbuminemia by adding 2.5–3 mmol/L for every 10 g/L [1.0 g/dL] decrease in serum albumin.

OXYGEN SATURATION GAP—>5% difference between pulse oximetry and oxygen saturation on ABG is seen with carbon monoxide, cyanide, hydrogen sulfide, and methemoglobin poisoning

ANTICHOLINERGIC AND SYMPATHOMIMETIC SYNDROMES—anticholinergic syndromes lead to dry skin whereas sympathomimetic syndromes are associated with diaphoresis

Hypothermia

CAUSES

INCREASED HEAT LOSS

- **ENVIRONMENTAL**—cold exposure
- **DERMATOLOGIC**—burns, extensive psoriasis, vasodilation (drugs, alcohol, sepsis, pancreatitis)
- **IATROGENIC**—cold fluid infusion, CPR, renal replacement therapy

DECREASED METABOLISM

- **ENDOCRINE**—hypothyroidism, hypopituitarism, adrenal insufficiency, hypoglycemia
- **METABOLIC**—anorexia nervosa, malnutrition

CAUSES (CONT'D)

ALTERED REGULATION

- **CENTRAL**—stroke, Parkinson disease, multiple sclerosis, hypothalamic dysfunction, anorexia nervosa, drugs (barbiturate, TCA, sedatives, alcohol)
- **PERIPHERAL**—neuropathies, diabetes

PATHOPHYSIOLOGY

DEFINITION OF HYPOTHERMIA—internal temperature <35 °C [<95 °F] (by rectal, tympanic, or esophageal thermometer). Hypothermia may

PATHOPHYSIOLOGY (CONT'D)

be mild (32–35 °C [90–95 °F]), moderate (28–32 °C [82–90 °F]), or severe (<28 °C [<82 °F])

RISK FACTORS—extremes of age, alcoholism, malnutrition, homelessness, mental illness

COMPLICATIONS—hypothermia affects most organs, causing cognitive (coma), neuromuscular (rigidity), respiratory (pulmonary edema), cardiac (arrhythmia), and cutaneous (frostbite) complications. Sepsis, pneumonia, hypokalemia, hypoglycemia, and rhabdomyolysis may also occur

CLINICAL FEATURES

HISTORY—exposure to cold (duration, environment), shivering, confusion, delirium, palpitations, weakness, ulcers, frostbite, fever, weight loss, past medical history (hypothyroidism, diabetes, alcoholism, psoriasis), medications, social history

PHYSICAL—vitals (bradycardia, apnea, hypertension/hypotension, hypoxemia), GCS, respiratory and cardiovascular examination (arrhythmia), rigidity, hyporeflexia, skin examination (frostbite, burns, psoriasis)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, Ca, CK, troponin, AST, ALT, ALP, bilirubin, TSH, urinalysis, random cortisol, serum lactate, fibrinogen, lipase, consider toxicology screen
- **MICROBIOLOGY**—blood cultures
- **IMAGING**—CXR, consider CT head
- **ECG**—Osborn wave (elevated J point), prolonged RR, PR, QRS, and QT intervals

MANAGEMENT

ACUTE—**ABC**, O₂ to keep sat ≥92%, **IV**, **rewarming**. Caution with fluid overload (decreased cardiac output in hypothermic patients) and vasopressors (arrhythmogenic potential). Resuscitation should continue until patient completely rewarmed

MONITORING—continuous cardiac monitoring. Also closely monitor electrolytes and glucose. Vagotonic maneuvers (e.g. intubation or suctioning) may precipitate asystole

MANAGEMENT (CONT'D)

REWARMING—**environment** (remove cold clothing, warming blanket). **Active rewarming** (warm IV fluids ~40–42 °C [104–108 °F]. If severe hypothermia, consider colonic/bladder irrigation, peritoneal or pleural lavage, extracorporeal blood rewarming. Goal of rewarming is 0.5–2 °C/h [1.8 °F/h] to minimize risk of VF and hypovolemic shock)

FROSTBITE—supportive care. Skin grafting and amputation may be required if gangrene develops

SPECIFIC ENTITIES**ELECTRICAL INJURY**

- **PATHOPHYSIOLOGY**—causes include lightning, taser, and stun gun
- **CLINICAL FEATURES**—injuries may involve the skin (burns), heart (VF, asystole, cardiac contusion), bones/muscles (deep electrothermal tissue injury, osteonecrosis, compartment syndrome, rhabdomyolysis with renal failure, posterior shoulder dislocation), and neurologic system (loss of consciousness, weakness or paralysis, respiratory depression, autonomic dysfunction)
- **DIAGNOSIS**—clinical. Obtain CBC, lytes, urea, Cr, glucose, CK, appropriate imaging, drug and alcohol levels, urinalysis, CXR, ABG, ECG
- **TREATMENTS**—ABC, O₂, IV. Supportive management of complications. Monitor for compartment syndromes. Psychiatry consult for post-traumatic stress disorder

SUBMERSION INJURY (drowning)

- **CLINICAL FEATURES**—assess for cause of drowning (accidental, suicidal, alcohol or illicit drug use, concomitant myocardial infarction/stroke). Complications include respiratory failure, ARDS, hypothermia, arrhythmia (atrial fibrillation, bradycardia, ventricular tachycardia), acidosis (metabolic, respiratory), anoxic brain injury, cerebral edema, and seizures
- **DIAGNOSIS**—clinical. Obtain CBC, lytes, urea, Cr, glucose, osmolality, drug and alcohol levels, urinalysis, CXR, ABG, and ECG
- **TREATMENTS**—ABC, O₂, IV. Supportive management of complications. 75% of near-drowning victims survive

Smoke Inhalation

PATHOPHYSIOLOGY

MECHANISM OF INJURY—thermal injury, hypoxic gas inhalation, bronchopulmonary toxins (airway inflammation, possible ARDS), systemic toxins (CO, CN)

CLINICAL FEATURES

HISTORY—exposure to smoke (duration, substance, environment), dyspnea, chest pain, confusion, loss of consciousness, burns, other injuries, past medical history (respiratory disorders), medications

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, temperature, hypoxemia), GCS, respiratory examination (cyanosis, cherry red lips, accessory muscle use, wheeze), cardiovascular examination (HF), burns, screening abdominal and neurologic examination

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, glucose, carboxy-hemoglobin level, cyanide level, methemoglobin level (↓ with cyanide poisoning), lactate (↑ with cyanide poisoning)
- **IMAGING**—CXR
- **ECG**
- **ABG**—to determine PaO₂, PaCO₂, and CO-Hb levels
- **LARYNGOSCOPY/BRONCHOSCOPY**—if significant burns

MANAGEMENT

ACUTE—**ABC**, high flow O₂ to keep S_pO₂ ≥92% (100% FiO₂ if CO poisoning suspected pending ABG; see below), **IV**. Consider early **intubation** if

MANAGEMENT (CONT'D)

severe injury/symptoms. *Salbutamol* and *ipratropium* for bronchodilation

SPECIFIC POISONING—see CO and CN poisoning

BURNS—fluids, wound care. Plastic surgery consult

SPECIFIC ENTITIES

CARBON MONOXIDE (CO) POISONING

- **PATHOPHYSIOLOGY**—CO is an odorless, colorless, and non-irritating gas. It has a high affinity for hemoglobin, preventing it from releasing O₂
- **CLINICAL FEATURES**—nausea, malaise, headache, dyspnea, angina, confusion, coma
- **TREATMENTS**—100% FiO₂ (decreases t_{1/2} of CO from 4 to 1.5 h). Hyperbaric oxygen may be used in selected patients (CO >25%, end-organ ischemia, or loss of consciousness); however, logistically challenging in critically ill patient

CYANIDE (CN) POISONING

- **PATHOPHYSIOLOGY**—produced by combustion of common household materials (polyurethane, nylon, wool, and cotton). CN binds to iron-containing enzymes (e.g. cytochrome) inhibiting aerobic metabolism
- **CLINICAL FEATURES**—severe lactic acidosis, cardiac dysfunction, apnea, coma
- **TREATMENTS**—cyanide antidotal treatment with *hydroxocobalamin* and *sodium thiosulfate*. If hydroxocobalamin not available give Cyanide Antidote Kit (inhaled *amyl nitrite*, intravenous *sodium nitrite*, *sodium thiosulfate*)

Anaphylaxis

See ANAPHYLAXIS (p. 413)



Nausea and Vomiting

DIFFERENTIAL DIAGNOSIS

NEUROLOGIC

- **ORGANIC**—migraine, increased IC pressure (infections, tumors, hemorrhage), multiple sclerosis, vestibular nerve or brain stem lesions
- **DRUGS**—chemotherapy, SSRI, opioids, antibiotics, hormonal therapy, cannabis hyperemesis
- **PSYCHIATRIC**—anorexia nervosa, bulimia nervosa, rumination

GASTROINTESTINAL

- **INFECTIONS**—acute gastroenteritis (viral/bacterial), UTI, pyelonephritis, pneumonia
- **NEOPLASTIC**—gastric, ovarian, paraneoplastic, renal
- **OBSTRUCTION**—stomach, small bowel, colon, gastric volvulus, chronic intestinal pseudoobstruction
- **INFLAMMATION**—esophagus, stomach, duodenum
- **GASTROPARESIS**—ischemic, diabetic, amyloidosis, scleroderma, drugs
- **OTHERS**—hepatobiliary disease, pancreatic disease, peritoneal irritation, functional gastrointestinal disorders, cyclic vomiting syndrome, retroperitoneal fibrosis

METABOLIC

- **ENDOCRINE**—diabetes, adrenal insufficiency, hypercalcemia, hyperthyroidism, hyperparathyroidism, porphyria
- **OTHERS**—uremia, pregnancy/hyperemesis gravidarum, post-operative

IDIOPATHIC

PATHOPHYSIOLOGY

REFLEX PATHWAY

- **AFFERENT**—(1) **humoral factors** (drugs, toxins, neurotransmitter, peptides) → area postrema in floor of 4th ventricle (chemoreceptor trigger zone) → **nucleus tractus solitarius** (NTS) in medulla serves as central pattern generator for vomiting; (2) neuronal **G1 tract**

PATHOPHYSIOLOGY (CONT'D)

- stimuli → vagus nerve → NTS; (3) **nociceptive** stimuli → sympathetic nervous system → brain stem nuclei and the hypothalamus
- **EFFERENT**—NTS → **paraventricular nuclei** of the hypothalamus and the limbic and cortical regions → gastric electromechanical events are perceived as normal sensations or nausea or discomfort → vagus nerve → gastric and lower esophageal sphincter relaxation, retrograde contraction in proximal small bowel and antrum, abdominal muscle contraction and initial cricopharyngeus contraction followed by relaxation seconds before vomiting

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, glucose, Ca, Mg, PO₄, AM cortisol, urinalysis
- **MICROBIOLOGY**—urine C&S
- **IMAGING**—CXR, AXR

SPECIAL

- **GASTROSCOPY, GASTRIC EMPTYING STUDY**
- **CT HEAD**

MANAGEMENT

SYMPTOM CONTROL

- **H1 ANTAGONISTS**—*dimenhydrinate* 25–50 mg PO/PR q4h, *diphenhydramine* 25–50 mg PO/IV/IM q4h, *cyclizine* 50 mg PO/IM q4h or 100 mg PR q4h, *meclizine* 25–50 mg PO daily, *promethazine* 12.5–25 mg PO/IM q4h or 12.5–25 mg PR daily
- **D2 ANTAGONISTS**—**benzamides** (*metoclopramide* 5–10 mg PO/IV/IM q4h), **phenothiazine** (*prochlorperazine* 5–10 mg PO q6–8 h, *chlorpromazine* 10–25 mg PO q4–6 h), **butyrophenones** (*droperidol* 1.25–5 mg IM q4h, *haloperidol* 0.5–1 mg IV/PO q4h), *domperidone* 10 mg PO TID

MANAGEMENT (CONT'D)

- **5HT₃ ANTAGONISTS**—*ondansetron* 4–8 mg PO/IV q8h, *granisetron* 2 mg PO or 1 mg IV, *dolasetron* 100 mg PO/IV daily
- **5HT₄ AGONISTS**—*prucalopride* 1–2mg PO daily
- **M₁ ANTAGONISTS**—*scopolamine* 1.5 mg TD q72h
- **STEROID**—*dexamethasone* 4 mg PO/SC/IV BID–TID

MANAGEMENT (CONT'D)

- **TUBE FEED**—NG/J tube, G tube
- TREAT UNDERLYING CAUSE**

Related Topics

Nausea and Vomiting in the Palliative Setting (p. 440)

Dysphagia**DIFFERENTIAL DIAGNOSIS**

OROPHARYNGEAL (pharynx or upper esophageal sphincter dysfunction)

- **NEUROLOGICAL**—stroke, multiple sclerosis, Parkinson, dementia, amyotrophic lateral sclerosis, Guillain-Barré syndrome, myasthenia gravis, cerebral palsy, Huntington, tardive dyskinesia, brain stem tumors, trauma
- **MYOPATHIC**—myotonic dystrophy, dermatomyositis, polymyositis, connective tissue disease, sarcoidosis, paraneoplastic
- **STRUCTURAL**—cricopharyngeal bar, Zenker diverticulum, cervical webs, oropharyngeal tumors, osteophytes and skeletal abnormality, cleft palate, ill-fitting dentures/poor dentition
- **INFECTIOUS**—syphilis, Lyme disease, botulism, mucositis (viral, fungal)
- **METABOLIC**—Cushing syndrome, thyrotoxicosis, Wilson syndrome, amyloidosis, Sjögren syndrome
- **IATROGENIC**—chemotherapy, neuroleptics, postsurgical, radiation
- **FUNCTIONAL** (globus sensation)

ESOPHAGEAL (body of esophagus, lower esophageal sphincter, cardia)

- **STRUCTURAL**—**tumors**, **esophagitis/stricture** (reflux, caustic/erosive, infectious, eosinophilic, pill, radiation), **iatrogenic** (post-surgery, radiation), esophageal ring/web, **extrinsic compression** (cardiac, mediastinal mass, lung cancer, lymphoma, osteophytes, subclavian artery)

MANAGEMENT (CONT'D)

- **MOTILITY**—achalasia, scleroderma, Chagas disease, diffuse esophageal spasm, hypertensive lower esophageal sphincter/EGJ outflow obstruction, jackhammer esophagus, ineffective esophageal motility

CLINICAL FEATURES

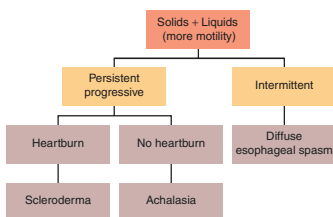
DIAGNOSTIC CLUES—heartburn may suggest GERD leading to erosive esophagitis, peptic stricture, or esophageal adenocarcinoma. History of atopic diseases in a young adult with recurrent dysphagia may suggest eosinophilic esophagitis. Also check for odynophagia, regurgitation, hematemesis, coffee ground emesis, respiratory symptoms, weight loss, and medications (tetracycline, bisphosphonates, potassium supplements)

PRACTICAL APPROACH TO DYSPHAGIA

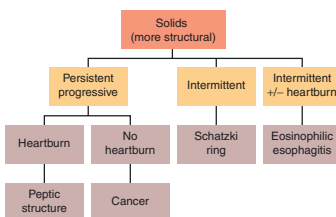
1. Features of oropharyngeal dysphagia (problems initiating swallowing, extending neck/arms when swallowing, changes in speech, coughing, choking, or nasal regurgitation)? Consider workup for oropharyngeal dysphagia. Otherwise, proceed to step 2
2. Difficulty swallowing both solids and liquids? If yes, consider motility disorders and proceed to step 3. If solid only or dysphagia progressing from solids to liquids, consider structural disorders and proceed to step 4

CLINICAL FEATURES (CONT'D)

3. For motility disorders, is the dysphagia progressive? If yes, consider achalasia or scleroderma. If intermittent, consider diffuse esophageal spasm or esophageal motility disorder

**CLINICAL FEATURES (CONT'D)**

4. For structural disorders, is the dysphagia progressive? If yes, consider tumors or stricture. If intermittent, consider esophageal ring, eosinophilic esophagitis
5. Any caustic ingestion history?

**INVESTIGATIONS****BASIC**

- **IMAGING**—barium swallow (esophageal), videofluoroscopy (oropharyngeal)
- **SWALLOWING ASSESSMENT**—occupational therapy or speech pathology

SPECIAL

- **GASTROSCOPY**—for esophageal structural lesions and esophageal biopsies
- **ESOPHAGEAL MANOMETRY**—definitive for achalasia, useful for diffuse esophageal spasm and esophageal motility disorders
- **pH MONITORING**—for refractory GERD, especially if gastroscopy normal (non-erosive GERD)
- **FIBEROPTIC NASOPHARYNGEAL LARYNGOSCOPY**—for oropharyngeal dysphagia

MANAGEMENT

SYMPTOM CONTROL—postural/nutritional/behavioral modifications, swallowing rehabilitation, esophageal dilation

TREAT UNDERLYING CAUSE**SPECIFIC ENTITIES****ACHALASIA**

- **PATHOPHYSIOLOGY**—a motor disorder with failure of relaxation of the lower esophageal sphincter and abnormal peristalsis in the body of the esophagus on manometry
- **DIAGNOSIS**—endoscopy essential for ruling out malignancy (“pseudoachalasia”). Barium swallow (beak-like narrowing), esophageal manometry (definitive)

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—endoscopic pneumatic dilation, surgical myotomy, peroral endoscopic myotomy (POEM), endoscopic botulinum toxin injection

INFECTIOUS ESOPHAGITIS

- **PATHOPHYSIOLOGY**—common organisms include *Candida*, CMV, and HSV. More commonly in immunocompromised host
- **DIAGNOSIS**—gastroscopy and biopsy/viral cultures

EOSINOPHILIC ESOPHAGITIS

- **PATHOPHYSIOLOGY**—food allergens and genetic factors leading to eosinophilic infiltration, formation of esophageal rings or stricture (frequently presents in young males with esophageal foreign body)
- **DIAGNOSIS**—gastroscopy (esophageal trachealization, eosinophilic exudates, linear furrows) and biopsy
- **TREATMENTS**—control reflux, dietary exclusion (six food elimination diet), topical corticosteroids (fluticasone administered as swallowed MDI, viscous budesonide slurry, budesonide orodispersible tablet), endoscopic dilation

Related Topics

Esophageal Cancer (p. 215)
Stroke (p. 321)

Dyspepsia

DIFFERENTIAL DIAGNOSIS

NON-GASTRIC CAUSES—cardiac (myocardial infarction), pulmonary (pneumonia), hepatobiliary (biliary colic), pancreatic (pancreatitis), colonic (irritable bowel syndrome), musculoskeletal, dietary indiscretion (carbohydrate malabsorption)

PEPTIC ULCER DISEASE (PUD, 10–20%)—*Helicobacter pylori*, ASA/NSAIDs, cancer

MEDICATION SIDE EFFECTS—NSAIDs, ASA, theophylline, calcium channel blockers, erythromycin, metronidazole, bisphosphonates, orlistat, acarbose, iron, potassium supplements, colchicine, glucocorticoids

GASTROESOPHAGEAL REFLUX DISEASE (GERD, 20%)

★ACIDS★

- **ACID HYPERSECRETION**—Zollinger–Ellison disease
- **ALCOHOL USE**
- **CONNECTIVE TISSUE DISEASE**—scleroderma
- **INFECTIONS OF ESOPHAGUS**—CMV, HSV, candidiasis
- **DIABETIC GASTROPARESIS**
- **DRUG THERAPY**
- **SMOKING**

FUNCTIONAL DYSPESPSIA (50%)—also termed non-ulcer or idiopathic. Chronic post-prandial fullness, early satiation, epigastric pain/burning, no structural cause

PATHOPHYSIOLOGY

COMPLICATIONS OF PUD—perforation, hemorrhage, gastric outlet obstruction, pancreatitis

COMPLICATIONS OF GERD—erosive esophagitis, esophageal stricture, Barrett esophagus, esophageal adenocarcinoma. Extra-esophageal complications include asthma, aspiration, chronic cough, hoarseness, chronic laryngitis, and dental erosions

CLINICAL FEATURES

SYMPTOM DEFINITIONS

- **DYSPESPSIA**—chronic or recurrent epigastric pain, often with regurgitation, heartburn, bloating, nausea, and post-prandial fullness (indigestion)
- **HEARTBURN**—retrosternal burning sensation secondary to lower esophageal sphincter relaxation = more specific for GERD

PRACTICAL APPROACH TO DYSPESPSIA

1. Consider **non-gastric causes** of dyspepsia (cardiac, pulmonary, hepatobiliary, colonic, musculoskeletal, medications [including

CLINICAL FEATURES (CONT'D)

NSAIDs], and dietary indiscretion) and investigate those causes if likely. Otherwise proceed to step 2

2. If age \geq 60 and alarm symptoms **★Very BAD★** (Vomiting [persistent], Bleed/anemia, Abdominal mass/weight loss [$>$ 5% body weight over 6–12 months], Dysphagia), refer for gastroscopy to evaluate for gastric cancer. Otherwise proceed to step 3
3. If age $<$ 60, **test and treat for *H. pylori*** (recommend non-invasive test for HP); treat with quadruple therapy if positive. Otherwise proceed to step 4
4. If age $<$ 60 and HP negative, **empirical PPI therapy trial** (once daily-BID)
5. In patients not responding HP eradication or PPI, **trial of prokinetic therapy** (cisapride, metoclopramide, domperidone) or **tricyclic antidepressant therapy**

2017 ACG/CAG Guideline Dyspepsia

INVESTIGATIONS

BASEIC

- **LABS**—CBC, lytes, glucose, AST, ALT, ALP, bilirubin, lipase, Ca, albumin
- **IMAGING**—upper GI series, US abd, CT abd

SPECIAL

- **UREA BREATH TEST**
- ***H. PYLORI* STOOL ANTIGEN**
- **24-H ESOPHAGEAL pH MONITORING**
- **ENDOSCOPY WITH BIOPSY**—rapid urease test, histopathology or C&S for *H. pylori*

MANAGEMENT

PEPTIC ULCER DISEASE—avoid NSAID use. **Antisecretory treatment** (omeprazole 20–40 mg PO daily, lansoprazole 15–30 mg PO daily, pantoprazole 40 mg PO daily; 8 week course). ***H. pylori* eradication**: first line options: **★PAMC★**: PPI BID, amoxicillin 1 g PO BID, metronidazole 250–500 mg PO BID, clarithromycin 500 mg PO BID \times 14 days; **★PBMT★** if penicillin allergy: PPI BID, bismuth subsalicylate 524mg PO QID, metronidazole 250–500 mg PO QID, tetracycline 500 mg PO QID \times 14 days; second line: **★PAL★** PPI BID, amoxicillin 1 g PO BID, levofloxacin 250 mg PO BID \times 14 days)

2016 Toronto Consensus Treatment of *Helicobacter pylori* Infection

MANAGEMENT (CONT'D)

GERD—lifestyle changes (avoid coffee, alcohol, chocolate, high-fat meals, acidic or spicy foods. More frequent/smaller meals, exercise/weight loss, smoking cessation, elevate head of bed). **Antisecretory treatment** (proton pump inhibitors more effective than H₂ blockers for esophagitis. Use antacids as breakthrough). **Nissen fundoplication** (optimally for high-volume reflux)

Related Topics

Esophageal Cancer (p. 215)
 Gastric Cancer (p. 217)
 Gastric Lymphoma (p. 194)

SPECIFIC ENTITIES**GERD**

- **CAUSES**—lower esophageal sphincter pressure (obesity, transient relaxation of LES), decreased esophageal peristalsis, gastric acid hypersecretion, delayed gastric emptying, anatomic disruption lower esophageal sphincter (hiatal hernia)
- **PATHOPHYSIOLOGY**—reflux of stomach contents, leading to heartburn, regurgitation, dysphagia, chest pain, complicated by erosive esophagitis, esophageal stricture, Barrett esophagus, and esophageal adenocarcinoma
- **CLINICAL FEATURES**—esophageal (heartburn, regurgitation), extra-esophageal (wheeze, cough, pneumonia, waterbrash, hoarseness, sore throat, dental erosions)
- **DIAGNOSIS**—clinical diagnosis and treatment if classic symptoms (≥ 2 /week). Exclude other causes in patients with non-classical symptoms (endoscopy for erosive esophagitis, rule out other potential diagnoses if not responsive to empiric treatment). Other tests (pH-impedance) if diagnostic uncertainty, treatment failure

Kahrilas NEJM 2008;359(16)

NSAID-INDUCED GASTROPATHY

- **PATHOPHYSIOLOGY**—NSAIDs inhibit COX-1 (normally protective effect through mucus secretion, bicarbonate secretion, mucosal circulation) and COX-2 (inducible inflammatory activity, also in kidneys). Direct toxic mucosal effect \rightarrow dose related but even low dose ASA may contribute to ulcer formation. Risk factors: age > 65 , previous peptic ulcer (especially if recent, or complicated PUD), mul-

SPECIFIC ENTITIES (CONT'D)

tipple/high-dose NSAIDs, concomitant glucocorticoid or anticoagulant therapy

- **TREATMENTS**—primary prophylaxis includes PPI, misoprostol. In patients who need to continue NSAIDs, prevention strategy based on cardiovascular + GI risk: use least ulcerogenic, lowest dose NSAID, combine with PPI/misoprostol if GI risk factors (as above)

BARRETT ESOPHAGUS

- **PATHOPHYSIOLOGY**—prolonged heartburn \rightarrow intestinal squamous metaplasia (abnormal salmon-colored mucosa extending proximally ≥ 1 cm from the gastroesophageal junction) \rightarrow low-grade dysplasia \rightarrow high-grade dysplasia \rightarrow adenocarcinoma (esophagus/gastric cardia). Risk of progression to cancer: BE without dysplasia (0.25%), low-grade dysplasia (0.5%), high-grade dysplasia (4-8%)
- **DIAGNOSIS**—screening in men with chronic (> 5 years) and/or frequent ($>$ weekly) reflux and ≥ 2 risk factors (age > 50 , Caucasian, central obesity, current/past smoking, first-degree relative with BE or esophageal adenocarcinoma). Mucosal biopsies to confirm metaplasia/dysplasia
- **TREATMENTS**—Once daily PPI therapy for chemoprevention. BE without dysplasia (surveillance q3-5 years); BE indefinite for dysplasia (repeat endoscopy in 3-6 months after acid suppression optimization); low-grade dysplasia (endoscopic resection/ablation OR surveillance in 12 months); high-grade dysplasia (evaluate for esophagectomy, endoscopic mucosal resection, or ablative therapy)

2015 ACG Guideline Barrett Esophagus**GASTROPARESIS**

- **CAUSES**—systemic diseases (diabetes, hypothyroidism, scleroderma), drugs (anticholinergic agents, narcotics, GLP-1 analog), idiopathic/iatrogenic (prior GI surgery), post-viral
- **PATHOPHYSIOLOGY**—impairment of gastric emptying due to dysfunction of the neuromuscular unit \rightarrow dyspepsia, bloating, nausea, vomiting, and weight loss
- **DIAGNOSIS**—gastric emptying study, barium swallow, gastroscopy to exclude obstruction, blood glucose
- **TREATMENTS**—fluid/electrolyte replacement, nutritional support (post-pyloric feeding if enteral nutrition required), optimize glycemic control. Oral intake and enteral nutrition preferred: frequent, small, low-fat, low-fiber feedings. Symptomatic treatment of nausea.

SPECIFIC ENTITIES (CONT'D)

Prokinetic agents (*metoclopramide* 10 mg PO TID ac meals, *erythromycin* 250 mg PO TID ac meals, *domperidone* 10 mg PO QID, *prucalopride* 1-2 mg PO daily). Venting in severe or refractory cases.

Camilleri et al. *Am J Gastroenterol* 2013;108(1)

HELICOBACTER PYLORI

- **PATHOPHYSIOLOGY**—chronic inflammation → causative role in 50–80% of duodenal ulcers, 40–60% of gastric ulcers, 80% of gastric cancers (including adenocarcinoma), and 90% of gastric lymphomas

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—testing indications (gastric lymphoma, peptic ulcer disease, early gastric cancer, dyspepsia in <60 years without alarm features, ITP, unexplained iron deficiency, prior to chronic NSAID use). Non-invasive tests (urea breath test [sens 90%, spc 95%], HP stool antigen [sens 94% spc 97%], serology [sens 90%, spc 80%]). UBT and HP stool antigen ideal for confirming eradication (test off antibiotic and PPI therapy), serology of limited value as it tests for IgG indicating previous exposure). Invasive tests (endoscopy for culture, histologic assessment, rapid urease testing)
- **TREATMENTS**—see *H. PYLORI* ERADICATION above

Acute Abdominal Pain**DIFFERENTIAL DIAGNOSIS**

GI—peptic ulcer disease, pancreatitis, cholangitis, hepatitis, cholecystitis, inflammatory bowel disease, gastroenteritis, appendicitis, diverticulitis, bowel obstruction (small, large), volvulus

GU—pyelonephritis, renal colic, cystitis, prostatitis, testicular torsion, inguinal hernia

GYNCOLOGIC—ectopic pregnancy, ruptured ovarian cyst, pelvic inflammatory disease, fibroid torsion, endometriosis, endometritis

VASCULAR—acute mesenteric ischemia, ischemic colitis, chronic mesenteric ischemia, abdominal aortic aneurysm rupture

SYSTEMIC—Addison disease, diabetic ketoacidosis, uremia, hypercalcemia, porphyria, familial Mediterranean fever

OTHERS—myocardial infarction, pneumonia, splenic injury, shingles, musculoskeletal, peritonitis

PATHOPHYSIOLOGY

CAUSES OF ABDOMINAL PAIN—any intra-abdominal organs (e.g. GI, GU, gynecological, spleen) × (ischemia, infection, obstruction, tumors) ± systemic causes ± referred pain

CLINICAL FEATURES

HISTORY—characterize abdominal pain (onset, location, duration, severity, radiation, aggravating and relieving factors), N&V, bleeding, fever, inquire about last menstrual period and pregnancy if female, past medical history (CAD, diabetes, hypertension, renal stones), past surgical history (abdominal adhesions), medication history (analgesics)

CLINICAL FEATURES (CONT'D)

PHYSICAL—vitals, respiratory and cardiac examination, abdominal examination, CVA tenderness, pelvic and rectal examination

APPENDICITIS SEQUENCE—vague pain initially located in the epigastric or periumbilical region; anorexia, nausea, or non-sustained vomiting; migration of the initial pain to the RLQ; low-grade fever

DISTINGUISHING FEATURES BETWEEN PERITONITIS, SMALL BOWEL OBSTRUCTION, AND ABDOMINAL WALL PAIN

- **PERITONITIS**—rigidity (LR+ 5.1), guarding (LR+ 2.0), rebound tenderness (LR+ 2.0), positive cough test (LR+ 2.0). Other special tests include Rovsing sign, psoas sign (flexion of hip against resistance increases abdominal pain), obturator sign (internal rotation of hip increases abdominal pain), and rectal/pelvic examination
- **SMALL BOWEL OBSTRUCTION**—visible peristalsis (LR+ 18.8), absent/tinkling/high-pitched bowel sounds (LR+ 5.0), abdominal bloating
- **ABDOMINAL WALL PAIN**—Carnett test (palpate area of most intense tenderness while patient supine, then palpate again with patient half sitting up. If pain is intra-abdominal, the pain will not increase as tensed rectus muscles protect the underlying viscus)

Related Topic

Acute Pancreatitis (p. 157)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, lipase, amylase, lactate, INR, PTT, Ca, albumin, urinalysis, urine β hCG (if ♀ of reproductive age)
- **MICROBIOLOGY**—urine C&S, stool C&S, *C. difficile*
- **IMAGING**—CXR, AXR, US abd/pelvic

SPECIAL

- **IMAGING**—CT abd, angiogram, KUB
- **ECG**—if suspect cardiac cause
- **ENDOSCOPY**

DIAGNOSTIC ISSUES**APPROACH TO ABDOMINAL X-RAYS**

- **FREE AIR**—pneumoperitoneum suggests perforation. Look for free air under right diaphragm on CXR view or R lateral decubitus view. On supine abd view, look for outline of bowel wall (normally can only see inside of lumen. If outside of bowel wall also seen, free air present)
- **SMALL BOWEL**—more central location, valvulae closer together, thin and cross completely. Dilated if >3 cm [1.2 in.], multiple air fluid levels suggest small bowel obstruction
- **LARGE BOWEL**—more peripheral location, colonic haustra wider apart, thick, and cross part way. Normally some air–fluid levels in ascending colon. Dilated if >5 cm [2 in.]. Thumb printing (mural edema) and dilated bowel suggest toxic megacolon. Check for air in bowel wall (pneumatosis intestinalis)
- **KIDNEYS**—ureter runs along transverse processes. May see calculi along tract. If see kidney outline, suggests pneumoretroperitoneum
- **PSOAS**—air around psoas suggests perforated retroperitoneal structures (rectum, duodenum). Lack of psoas outline suggests retroperitoneal inflammation
- **BILIARY STRUCTURES**—common bile duct up to 6 mm in size. Check for air in portal vein or common bile duct (bowel infarction)
- **OTHER STRUCTURES**—liver, spleen, bones

MANAGEMENT

ACUTE—ABC, O₂, IV hydration. **NPO**, NG if severe N&V/obstruction. **Morphine** 2.5–5 mg SC q3–4 h PRN and 1–2.5 mg IV q1h PRN. **Hydromorphone** 0.5–2 mg IV q2h PRN. **Dimenhydrinate** 50 mg IM/IV q4h PRN

TREAT UNDERLYING CAUSE—early surgical consult if peritonitis or pain out of proportion. **Empiric antibiotics** if fever or suspect peritonitis (ceftriaxone 1 g IV q24h plus

MANAGEMENT (CONT'D)

metronidazole 500 mg IV q12h, or piperacillin-tazobactam 3.375 g IV q6h, or ciprofloxacin 400 mg IV q12h plus metronidazole 500 mg IV q12h)

SPECIFIC ENTITIES

GALLSTONE DISEASE SPECTRUM—asymptomatic (70%), biliary colic (20%, intermittent obstruction), acute cholecystitis (cystic duct obstruction with gallbladder inflammation), choledocholithiasis (common bile duct obstruction), ascending cholangitis (stasis and infection of biliary tract; may be secondary to choledocholithiasis; see p. 156 for more details), gallstone pancreatitis (pancreatic duct obstruction), gallstone ileus (bowel obstruction from impacted stone after passing through biliary-enteric fistula)

ACUTE CHOLECYSTITIS

- **PATHOPHYSIOLOGY**—abnormalities of bile acid secretion, mucus generation, and gallbladder motility → gallstone formation → migrate to obstruct cystic duct and/or common bile duct/pancreatic duct → gallbladder inflammation +/- secondary infection → gallbladder necrosis and gangrene with perforation in severe cases. Risk factors include older age, obesity, fertility, women (i.e. forty, fat, fertile, female), ethnicity (Indigenous, Hispanic), TPN, diabetes, dyslipidemia, and rapid weight loss. Stone types: **cholesterol** (from bile supersaturation with cholesterol); **black pigment** (hemolysis—calcium bilirubinate); **brown pigment** (bacterial/parasitic biliary infection)
- **ACALCULOUS CHOLECYSTITIS**—acute necroinflammation from gallbladder stasis/ischemia, typically in hospitalized, critically ill patients. Risk factors: sepsis, shock, heart failure, mechanical ventilation, major trauma, post-CPR, burns, post-transplantation, ESRD, immunosuppression. Presentation: fever, RUQ pain, ± jaundice, leukocytosis. Complications: emphysematous cholecystitis, gangrene, perforation with cholecystenteric fistula, abscess, peritonitis.
- **DIAGNOSIS**—US abd, endoscopic US, percutaneous transhepatic cholangiography, MRCP, HIDA cholecistigraphy (acalculous cholecystitis), CT abd
- **TREATMENTS**—supportive measures include IV fluids, pain control, antiemetics and antibiotics (ceftriaxone 1 g IV q24h plus metronidazole 500 mg IV q8h, or piperacillin-tazobactam 3.375 g IV q6h, or ciprofloxacin 400 mg IV q12h plus metronidazole 500 mg IV q8h, or

SPECIFIC ENTITIES (CONT'D)

meropenem 1 g IV q8h). Cholecystectomy (laparoscopic, open) or percutaneous cholecystostomy to facilitate drainage (if non-operative because of high risk). If biliary pain despite cholecystectomy, consider retained CBD stone, bile leak, sphincter of Oddi dysfunction, or functional pain

Strasberg NEJM 2008;358(26)

ACUTE MESENTERIC ISCHEMIA

- **PATHOPHYSIOLOGY**—sudden small bowel hypoperfusion, arterial or venous; **arterial occlusion** from embolism (typically superior mesenteric artery, secondary to valvular heart disease or atrial fibrillation) or thrombosis (from atherosclerosis), **non-occlusive** mesenteric ischemia (shock/low flow state, vasoconstriction, arrhythmia), or **mesenteric venous occlusion** (from thrombosis secondary to abdominal mass, myeloproliferative disorder, portal hypertension/cirrhosis, thrombophilia, pancreatitis/diverticulitis) → sudden and severe periumbilical pain **out of proportion** with physical findings, N&V, leukocytosis, ↑ lactate, ileus
- **DIAGNOSIS**—high clinical suspicion, CT abd (+ contrast). Angiography gold standard
- **TREATMENTS**—IV fluids, immediate surgery, anticoagulation if mesenteric arterial embolism or mesenteric venous thrombosis, broad-spectrum antibiotic therapy

SPECIFIC ENTITIES (CONT'D)**ISCHEMIC COLITIS**

- **PATHOPHYSIOLOGY**—low-flow state in the mesentery affecting mainly the “watershed” area of the middle colic and inferior mesenteric arteries (splenic flexure, rectosigmoid junction) → abdominal cramping followed by mild-moderate hematochezia
- **DIAGNOSIS**—AXR (“thumbprinting” or edematous haustral folds), CT (focal or segmental bowel wall thickening or intestinal pneumatosis with portal vein gas), colonoscopy, laparoscopy
- **TREATMENTS**—supportive (hydration), antibiotics, surgery if severe colonic necrosis

CHRONIC MESENTERIC ISCHEMIA

- **PATHOPHYSIOLOGY**—↓ blood flow from atherosclerosis of the proximal mesenteric vessels → intestinal angina with post-prandial abdominal pain → fear of eating, extensive weight loss
- **DIAGNOSIS**—CT abdomen/pelvis (initial), mesenteric duplex US (sens 90% for stenosis of >50%), CT angiography
- **TREATMENTS**—angioplasty, surgical revascularization, management of vascular risk factors

2015 ACG Guideline Colon Ischemia

Upper GI Bleed**DIFFERENTIAL DIAGNOSIS**

PEPTIC ULCER DISEASE (PUD)—gastric, duodenal

INFLAMMATION—**esophagitis** (CMV/HSV, medications, reflux), **gastritis** (acute, chronic), **inflammatory bowel disease** (Crohn)

VARICES—esophagus, stomach

TUMORS—esophagus, stomach, duodenum

STRUCTURAL—Mallory–Weiss tear, Dieulafoy lesion, arteriovenous malformation/angiodysplasia, aortoenteric fistula, hemobilia

OTHERS—epistaxis, hemoptysis

CLINICAL FEATURES

HISTORY—volume of hematemesis/coffee-ground emesis, melena, hematochezia. Associated symptoms: abdominal pain (PUD), vomiting/retching (MWT), dysphagia/GERD, jaundice/ascites (portal hypertension), constitutional symptoms (malignancy). Past medical history (PUD, *H. pylori* infection, alcohol-related

CLINICAL FEATURES (CONT'D)

disorders, liver cirrhosis with varices, renal failure, metastatic cancer, heart disease/HF), medication history (anticoagulants, NSAIDs, SSRI, drugs causing pill esophagitis)

PHYSICAL—acute bleeding, resting tachycardia, supine hypotension, orthostatic changes (postural pulse increase >30/min, SBP decrease ≥20mmHg, DBP decrease ≥10mmHg), anemia (conjunctival, facial or palmar pallor), cirrhosis (facial telangiectasia, palmar erythema, spider angiomas, gynecomastia, abdominal wall veins, Terry nails/leukonychia, peripheral edema). Perform a **rectal examination**. Do NOT test for fecal occult blood. Examine vomitus. Nasogastric lavage not routinely required.

BLACK STOOL THAT MAY MIMIC MELENA—bismuth subsalicylate, iron, spinach, charcoal

Stanley et al. BMJ 2019;364

CLINICAL FEATURES (CONT'D)**RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A SEVERE UPPER GASTROINTESTINAL BLEED?**

	LR+	LR-
Clinical Factors Distinguishing UGIB vs. LGIB		
Prior history of UGIB	6.2	0.81
Age <50 years	3.5	0.80
Cirrhosis	3.1	0.97
History of melena	5.1–5.9	0.06–0.27
Melenic stool on examination	25	0.52
Nasogastric lavage with blood or coffee grounds	9.6	0.58
Clots in stool	0.05	1.2
Serum urea nitrogen:creatinine ratio >30	7.5	0.53
Clinical Factors Determining Need for Urgent Evaluation of UGIB		
History of malignancy or cirrhosis	3.7	0.83
Cirrhosis	3.2	0.89
Syncope	3.0	0.95
Pulse rate >100/min	4.9	0.34
Nasogastric lavage with red blood	3.1	0.32
Hemoglobin level <8 g/dL	4.5–6.2	0.36–0.41
Serum urea nitrogen >90 mg/dL	3.6	0.45
Blatchford score = 0	1.2	0.02

Blatchford score: determined by blood urea, hemoglobin, systolic blood pressure, pulse > 99 beats/min, presentation with melena, presentation with syncope, hepatic disease, cardiac failure. Blatchford score ≤ 1 indicates low risk rebleeding or mortality.

APPROACH—Tachycardia (pulse rate of >100/min; LR, 4.9), a history of cirrhosis or malignancy (LR+ 3.7), hemoglobin level of less than 8 g/dL (LR+ range, 4.5–6.2), or a nasogastric lavage with red blood (LR+ 3.1) increase the likelihood of severe bleeding. All patients with a UGIB should have a Blatchford score, which does not require a nasogastric lavage, to help assess the severity (Blatchford score = 0; LR- 0.02 for identifying patients requiring urgent evaluation). When negative, prediction rules combining symptoms, signs, and routine laboratory

CLINICAL FEATURES (CONT'D)

test results almost definitively rule out severe UGIB, thereby identifying at least some patients who can be safely evaluated as an outpatient.”

Srygley et al. *JAMA* 2012;307(10)

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT HYPOVOLEMIC? HYPOVOLEMIA DUE TO ACUTE BLOOD LOSS

	Sens	Spc
For moderate blood loss		
Postural pulse increment ≥ 30 /min or severe postural dizziness	22%	–
Postural hypotension ≥ 20 mmHg SBP drop	9%	94%
Supine tachycardia	0%	96%
Supine hypotension	13%	97%
For large blood loss		
Postural pulse increment ≥ 30 /min or severe postural dizziness	97%	98%
Supine tachycardia	12%	96%
Supine hypotension	33%	97%

NOTE—postural change is measured first with supine vitals counting pulse for 30 s (after waiting 2 min), then standing vitals (after waiting 1 min)

McGee et al. *JAMA* 1999;281(11)

Related Topic

Shock (p. 116)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, type/cross-match, PTT, INR, AST, ALT, ALP, bilirubin, albumin
- **IMAGING**—CXR, AXR
- **GASTROSCOPY**

PROGNOSTIC ISSUES**RISK STRATIFICATION FOR PEPTIC ULCER DISEASE**

- **ROCKALL SCORE**—age 60–79 = 1; age ≥ 80 = 2; heart rate >100 beats/min = 1; systolic BP <100 mmHg = 2; co-existing illnesses (ischemic heart disease, HF, other major illness) = 2; co-existing illnesses (renal failure, hepatic failure, metastatic cancer) = 3; endoscopic findings: no lesion observed, Mallory–Weiss tear = 0; peptic

PROGNOSTIC ISSUES (CONT'D)

ulcer, erosive disease, esophagitis = 1; cancer of upper GI tract = 2; clean base ulcer, flat pigmented spot = 0; blood in upper GI tract, active bleeding, visible vessel, clot = 2

- **INTERPRETATION**—low risk for bleeding or death = Rockall score ≤ 2

RISK OF ULCER RE-BLEED

- **Forrest classification** used to stratify endoscopic stigmata, risk of rebleeding. Other factors to consider include size, depth, location of ulcer
- **HIGH-RISK FEATURES**—active spurting/oozing during endoscopy (55-90% rebleeding rate), non-bleeding visible vessel (40-50% risk), adherent clot (25-30% risk). Ulcers with high-risk features require endoscopic therapy, inpatient admission, and 72 hours of IV PPI
- **LOW-RISK FEATURES**—flat spot (10% rebleeding rate), clean ulcer base (3-5% risk). If no high risk features and clinically non-severe bleed, low chance of rebleed and may consider discharging shortly after on PO PPI

MANAGEMENT

ACUTE—ABC, O₂, **IV fluid resuscitation** (two large-bore IVs). **Restrictive PRBC transfusion** strategy improves outcomes compared to liberal transfusions. NPO, consider NG tube. **Hold** antihypertensive and diuretic therapy. If prolonged PT/PTT, **vitamin K** 10 mg IV (small risk of anaphylaxis) and **FFP** 2-4 U IV or **unactivated prothrombin complex concentrates (PCC)** 1000-3000 U IV (dosing based on INR and severity of bleeding), if rapid reversal required. If on heparin, consider **protamine** infusion (1 mg antagonizes 100 U of heparin—avoid excessive protamine, which can cause paradoxical coagulopathy). **Pantoprazole** 80 mg IV bolus, then 8 mg/h; or 40 mg q12h until endoscopy. If cirrhosis and suspected acute variceal hemorrhage, **octreotide** 50 µg IV bolus, then 25-50 µg/h, **transfuse** PRBC, platelet and FFP PRN, antibiotics for 7 days (**ceftriaxone** 1 g IV q24h, **cefotaxime** 1 g IV q8h, **ciprofloxacin** 400 mg IV q12h, **ciprofloxacin** 500 mg PO BID, or **norfloxacin** 400 mg PO BID). **Consult GI**

TREAT UNDERLYING CAUSE—avoid NSAIDs.

Peptic ulcer (endoscopic hemostasis with thermal coagulation/endoclips plus 1:10,000 ratio

MANAGEMENT (CONT'D)

epinephrine injection. After endoscopy, start **pantoprazole** 80 mg IV bolus if not given already, then 8 mg/h or 40 mg q12h $\times 72$ h [if high-risk lesion], switch to 40 mg PO BID $\times 1$ month, then daily).

Varices (endoscopy within 12 h with ligation/band/glue/sclerotherapy \rightarrow balloon tamponade for refractory varices (Linton or Blakemore tube) \rightarrow transjugular intrahepatic portosystemic shunt (TIPS) \rightarrow portacaval/distal splenorenal shunt, or liver transplant. Continue octreotide for 3 days, antibiotic prophylaxis. Repeat endoscopy every 2-4 weeks until varices obliterated, then at 1-3 months and again every 6-12 months afterward. Consider non-selective β -blocker such as **nadolol** 40-80 mg PO daily or **propranolol** 20 mg PO BID (avoid if hyponatremia <130 mEq/L, acute kidney injury, diuretic resistant ascites, SBP, hypotension). **Mallory-Weiss tear** (PPI PO daily $\times 2-4$ weeks, anti-emetics). **H. pylori** eradication (see DYSPEPSIA p. 130 for treatment). **Intractable or recurrent bleed** (consult surgery. See TREATMENT ISSUES below)

TREATMENT ISSUES

CRITERIA FOR SURGICAL CONSULT FOR ULCER BLEED—hemodynamic instability despite resuscitation (>3 U PRBC), shock, recurrent hemorrhage after two endoscopic attempts, continued bleed requiring >3 U PRBC/day)

COMPLICATIONS OF ENDOSCOPY—perforations, bleeding, sedation-related respiratory failure

DISCHARGE DECISIONS FOR PEPTIC ULCER DISEASE—patients with low-risk of re-bleed (Rockall score ≤ 2 , low risk endoscopic features), with Hb $>80-100$ g/L [$>8-10$ g/dL] without further need of transfusions, normal INR/PTT, and have adequate social support may be safely discharged home shortly after endoscopy with follow-up

GASTRIC ULCERS—small risk of underlying gastric malignancy, may require repeat endoscopy in 8-12 weeks to check ulcer healing and biopsy if persistent symptoms, unclear etiology, giant ulcer >2 cm, suspicious-appearing ulcer, or other risk factors for gastric cancer (age >50 , family history, gastric dysplasia/intestinal metaplasia)

Lower GI Bleed

DIFFERENTIAL DIAGNOSIS

UPPER GI SOURCE WITH BRISK BLEEDING (10%)

INFECTIOUS—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *Escherichia coli*. (EHEC, EIEC), *Clostridioides* (formerly *Clostridium*) *difficile*, *Amoeba*

TUMORS—colorectal cancer, small bowel cancer, polyp

INFLAMMATORY—inflammatory bowel disease (IBD)

ISCHEMIC—ischemic colitis

STRUCTURAL—angiodysplasia, diverticulosis, radiation colitis, hemorrhoids, anal fissure, intussusception, Meckel diverticulum

CLINICAL FEATURES

HISTORY—volume and character of bleed (maroon, bright red, clots), melena, painful vs. painless bleeding, past medical history (IBD, cancer, diverticulosis), medication history (anticoagulants, antiplatelet drugs, NSAIDs)

PHYSICAL—acute bleeding, signs of hypovolemia, anemia (conjunctival, facial or palmar pallor), abdominal tenderness. Perform a rectal examination

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, type/X-match, PTT, INR, AST, ALT, ALP, bilirubin, albumin
- **MICROBIOLOGY**—stool C&S
- **ENDOSCOPY**—colonoscopy, gastroscopy

SPECIAL

- **IMAGING**—for obscure bleed, consider ⁹⁹Tc RBC scan (detects 0.1 mL/min), angiography (detects 0.5 mL/min), capsule endoscopy, push enteroscopy, double balloon enteroscopy, CT/MR enterography and/or Meckel scan

DIAGNOSTIC ISSUES

OCCULT BLEED—no obvious melena or bright red blood per rectum (BRBPR), but possible bleed as fecal occult blood or fecal immunochemical test (FIT) positive and/or iron deficiency anemia. **FOBT/FIT testing should be reserved for average risk colon cancer screening** (see p. 240)

OBSCURE BLEED—obvious bleeding but source cannot be found

OVERALL APPROACH—gastroscopy and colonoscopy → if negative, consider repeat endoscopy +/- push enteroscopy → if negative, evaluate for small bowel bleeding: ongoing bleeding (consider angiography, RBC scan) vs. no ongoing bleeding (consider video capsule or CT/MR enterography); reserve double balloon enteroscopy for persistent ongoing bleeding or identified source on other investigations. If no source found, consider Meckel scan, laparotomy +/- intraoperative enteroscopy

MANAGEMENT

ACUTE—ABC, O₂, **IV hydration** (two large-bore IVs). **Transfusion** (especially if hemoglobin <70 g/L [<7 g/dL], platelets $<50 \times 10^9/L$). NPO. **Hold** antihypertensive and diuretic therapy. If prolonged PT/PTT, **vitamin K** 10 mg IV (small risk of anaphylaxis) [see above comment for UGIB] and **FFP** 2–4 U IV or **unactivated prothrombin complex concentrates (PCC)** 1000–3000 U IV (dosing based on INR and severity of bleeding), if rapid reversal required. If on unfractionated heparin, **protamine** infusion (1 mg antagonizes 100 U of heparin). **Consult GI**. Colonoscopy within 24 hours AFTER resuscitation and bowel preparation; typically no significant advantage to urgent colonoscopy for LGIB. **Interventional radiology** for mesenteric/CT angiography for massive LGIB that cannot be stabilized for colonoscopy. **Consult Surgery** for exsanguinating LGIB
TREAT UNDERLYING CAUSE

Acute Diarrhea

DIFFERENTIAL DIAGNOSIS

INFLAMMATORY/INVASIVE (fever, bloody diarrhea, tenesmus)

- **INVASIVE INFECTIONS**—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, EHEC, EIEC, *Vibrio parahaemolyticus*, *C. difficile*, *Entamoeba*

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **INFLAMMATORY**—ulcerative colitis, Crohn disease
- **ISCHEMIC/RADIATION COLITIS**

NON-INFLAMMATORY

- **NON-INVASIVE INFECTIONS**—**bacterial** (*Vibrio cholera*, *Staphylococcus aureus*, *Bacillus*

DIFFERENTIAL DIAGNOSIS (CONT'D)

cereus, *Clostridium perfringens*, *C. difficile*, ETEC, EPEC), **viral** (rotavirus, norovirus, CMV), **parasites** (*Giardia*, *Cryptosporidium*, *Amoeba*)

- **MEDICATIONS**—antibiotics, laxatives, chemotherapy

PATHOPHYSIOLOGY

DEFINITION OF DIARRHEA—>3 loose/watery bowel movements/day or at least 200 g of stool/day. Acute diarrhea is defined as <2 weeks, chronic diarrhea ≥4 weeks duration

DIARRHEA AND ASSOCIATED SYNDROMES

- **SALMONELLA**—may cause septicemia in patients with sickle cell anemia or AIDS
- **SHIGELLA**—precedes reactive arthritis
- **CAMPYLOBACTER**—precedes 10–30% of Guillain-Barré syndrome
- **YERSINIA**—mesenteric adenitis, erythema nodosum, polyarthritis, reactive arthritis, bacteremia, may mimic appendicitis

DIARRHEA AT VARIOUS SETTINGS

- **COMMUNITY ACQUIRED**—*Salmonella* (prevalence 16/100,000), *Campylobacter* (13/100,000), *Shigella* (10/100,000), *E. coli* O157:H7 (1.7/100,000), *Cryptosporidium* (1.4/100,000)
- **TRAVELER'S**—ETEC
- **NOSOCOMIAL**—*C. difficile*
- **PERSISTENT DIARRHEA** (>7 days)—*Giardia*, *Isospora belli*, *Cyclospora*, *Cryptosporidium*
- **IMMUNOCOMPROMISED**—*Microsporidia*, MAC, CMV

NATURAL HISTORY—most diarrheal illnesses are self-limited or viral-induced and nearly 50% last <1 day

CLINICAL FEATURES

HISTORY—characterize diarrhea (duration, frequency, volume, blood, floating), infectious contacts, recent food intake, abdominal pain, past medical history (IBD, lactose intolerance), medication history (laxatives, antibiotics), travel history

PHYSICAL—vitals and check for dehydration. Abdominal tenderness. Perform a rectal examination. Inspect stool sample if available

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, lactate
- **MICROBIOLOGY**—stool C&S (sens 1.5–5.6%), O&P, *Giardia* antigen testing/nucleic acid amplification assay (NAAT), *C. difficile* NAAT, enzyme immunoassay for glutamate dehydrogenase, toxin A + B, viral culture

INVESTIGATIONS (CONT'D)**SPECIAL**

- **FECAL TESTING**—fecal leukocytes (inflammatory, sens 73%, spc 84%), fecal lactoferrin (inflammatory, sens 92%, spc 79%)
- **ENDOSCOPY**—flexible sigmoidoscopy, colonoscopy

MANAGEMENT**SYMPTOM CONTROL—IV hydration.**

Antidiarrheal agents if not inflammatory (*bismuth subsalicylate* 2 tab PO q1h PRN or *loperamide* 4 mg×1 dose, then 2 mg PO PRN, maximum 16 mg/day)

TREAT UNDERLYING CAUSE—*Shigella*,

Salmonella*, *Campylobacter*, *E. coli other than EHEC (*ciprofloxacin* 500 mg PO BID×3 days, *levofloxacin* 500 mg PO daily×3 days). **V. cholera** (*tetracycline* 500 mg PO QID×3 days, *doxycycline* 300 mg PO×1 dose, or *azithromycin* 1 g PO×1 dose). ***Isospora* and *Cyclospora*** (*trimethoprim-sulfamethoxazole* 160/800 PO BID×7–10 days). **C. difficile** (*vancomycin* 125–250 mg PO QID×10 days), ***Giardia***, and ***Entamoeba*** (*metronidazole* 500 mg PO TID×10 days)

DuPont NEJM 2014;370(16)

Related Topic

Acute Abdominal Pain (p. 132)

SPECIFIC ENTITIES**ANTIBIOTICS-ASSOCIATED DIARRHEA AND PSEUDOMEMBRANOUS COLITIS**

- **PATHOPHYSIOLOGY**—most commonly *C. difficile* (particularly with clindamycin, cephalosporins, penicillins). Relapse occurs in 20–25% of patients and typically between 3 and 21 days after discontinuation of treatment: 3–5% of patients have more than 6 relapses. Virulent *C. difficile* strain NAP-1/027 characterized by increased secretion of toxins A/B and fluoroquinolone resistance, and associated with increased outbreaks and mortality
- **RISK FACTORS**—onset of diarrhea ≥6 days after the initiation of antibiotic therapy, hospital stay ≥2 weeks, fecal leukocytes, semi-formed stools, cephalosporin use
- **CLINICAL FEATURES**—usually watery diarrhea (may be bloody if severe colitis), abdominal pain, fever, leukocytosis. *C. difficile* spectrum: non-severe disease; **severe colitis** (WBC >15×10⁹/L, Cr ≥130 umol/L, abdo distention,

SPECIFIC ENTITIES (CONT'D)

- fever, hypovolemia, hypoalbuminemia); **fulminant colitis** (hypotension, shock, ileus, toxic megacolon (see p. 142), multisystem organ failure (including acute renal failure))
- **DIAGNOSIS**—*C. difficile* GDH antigen or toxin A/B from stool sample, NAAT if indeterminate results. Flexible sigmoidoscopy (pseudomembranous colitis). Repeat *C. difficile* testing unnecessary immediately after treatment if symptomatic resolution, as up to one-third of patients have positive assays despite successful treatment. If symptomatic, consider post-infectious diarrhea vs. recurrence
 - **TREATMENTS**—**IV hydration**. **Discontinue** implicated antibiotics. **Hand hygiene** (soap and water). **Avoid** use of antiperistaltic agents (opiates, loperamide). **C. difficile treatment** (*vancomycin* 125–250 mg PO QID × 10 days or *fidaxomicin* 200 mg PO BID × 10 days). If fulminant disease, give *vancomycin* 500 mg PO/NG QID and add *metronidazole* 500 mg IV

SPECIFIC ENTITIES (CONT'D)

q8h. If ileus/toxic megacolon, add *vancomycin* rectal retention enema 500 mg in 100 mL normal saline q6h; **General surgery consult**. Avoid repeating stool assays after treatment unless patient has moderate or severe diarrhea. A positive *C. difficile* toxin without significant symptoms should not prompt treatment. For **C. difficile recurrence**, pulsed-tapered *vancomycin* 125 mg PO QID × 10–14 days, then BID × 1 week, then daily × 1 week, then every other day × 1 week, then every 3 days × 2–8 weeks, or *fidaxomicin* 200 mg PO BID × 10 days. Alternatives include *vancomycin* 125 mg PO QID followed by *rifaximin* 600 mg TID × 20 days, or **fecal microbiota transplantation**. Inconsistent evidence to support probiotic use for treatment or prevention of *C. difficile* infection

Leffler et al. *NEJM* 2015;372(16)
2017 ISDA SHEA Guideline
Clostridium difficile

Chronic Diarrhea**DIFFERENTIAL DIAGNOSIS****★ MISO ★**

MOTILITY—hyperthyroidism, diabetic neuropathy, bacterial overgrowth, irritable bowel syndrome (IBS) or functional diarrhea, scleroderma

INFLAMMATORY

- **INFECTIONS**—*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *E. coli* (EHEC, EIEC), *C. difficile*, *Amoeba*
- **INFLAMMATORY**—ulcerative colitis, Crohn disease, ischemic, radiation, toxic

SECRETORY

- **INFECTIONS**—cholera, *Staphylococcus*, *B. cereus*, *C. perfringens*, *E. coli* (ETEC, EPEC), rotavirus, norovirus, CMV, *Giardia*, *Cryptococcus*, *Amoeba*
- **NEUROENDOCRINE TUMORS**—carcinoid, VIPoma, calcitonin excess, gastrinoma, somatostatinoma
- **MEDICATIONS**—laxatives
- **OTHERS**—bile salt diarrhea, microscopic (collagenous or lymphocytic) colitis

OSMOTIC

- **MALDIGESTION OR MALABSORPTION**—pancreatic insufficiency, celiac disease, lactose intolerance, short bowel syndrome, enteric fistula

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **MEDICATIONS**—antacids, antibiotics, Mg citrate, Mg hydroxide, lactulose, sorbitol (i.e. “chewing gum diarrhea”), colchicine, metformin

Related Topics

Inflammatory Bowel Disease (p. 140)
Irritable Bowel Syndrome (p. 143)

CLINICAL FEATURES

HISTORY—characterize diarrhea (duration, frequency, volume, blood), infectious contacts, abdominal pain, weight loss, past medical history (diabetes, hyperthyroidism, IBS, lactose intolerance, bowel surgery, scleroderma), medication history (laxatives)

PHYSICAL—obtain body weight and inspect stool sample. Abdominal tenderness. Perform a rectal examination

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, albumin, TSH, anti-transglutaminase antibody, endomysial antibody

INVESTIGATIONS (CONT'D)

- **MICROBIOLOGY**—stool C&S, O&P, *C. difficile* toxin A + B, *Giardia* toxin

SPECIAL

- **FECAL TESTING**—fecal calprotectin (to evaluate for colonic inflammation), fecal leukocytes, fecal fat, fecal electrolytes, stool for phenolphthalein (laxative abuse), fecal α -1 antitrypsin
- **IMAGING**—⁷⁵SeHCAT scan for bile acid wasting, CT/MR enterography
- **ENDOSCOPY**—upper endoscopy and colonoscopy, for biopsy
- **CARBOHYDRATE BREATH TEST**—for SIBO, carbohydrate/lactose malabsorption

INVESTIGATION ISSUES**DISTINGUISHING FEATURES**

- **INFLAMMATORY**—bloody stool, elevated fecal calprotectin, fecal leukocytes

INVESTIGATION ISSUES (CONT'D)

- **SECRETORY**—fecal osmotic gap <50 mOsm/kg, >500 g of stool with fasting
- **OSMOTIC**—fecal osmotic gap >50 mOsm/kg; <500 g of stool with fasting

FECAL OSMOTIC GAP— $280 - 2 \times (\text{stool Na} + \text{K})$

MANAGEMENT

SYMPTOM CONTROL—**hydration** and **nutritional support**. Empiric treatment with **antidiarrheal** agents if not inflammatory (*bismuth subsalicylate* 2 tab PO q1h PRN or *loperamide* 4 mg \times 1 dose, then 2 mg PO PRN, maximum 16 mg/day)

TREAT UNDERLYING CAUSE—cholestyramine for bile acid-induced diarrhea

2018 BSG Guidelines Chronic Diarrhoea Adults

SPECIFIC ENTITIES Inflammatory Bowel Disease**DIFFERENTIAL DIAGNOSIS**

See differential diagnosis for
ACUTE ABDOMINAL PAIN (p. 132)
LOWER GI BLEED (p. 137)
CHRONIC DIARRHEA (p. 139)

PATHOPHYSIOLOGY**TYPES**

- **CROHN DISEASE**—**disease extent** (ileal, ileocolonic, colonic, upper GI); **disease behavior** (inflammatory, stricturing, penetrating, perianal disease); **risk stratification** (moderate/high risk features: age <30 at diagnosis, extensive anatomic involvement, perianal/rectal dis-

PATHOPHYSIOLOGY (CONT'D)

- ease, deep ulcerations, previous surgery, stricturing or fistulizing disease behavior)
- **ULCERATIVE COLITIS**—**disease extent** (*ulcerative proctitis* limited to rectum/rectosigmoid junction, *left-sided colitis* extending up to splenic flexure, *pancolitis* extending beyond splenic flexure); **risk stratification** (high risk features: age <40 y at diagnosis, extensive disease, large/deep ulcers, early need for corticosteroids); **disease severity** (*mild* <4 BM/day with intermittent blood; *severe* >6 BM/day, frequent bleeding, fever >37.5°C, tachycardia HR>90, anemia, ESR>30mm/h, abdominal pain)

CLINICAL FEATURES**DISTINGUISHING FEATURES BETWEEN CROHN DISEASE AND ULCERATIVE COLITIS**

	Crohn disease	Ulcerative colitis
Degree of involvement	Segmental ("skip lesions")	Continuous from rectum
Symptoms	Rectal sparing Abd pain Diarrhea Anorexia Perianal disease	Cecal patch/backwash ileitis Bloody diarrhea Urgency/tenesmus Fever

CLINICAL FEATURES (CONT'D)

	Crohn disease	Ulcerative colitis
Serology	Anti- <i>Saccharomyces cerevisiae</i> IgG antibody (sens 77%, spec 92%, PPV 82%)	p-ANCA (sens 70%, spc 88%, PPV 75%)
Pathology	Transmural inflammation Granulomas	Mucosal inflammation No granulomas
Complications	Obstruction Strictures Fistulas Fissures Colorectal cancer	Toxic megacolon (1–2%) Colorectal cancer (1%/year after 10 years)

CLINICAL FEATURES (CONT'D)

EXTRAIESTINAL MANIFESTATIONS—ocular (episcleritis, scleritis, uveitis, iritis), hepatic (gallstones, primary sclerosing cholangitis), oral (aphthous ulcers), arthritis (spondylitis; peripheral arthritis pauciarticular large joint or polyarticular small joint), dermatologic (erythema nodosum, pyoderma gangrenosum, Sweet syndrome), hematologic (DVT, anemia, amyloidosis), renal (nephrolithiasis)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, ESR, CRP, ferritin, iron indices, AST, ALT, ALP, bilirubin, albumin, Ca, Mg, PO₄, vitamin B12, folate, fecal calprotectin/lactoferrin
- **MICROBIOLOGY**—stool C&S, O&P, stool for *C. difficile* toxin assay
- **SEROLOGY**—antineutrophil cytoplasmic antibodies (pANCA), anti-*Saccharomyces cerevisiae* antibodies (ASCA)
- **IMAGING**—AXR, CT/MR enterography, contrast-enhanced US
- **ENDOSCOPY**—flexible sigmoidoscopy, colonoscopy, double-balloon enteroscopy, video capsule endoscopy (if non-stricturing disease)

MANAGEMENT**TREATMENT CONCEPTS**

- **SELECTING TREATMENT**—based on disease phenotype and severity, risk factors for disease progression, shared decision making with patient
- **TREATING TO TARGET**—UC (resolution of rectal bleeding and diarrhea, endoscopic remission); CD (resolution of abdominal pain and diarrhea, resolution of ulcers on endoscopy or inflammatory findings on cross-sectional imaging)

MANAGEMENT (CONT'D)

- **CLOSE MONITORING IN MAINTENANCE**—monitor patient symptoms and objective measures of inflammation including biomarkers (CRP, fecal calprotectin), radiology, or endoscopy

Peyrin-Biroulet et al. *Am J Gastroenterol* 2015;110(9)

SUPPORTIVE THERAPY

- **DIET AND NUTRITION**—low residue diet for patients with stricturing disease, nutritional support for malnourished patients/patients with malabsorption, enteral preferred to parenteral nutrition if possible. Protein needs 1–1.5g/kg/day
- **ANTI-DIARRHEAL AGENTS**—can be used for symptom control after achieving objective remission in patients with overlapping functional pain/diarrhea, but contraindicated in severe exacerbation and toxic megacolon

ANTIINFLAMMATORY AGENTS

- **5ASA TOPICAL PREPARATIONS**—for proctitis or in combination with oral 5ASA for left-sided UC. Suppositories for proctitis, enemas for left-sided disease. *Mesalamine* 1 g suppository/4 g enema PR daily, glucocorticoid enema daily to BID
- **SYSTEMIC 5ASA**—for induction and maintenance in UC. *Sulfasalazine* 3–4 g/day divided dose TID; *mesalamine* 2.4 g–4.8 g once daily
- **GLUCOCORTICOIDS**—corticosteroids should be used as induction therapy only, and NOT as maintenance therapy (*methylprednisolone* 30 mg IV BID, *prednisone* 50 mg PO daily, reduce by 5 mg/week), *budesonide* (enteric release for ileal/right sided CD, 9 mg PO daily × 4–8 weeks, tapered by 3 mg/month), *budesonide multi matrix* (for colonic UC, 9 mg daily × 8–12 weeks)

MANAGEMENT (CONT'D)

- **IMMUNOSUPPRESSIVE AGENTS**—*azathioprine* (dosing directed by TPMT activity, 2–2.5 mg/kg/day as tolerated while monitoring CBC, liver enzymes), *methotrexate* 15–25 mg PO/IM/SC weekly (with folic acid replacement)
- **ANTIBIOTICS**—*metronidazole* 500 mg PO BID, *ciprofloxacin* 500 mg PO BID
- **TUMOR NECROSIS FACTOR ANTAGONISTS**—*infliximab* IV induction (5 mg/kg at 0, 2, 6 weeks), maintenance (5 mg/kg q 8 weeks); *adalimumab* SC induction (160 mg week 0, then 80 mg week 2), maintenance (40 mg every other week); *golimumab* (UC only) SC induction (200 mg week 0, then 100 mg week 2), maintenance (100 mg q 4 weeks)
- **ANTI-INTEGRIN BIOLOGICS**—*vedolizumab* IV induction (300 mg at 0, 2, 6 weeks), IV maintenance (300 mg q 8 weeks), SC maintenance (108 mg q 2 weeks)
- **ANTI-INTERLEUKIN BIOLOGICS**—*ustekinumab* (anti-IL12/23) single IV induction dose (260 mg if ≤ 55 kg, 390 mg if 55–85 kg, 520 mg if >85 kg), SC maintenance (90 mg q8–12 weeks)
- **JANUS KINASE INHIBITORS**—*tofacitinib* (UC only) induction (10 mg PO BID \times 8–16 weeks), maintenance (5 mg PO BID)

SURGERY

Related Topics

Clostridioides difficile Colitis (p. 142)
Inflammatory Arthritis (p. 297)

SPECIFIC ENTITIES

CROHN DISEASE

- **PERIANAL CROHN**—accurate staging (MR pelvis, **surgical consultation** for examination under anesthesia), antibiotics for initial symptom control and to clear perianal sepsis, anti-TNF +/- concomitant immunosuppressant for long-term control
- **STRICTURING CROHN**—endoscopic dilation for short strictures <4 cm, anti-inflammatory therapies for inflamed strictures, surgical resection or stricturoplasty for non-inflamed 'cold' strictures

Torres et al. *Lancet* 2017;389(10080)

ULCERATIVE COLITIS

- **ULCERATIVE PROCTITIS**—rectal 5ASA ≥ 1 g daily for 4 weeks to induce symptomatic remission. Maintenance therapy may be required with rectal 5ASA

SPECIFIC ENTITIES (CONT'D)

- **LEFT-SIDED COLITIS**—combination rectal ≥ 1 g daily and oral 5ASA 2.0–4.8 g daily for induction and maintenance in mild-to-moderate disease. Escalate to biologic therapy if non-responsive to optimized dosing 5ASA
- **PANCOLITIS** (mild-moderate)—combination rectal ≥ 1 g daily and oral 5ASA 2.0–4.8g daily for induction and maintenance. Escalate to biologic therapy if non-responsive to optimized dosing 5ASA
- **ACUTE SEVERE UC** (severe)—hospitalize, hydration, nutrition, parenteral steroids, and **pharmacologic VTE prophylaxis**. Early surgical consultation. Monitor daily CRP, abdominal examination. Rescue therapy with *infliximab* or *cyclosporine*

2015 Toronto Consensus Guidelines
Nonhospitalized Ulcerative Colitis

TOXIC MEGACOLON

- **PATHOPHYSIOLOGY**—a potential complication of IBD, infectious colitis (especially *C. difficile*), ischemic colitis, and obstructive colon cancer
- **CLINICAL FEATURES**—combination of abdominal distension and diarrhea should prompt investigations for toxic megacolon. Patient usually toxic with fever, hypotension, delirium, and abdominal pain
- **DIAGNOSIS**—**radiographic colonic dilation** (transverse or right colon, >6 cm), plus **three of the following** (fever >38 °C [100.4 °F], tachycardia >120 /min, leukocytosis $>10.5 \times 10^9$ /L, anemia), plus **one of the following** (dehydration, delirium, electrolyte disturbances, hypotension)
- **TREATMENTS**—supportive therapy (NPO, IV fluids, hold opioids, antidiarrheal and anticholinergic agents). For IBD-related toxic megacolon, give *hydrocortisone* 100 mg IV q6h and antibiotics (ceftriaxone plus metronidazole). For *C. difficile*-related toxic megacolon, treat with IV metronidazole and PO/NG/PR vancomycin. Patients who do not respond to therapy within 72 h should be considered for colectomy. ICU admission for monitoring. Serial blood tests and AXR daily to assess progress

CELIAC DISEASE

- **PATHOPHYSIOLOGY**—sensitivity to gluten **Barley, Rye, Oat, Wheat** ★**BROW**★ → T-cell-mediated immune reaction to gliadin → intestinal epithelial cell death → villous atrophy, crypt hyperplasia → small bowel malabsorption. More common in females (2–3:1). Associated with type 1 diabetes, autoimmune

SPECIFIC ENTITIES (CONT'D)

thyroid disease, dermatitis herpetiformis (p. 398), IgA deficiency, small bowel lymphoma

- **CLINICAL FEATURES**—abdominal bloating (especially after inadvertent gluten ingestion), weight loss, iron-deficiency anemia, hyposplenism, nutritional deficiencies, metabolic bone disorders (osteoporosis, osteomalacia), diarrhea, liver dysfunction
- **DIAGNOSIS**—serology testing accurate only on gluten-containing diet. Anti-transglutaminase (TTG) IgA (sens 94%, spc 99%), antiendomysial IgA, anti gliadin IgG (celiac patients with IgA deficiency may not be anti-TTG IgA positive).

SPECIFIC ENTITIES (CONT'D)

Small bowel biopsy required to confirm (intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy). >99% of celiac patients have HLA DQ2/DQ8 (absence excludes celiac; use genetic testing in patients with discordant serology/histology or in patients already on and unwilling to trial off gluten-free diet)

- **TREATMENTS**—gluten-free diet lifelong (consult dietitian). Evaluate for 'hidden' gluten sources in patients with refractory symptoms. Steroids for refractory celiac despite strict GFD, consider workup for enteropathy-associated lymphoma
Fasano et al. NEJM 2012;367(25)

Constipation**DIFFERENTIAL DIAGNOSIS****★ DUODENUM ★**

DIET—low fiber, dehydration

ΨYCHIATRY—depression, somatization, obsessive compulsive disorder

OBSTRUCTION—cancer, strictures, adhesions

DRUGS—opioids, TCAs, neuroleptics, antihistamines, calcium channel blockers, iron, antacids

ENDOCRINE—hypothyroidism, hypercalcemia, hypokalemia, hypomagnesemia, diabetes, uremia

NEUROLOGIC—spinal cord compression/injury, Parkinson, multiple sclerosis, stroke, autonomic neuropathy (cachexia-anorexia syndrome)

UNKNOWN—functional constipation

MISCELLANEOUS—irritable bowel syndrome, constipation predominant (IBS-C), amyloidosis, scleroderma, immobility

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, TSH, Ca, Mg
- **IMAGING**—AXR, Sitz marker study for slow motility, defecography

DIAGNOSTIC ISSUES

CONSTIPATION SUBTYPES—differentiate primary vs. secondary constipation. Primary constipation can be associated with normal or slowed colonic transit, or from primary defecation disorders (e.g. anorectal dyssynergia). Slow transit characterized by lack of urge to defecate despite infrequent bowel movements. Dyssynergic defecation characterized by significant straining, associated with poor toiletting habits

MANAGEMENT

LIFESTYLE CHANGES—fiber supplementation (add stool bulk: wheat bran, psyllium/Metamucil® 2–3 teaspoon/day), **exercise**, **hydration** (8–10 glasses/day), biofeedback for dyssynergic defecation

SYMPTOM CONTROL—**surfactants/stool**

softeners (*docusate* 100–240 mg PO daily-QID, *tap water enema* 500 mL PR PRN, *mineral oil enema* 100–250 mL PR PRN), **stimulant laxatives**

(*senna* 1–4 tabs PO daily-QID, *bisacodyl/dulcolax suppositories* PR, *sodium picosulfate* 10 mg daily; stimulant laxatives should only be used PRN), **osmotic laxatives**

(*sorbitol* 15–30 mL PO daily-BID, *lactulose* 15–60 mL PO daily, *polyethylene glycol electrolyte solution [PEG]* 250–4000 mL PO PRN), **guanylate cyclase-C**

receptor agonists (*linaclotide* 72–145 mcg daily for constipation, *linaclotide* 290 mcg daily for IBS-C, *plecanitide* 3 mg daily), **chloride**

channel activators (*Lubiprostone* 24 mg PO BID), **serotonin 5-HT₄ receptor agonists**

(*prucalopride* 1–2 mg PO daily), **opioid receptor antagonists** (for refractory opioid-induced constipation only; *methylnaltraxone* 12 mg SC daily or q2d PRN, *naloxegol* 12.5–25 mg PO daily; avoid in patients with bowel obstruction).

Manual disimpaction. For patients with spinal cord injury, it is important to use rectal measures (enemas, suppositories) as significant diarrhea/leakage could occur with oral medications alone

TREAT UNDERLYING CAUSE—stop potentially constipation-causing medications if possible

Schiller Lancet Gastroenterol Hepatol 2019;4(11)

SPECIFIC ENTITIES

IRRITABLE BOWEL SYNDROME (IBS)

- **PATHOPHYSIOLOGY**—disordered gut-brain interaction, resulting in GI symptoms due to motility disturbance, visceral hypersensitivity, altered mucosal/immune function, gut microbiota, and/or CNS processing
- **CLINICAL FEATURES**—Rome IV Criteria for IBS: recurrent abdominal pain ≥ 1 day/week \times last 3 months, with ≥ 2 of: related to defecation (either increasing or improving), change in stool frequency, change in stool form/appearance. Constipation/diarrhea-predominant subtypes, mixed subtype. Other functional bowel disorders: functional constipation, functional diarrhea, functional abdominal bloating distention, opioid-induced constipation, unspecified functional bowel disorder
- **ASSOCIATIONS**—patients with IBS are more likely to have functional dyspepsia, urinary symptoms, dysmenorrhea, dyspareunia, sexual dysfunction, proctalgia fugax, a history of physical or sexual abuse, and fibromyalgia
- **DIAGNOSIS**—in updated Rome IV, IBS is positive diagnosis (rather than diagnosis of exclusion).

SPECIFIC ENTITIES (CONT'D)

However, consider colonoscopy, evaluation for celiac (p. 142), fecal calprotectin and stool cultures to rule out other diseases

- **TREATMENTS**—reassurance, stress reduction, fiber supplementation. For constipation-prone IBS, consider osmotic laxatives (first-line), *linaclotide* 290 μg PO daily, *plecanatide* 3 mg PO daily, or *lubiprostone* 8 μg BID (♀). For diarrhea-prone IBS, consider *loperamide* 2–4 mg PO daily (first-line), *eluxadoline* 75–100 mg PO BID (mixed mu-opioid receptor agonist, delta opioid receptor antagonist, κ opioid receptor agonist), *rifaximin* 550 mg TID \times 14 days (for moderate-to-severe IBS-D), *alosectron* 0.5–1 mg PO BID \times 12 weeks (for ♀ with severe diarrhea; 5HT₃ antagonist). For abdominal pain, consider antispasmodics (*hyosciamine* 0.125–0.25 mg PO q4–6 h PRN), TCAs (*amitriptyline* 10–75 mg nightly), and SSRIs for abdominal pain. Cognitive behavioral therapy may also be useful

Lacy et al. *Gastroenterology* 2016;150(6)
2019 CAG Guideline Irritable Bowel Syndrome

Abnormal Liver Enzymes

HEPATOCELLULAR INJURY PATTERN (\uparrow AST/ALT \pm \uparrow ALP/BILI)

INFECTIOUS—HAV, HBV, HCV (rare), HDV, HEV, EBV, CMV, HSV, VZV, schistosomiasis, toxoplasmosis, bacterial cholangitis

FATTY LIVER—alcoholic, non-alcoholic steatohepatitis (NASH)

TOXIC—acetaminophen, NSAIDs, amiodarone, labetalol, statins, phenytoin, valproic acid, fluoroquinolones, amoxicillin/clavulanate, sulfonamides, tetracyclines, isoniazid, azoles, halothane, glyburide, propylthiouracil, *Amanita phalloides* mushroom, heavy metals, anabolic steroids, cocaine, phenacyclidine

VASCULAR—ischemic (“shock liver”), Budd-Chiari, congestive, venoocclusive disease (BMT, chemotherapy, OCP)

NEOPLASTIC—hepatoma

AUTOIMMUNE—autoimmune hepatitis

HEREDITARY—Wilson disease, hemochromatosis, $\alpha 1$ -antitrypsin deficiency, glycogen storage disease

PREGNANCY—acute fatty liver of pregnancy, HELLP

OTHERS—liver surgery, Reye syndrome with viral illness and ASA use

NON-HEPATIC—celiac sprue, adrenal insufficiency, myopathy, strenuous exercise

CHOLESTATIC PATTERN (\uparrow ALP/BILIRUBIN \pm AST/ALT)

BACTERIAL CHOLANGITIS

BILIARY EPITHELIAL DAMAGE—hepatitis, cirrhosis, biliary colic

INTRAHEPATIC CHOLESTASIS—sepsis, drugs (amoxicillin-clavulanate, erythromycin, trimethoprim-sulfamethoxazole, indinavir, nevirapine, allopurinol, carbamazepine, captopril, chlorpromazine, diltiazem, estrogens, fluphenazine, gold, imipramine), TPN, primary biliary cirrhosis

BILIARY DUCTAL OBSTRUCTION—choledocholithiasis, pancreatic cancer, cholangiocarcinoma, pancreatitis, primary sclerosing cholangitis

INFILTRATIVE PATTERN (\uparrow ALP WITH \uparrow GGT \pm \uparrow BILI/AST/ALT)

INFECTIOUS—TB, histoplasmosis, abscess (bacterial, amoebic)

NEOPLASM—hepatoma, lymphoma

GRANULOMATOUS DISEASE—sarcoidosis, TB, fungal

OTHERS—amyloidosis

ISOLATED HYPERBILIRUBINEMIA (\uparrow BILIRUBIN ONLY)

see JAUNDICE (p. 155)

NON-INVASIVE MEASURES OF FIBROSIS

RADIOGRAPHIC—US transient elastography, shear wave elastography, acoustic radiation force impulse imaging (ARFI), MR elastography

SEROLOGIC—AST to platelet ratio index (APRI), AST:ALT > 1, combination panels (FIB-4 index, HepaScore®, FibroTest/FibroSure®, ActiTest®, FibroIndex®, others)

Related Topics

Acetaminophen Overdose (p. 121)
 Alcohol-Related Issues (p. 478)
 Hemochromatosis (p. 482)
 Hepatitis B (p. 147)
 Hepatitis C (p. 148)

NON-INVASIVE MEASURES OF FIBROSIS (CONT'D)

Hepatoma (p. 226)
 Liver Diseases in Pregnancy (p. 467)
 Wilson Disease (p. 151)

LIVER ENZYMES BY CATEGORY

SYNTHETIC FUNCTION—INR (dependent on factors I, II, V, VII, IX, X), bilirubin (heme breakdown product), albumin (synthesis), fibrinogen

HEPATIC INJURY—AST (intracellular; liver, heart, skeletal, kidneys, brain, pancreas, lungs, RBC, WBC), ALT (intracellular; specific for Liver), ALP (liver, gut, bone, placenta), GGT, LDH (bone, muscle, liver, lungs)

Acute Liver Failure**DEFINITIONS**

ACUTE (FULMINANT) LIVER FAILURE—acute liver injury with encephalopathy *and* impaired synthetic function (INR ≥ 1.5); subclassified into hyperacute (day 0–7), acute (day 8–21) and subacute (day > 21 and < 26 weeks)

COMPLICATIONS OF HEPATIC FAILURE**★ SCREAM ★**

- SEPSIS
- COAGULOPATHY
- RENAL FAILURE
- ENCEPHALOPATHY
- ASCITES
- METABOLIC CHANGES (hypoglycemia, electrolyte abnormalities, acidosis)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, type and screen, peripheral smear, lytes (including Ca/Mg/PO₄), urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HAV IgM, HAV IgG, HBsAg, HBsAb, HBcIgM, anti-HCV and HCV RNA, lactate, ABG
- **IMAGING**—US abd (with Doppler), CT abd/MR venogram, echocardiogram

SPECIAL

- **LABS**—EBV, CMV, HSV (type 1 and 2 DNA PCR), VZV, HDV, HEV, ANA, anti-smooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA), quantitative Ig, ferritin, Fe, TIBC, % sat, ceruloplasmin, α1-antitrypsin, AFP, anti-TTG, lipase, amylase, LDH, haptoglobin, acetaminophen, CK, TSH, ammonia (arterial)
- **LIVER BIOPSY**

INVESTIGATIONS (CONT'D)

- ERCP/MRCP
- GASTROSCOPY

DIAGNOSTIC AND PROGNOSTIC ISSUES

↑ **AST/SGOT**—do panel of liver function tests. If isolated rise, consider non-hepatic causes. Otherwise, same as ALT workup. AST > ALT suggests alcoholic liver disease, fatty liver, or cirrhosis

↑ **ALT/SGPT**—if symptomatic and presence of risk factors for liver disease, liver dysfunction (↓ albumin, ↑ INR, ↑ bili), ↑ ALT or AST > 3 × upper limit of normal, or ↑ ALT > 6 months, consider basic workup including abd US with Doppler, viral serologies, ANA, ASMA, quantitative Ig, ceruloplasmin, iron studies, anti-TTG, +/- liver biopsy

↑ **ALP/BILI**—ask about pain, symptoms of infiltrative disease, or IBD. To confirm liver involvement, perform bilirubin fractionation, GGT, 5'NT, abdominal US, AMA, and quantitative Ig. Consider MRCP/EUS and liver biopsy

MONITORING—INR and bilirubin are much more useful to monitor liver function compared to transaminases

MANAGEMENT**SYMPTOM CONTROL**

- **ACUTE**—ABC, O₂, IV hydration, monitoring (including **ICU consultation**)
- **ELEVATED INTRACRANIAL PRESSURE**—for cerebral edema, consider prophylactic *phenytoin* (prompt treatment if seizures develop), raise head of bed, hyperventilate (monitor PaCO₂), *dexamethasone*, *mannitol* (0.5–1.0g/kg)

MANAGEMENT (CONT'D)

- bolus, monitor serum osmolality), barbiturates for severe ICP, avoid excessive fluids/stimulation/agitation
- **SEPSIS**—antibiotics
 - **COAGULOPATHY**—*vitamin K* 10 mg IV/PO, FFP 2–4 U IV (only if active bleeding or invasive procedures, or difficult to follow INR afterward)
 - **ACUTE RENAL FAILURE**—supportive renal replacement. Consider midodrine, octreotide, and albumin
 - **ENCEPHALOPATHY**—*lactulose* 30 g PO BID to QID PRN titrate to 2–4 bowel movements/day; if patient obtunded and NPO, consider intubation + *lactulose* 300 mL (mixed with 700 mL of H₂O or NS) PR QID until awake
 - **ACIDOSIS**—3 amp NaHCO₃ diluted in 1000 mL D5W (i.e. 150 mmol/L of HCO₃⁻) as continuous IV infusion at 150–250 mL/h. Give with caution as risk of cerebral edema with increased fluid
 - **HYPOGLYCEMIA**—D10W, tube feed, TPN
 - **DETOXIFICATION**—*N-acetylcysteine* may be considered when cause of acute liver failure is unknown or if acetaminophen toxicity may be contributing

PREVENTION—**hepatitis B vaccine** (0, 1, 6 months), **HBIG** (post-exposure), hepatitis A vaccine (see p. 291)

TREAT UNDERLYING CAUSE—**hepatitis B** (antiviral therapy). **Acetaminophen toxicity** (*N-acetylcysteine* 150 mg/kg IV over 1h, then 50 mg/kg over 4h, then 100 mg/kg over 16h). **HSV infection** (*acyclovir* 5–10 mg/kg IV q8h). **Autoimmune hepatitis** (*prednisone* or *prednisolone* 40–60 mg/day and *azathioprine* 50–100 mg/day). **Wilson disease** (plasma exchange, liver transplantation, no role for chelation in acute liver failure)

LIVER TRANSPLANT—patients with fulminant liver failure should be transferred to acute care centers with liver transplant expertise

TREATMENT ISSUES

LIVER TRANSPLANT

- **ALLOCATION**—based on ABO blood type, body size, wait designation, urgency. King's College Criteria or Model for End Stage Liver Disease (MELD) score used for predicting outcome in acute hepatic failure (AHF), identify patients likely to benefit from liver transplantation
- **KING'S COLLEGE CRITERIA FOR ACETAMINOPHEN TOXICITY IN AHF** (rule of 3's)—either arterial pH <7.3 or grade ≥ III encephalopathy plus both Cr >300 μmol/L [>3.4 mg/dL] and INR >6.5 (or PT >100 s)

TREATMENT ISSUES (CONT'D)

- **KING'S COLLEGE CRITERIA FOR NON-ACETAMINOPHEN INDUCED AHF ACUTE HEPATIC FAILURE**—INR >3 or any 3 of following: age <10 or >40, unfavorable disease etiology (non-A non-B viral hepatitis, idiosyncratic drug reaction, Wilson), duration of jaundice before encephalopathy >7 days, INR >1.5, bilirubin >308 μmol/L [18 mg/dL]
- **CONTRAINDICATIONS**—malignancy (except hepatocellular carcinoma), irreversible cardiopulmonary comorbidities, neuropsychiatric comorbidities, sepsis, uncontrolled substance abuse, non-compliance

SPECIFIC ENTITIES

AST/ALT THOUSANDS CLUB—viral hepatitis, ischemic liver (hypotension, hypoxia, sepsis), drugs/toxins (acetaminophen/paracetamol), autoimmune hepatitis, gallstone disease (acute bile duct obstruction), acute Budd–Chiari syndrome, hepatic artery ligation

ALCOHOLIC LIVER DISEASE

- **SUBTYPES**—alcoholic fatty liver, alcoholic hepatitis, micronodular cirrhosis
- **DIAGNOSIS**—AST:ALT ≥2:1 (low ALT due to alcohol-related pyridoxal 5-phosphate deficiency), rare for AST to be >8 × normal and for ALT to be >5 × normal. GGT ↑, ALP ↑, bilirubin ↑
- **ALCOHOLIC HEPATITIS**—jaundice, fever, hepatomegaly, transaminitis, ascites, coagulopathy, fever, leukocytosis. Exclude other causes of hepatitis, underlying chronic liver disease/cirrhosis, infection. High mortality (25% at 1 month)
- **TREATMENTS**—**abstinence**, nutrition, folate/thiamine, for patients with alcoholic hepatitis assess severity using Maddrey DF. Steroids not recommended if mild/moderate alcoholic hepatitis (DF <32); *prednisolone* 40 mg PO daily and assess for improvement after 7 days if moderate/severe alcoholic hepatitis (DF ≥32); if improved by Lille score, continue × 28 days

NON-ALCOHOLIC STEATOHEPATITIS (NASH)

- **ASSOCIATIONS**—obesity, hyperlipidemia, diabetes, Cushing, TPN, high-protein diets for weight loss, amiodarone, tamoxifen
- **DIAGNOSIS**—liver biopsy
- **TREATMENTS**—weight loss (5–10%, 0.5–1.0 kg/week through diet, exercise, consider bariatric surgery), metformin for diabetes (consider pioglitazone, liraglutide if biopsy-proven NASH), statins for dyslipidemia, *vitamin E* 800 IU/day if biopsy-proven NASH with fibrosis stage ≥2 without diabetes

Diehl et al. *NEJM* 2017;377(21)

Lucey et al. *NEJM* 2009;360(26)

Hepatitis B

Seto et al. *Lancet* 2018;392(10161)
2018 AASLD Hepatitis B Update

PATHOPHYSIOLOGY

NATURAL HISTORY—vertical vs. horizontal transmission (acute hepatitis → chronic disease develops in >90% of neonates and in <5% if >12 years old) → 12–20% with chronic hepatitis progress to cirrhosis in 5 years → 20% with compensated cirrhosis progress to decompensation in 5 years and 6–15% progress to hepatocellular carcinoma (HCC)

ACUTE HEPATITIS B—may range from subclinical/anicteric hepatitis (70%) to icteric hepatitis (30%) and even fulminant hepatic failure (0.5–1%). Symptoms: fever, anorexia, rash, nausea, jaundice, RUQ tenderness, arthralgia, and arthritis. ↑↑ ALT and AST

CHRONIC HEPATITIS B—HBsAg+ ≥6 months with chronic hepatitis, subdivided by HBeAg positive/negative status (lower HBV DNA in HBeAg- patients)

- **IMMUNE TOLERANT CHRONIC HEPATITIS B** (if vertical transmission)—high HBV DNA, HBeAg+, but no active liver inflammation, asymptomatic, normal ALT, as lack of immune response in children. Lasts 10–30 years
- **IMMUNE ACTIVE CHRONIC HEPATITIS B**—immune response against HBV resulting in chronic hepatitis w/moderate-severe necroinflammation +/- fibrosis; may seroconvert HBeAg (HBV DNA usually >20,000 IU/mL if HBeAg+ vs. >2,000 IU/mL if HBeAg-)
- **INACTIVE CHRONIC HEPATITIS B**—HBeAg-, HBeAb+, low level of viral replication (HBV DNA <2,000 IU/mL), usually normal liver enzymes, biopsy with minimal necroinflammation but variable fibrosis

RISK FACTORS—vertical transmission, endemic areas, transfusions, dialysis, healthcare workers, IVDU, high-risk sex, body piercing, tattoos, organ transplantation

CLINICAL FEATURES

HISTORY—symptoms of liver dysfunction (jaundice, bleeding, infections, ascites, confusion), weight change, risk factors of hepatitis (family history, sexual activity, IDU, tattoos, piercing, healthcare worker, transfusions, dialysis), past medical history (alcohol, HCV, HIV), medication history

PHYSICAL—liver examination, stigmata of chronic liver disease (see p. 149), weight

CLINICAL FEATURES (CONT'D)

EXTRAHEPATIC MANIFESTATIONS OF HBV—polyarteritis nodosa, membranous nephropathy, membranoproliferative glomerulonephritis

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HBV serology (HBsAb, HBsAg, HBcIgM, HBcIgG to determine infection/immune status, HBeAg, HBeAb, quantitative HBsAg, HBV DNA for active replication), HAV serology, HCV serology, HDV serology, HIV serology
- **IMAGING**—US abd, Fibroscan® (non-invasive assessment of liver fibrosis using US)

SPECIAL

- **LIVER BIOPSY**

DIAGNOSTIC ISSUES

HEPATITIS B SEROLOGY

- **HBsAg**—hepatitis B surface antigen. Positive if active infection
- **HBsAb**—antibody against hepatitis B surface antigen. Positive if immunized (through past infection or vaccination)
- **HBcIgM**—IgM antibody against hepatitis B core antigen. Suggestive of early infection (indicates the window period) or reactivation
- **HBcIgG**—IgG antibody against hepatitis B core antigen. Suggestive of hepatitis B exposure (not from vaccination)
- **HBeAg**—e-antigen, indicator of viral replication and infectivity. HBeAg- without HBeAb positivity suggests chronic HBV infection with pre-core mutant/promoter mutations: higher risk of treatment failure and progressive hepatic injury even with low HBV DNA
- **HBeAb**—antibody against hepatitis B envelope protein. Suggests low/no viral replication, usually with low infectivity
- **HBV DNA**—direct determination of HBV DNA, reflects viral replication activity, associated with the risk of cirrhosis and HCC. HBV DNA important in both HBeAg+ and HBeAg- individuals to determine need for antiviral therapy

DIAGNOSTIC ISSUES (CONT'D)

	HBsAg	HBcIgM	HBsAb	HBcIgG	HBeAg	HBeAb
Acute infection						
Early	+	-	-	-	+	-
Window	-	+	-	-	+	-
Late	-	+/-	+	-	+	-
Immunity						
Vaccinated	-	-	+	-	-	-
Chronic infection						
Infectious/active	+	-	-	+	+	-
Pre-core mutant	+	-	-	+	-	-
Low replicative	+	-	-	+	-	+

MANAGEMENT

LIFESTYLE CHANGES—avoid alcohol use, sexual education, HBV vaccination

TREATMENT—nucleos(t)ide analogues (*tenofovir alafenamide* 25 mg PO daily or *tenofovir disoproxil fumarate* 300 mg daily, *entecavir* 0.5 mg daily)

VACCINATION—household and sexual contacts

TREATMENT ISSUES**TREATMENT FOR CHRONIC HEPATITIS B WITHOUT CIRRHOSIS**

- **HBeAg positive patients**—consider treatment if HBV DNA level >20,000 IU/mL and elevated ALT >2× ULN × 3–6 months (normal ALT 19–25 U/L ♀, 29–33 U/L ♂); or significant inflammation and fibrosis (≥F2); treat × 12 months after HBeAg seroconversion
- **HBeAg negative patients (pre-core or core promoter mutations)**—consider treatment if HBV DNA >2000 IU/mL and elevated ALT >2× ULN × 3–6 months; or significant inflammation and fibrosis (≥F2); treat to HBsAg loss

TREATMENT ISSUES (CONT'D)**SPECIAL CONSIDERATIONS**

- **COMPENSATED CIRRHOSIS**—if detectable HBV DNA >2000 IU/mL, treat indefinitely; if HBV DNA <2000 IU/mL, consider treatment if ALT elevated
- **DECOMPENSATED CIRRHOSIS**—treat immediately, regardless of ALT/HBV DNA, prefer treatment with *entecavir* 1 mg PO daily, consider liver transplantation
- **PREGNANCY**—check HBsAg in first trimester, if positive then check baseline HBV DNA, HBeAg/anti-HBe, ALT and repeat at 26–28 weeks. If HBV DNA >200,000 IU/mL, antiviral treatment for mother + vaccinate + HBIG for infant within 12 hours of birth. If HBV DNA ≤ 200,000 IU/mL, vaccinate + HBIG within 12 hours of birth
- **HCC SURVEILLANCE**—surveillance indications: family history of HCC, Asian ♂ >40 years, Asian ♀ >50 years, Blacks, HBV DNA >20,000 IU/mL + high ALT, Child-Pugh A/B cirrhotics or C if wait-listed for transplant. US q6 months +/- AFP

Hepatitis CSpearman et al. *Lancet* 2019;394(10207)

2018 Canadian Assoc Study Liver Guideline Chronic Hepatitis C

PATHOPHYSIOLOGY

NATURAL HISTORY—acute infection → 55–85% will develop chronic infection (+HCV RNA), spontaneous clearance typically within 12 weeks of seroconversion → 5–20% of total will develop cirrhosis → among cirrhotics, 3–5%/year of acute decompensation, 1–3%/year of HCC. Direct acting antiviral (DAA) therapy curative

PATHOPHYSIOLOGY (CONT'D)

RISK FACTORS FOR TRANSMISSION—IVDU, blood products (prior to routine screening), perinatal transmission, body piercing/tattooing, long-term dialysis, occupational exposure (healthcare workers), high risk sexual partners

CLINICAL FEATURES

HISTORY—symptoms of liver dysfunction (jaundice, bleeding, infections, ascites, confusion), associated symptoms (fatigue, anorexia, myalgia/arthralgia, weakness), risk factors of hepatitis, past medical history (alcohol, HBV, HIV), medication history

PHYSICAL—liver examination, stigmata of chronic liver disease, weight. Also examine for extrahepatic manifestations of HCV

SCREENING—one time in all adults ≥ 18 years, repeat screening if high risk exposures

EXTRAHEPATIC MANIFESTATIONS OF HCV

- **HEENT**—uveitis, corneal ulcer, sialadenitis
- **HEMATOLOGIC**—aplastic anemia, lymphoma, mixed cryoglobulinemia, ITP
- **VASCULAR**—necrotizing vasculitis, polyarteritis nodosa (PAN)
- **RENAL**—MPGN type I (w/cryoglobulinemia), membranous nephropathy, PAN
- **RHEUMATOLOGIC**—arthralgias, arthritis, myalgia, sicca
- **NEUROLOGIC**—weakness, peripheral neuropathy
- **ENDOCRINE**—diabetes, antithyroid antibodies
- **DERMATOLOGIC**—porphyria cutanea tarda, lichen planus, psoriasis (20%), pruritus, Raynaud syndrome, cutaneous necrotizing vasculitis

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, anti-HCV IgM and total (sens 92–97%), HCV RNA PCR (qualitative, quantitative), genotyping, β hCG (before treatment), other viral hepatitis serology, HIV
- **IMAGING**—US abd, Fibroscan[®]

SPECIAL

- **LIVER BIOPSY**

MANAGEMENT

TREATMENT CONSIDERATIONS—genotype, liver fibrosis, co-infection with HIV/HBV, renal function, medication interactions, other comorbidities

TREAT UNDERLYING CAUSE

- **GENOTYPE 1**—ledipasvir-sofosbuvir, sofosbuvir-velpatasvir, elbasvir-grazoprevir, ombitasvir-paritaprevir-ritonavir + dasabuvir with or without ribavirin, simeprevir + sofosbuvir, daclatasvir + sofosbuvir
- **GENOTYPE 2/3**—sofosbuvir-velpatasvir, glecaprevir-pibrentasvir
- **GENOTYPE 4/5/6**—ledipasvir-sofosbuvir, sofosbuvir-velpatasvir, glecaprevir-pibrentasvir

ORTHOTOPIC LIVER TRANSPLANT**TREATMENT ISSUES****ANTIVIRAL THERAPIES**

- **MECHANISM OF ACTION**—target HCV-encoded proteins involved in viral replication. NS3/NS4A serine protease responsible for post-translation processing. NS5A organizes HCV replication complex. NS5B RNA-dependent RNA polymerase for viral replication
- **NS3/4A**—glecaprevir, grazoprevir, paritaprevir, simeprevir
- **NS5A**—daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir
- **NS5B**—sofosbuvir, dasabuvir

MONITORING DURING HCV THERAPY—CBC weekly for 4 weeks, then CBC, AST, ALT, uric acid monthly, TSH and ANA every 3 months, and HCV RNA at 4, 12, and 24 weeks during treatment and 6 months after therapy. For significant anemia and neutropenia, give EPO and GCSF, respectively. Also monitor for depression

Chronic Liver Disease: Cirrhosis**DIFFERENTIAL DIAGNOSIS**

INFECTIONS—HBV, HCV, HDV, brucellosis, schistosomiasis, toxoplasmosis

STEATOHEPATITIS—alcohol, non-alcoholic steatohepatitis (NASH)

MEDICATIONS—methotrexate, isoniazid

AUTOIMMUNE—autoimmune hepatitis

NEOPLASM—hepatoma, cholangiocarcinoma

VASCULAR—veno-occlusive disease, hereditary hemorrhagic telangiectasia

DIFFERENTIAL DIAGNOSIS (CONT'D)

METABOLIC—hemochromatosis, Wilson disease, $\alpha 1$ -antitrypsin deficiency, glycogen storage disease, celiac disease

STRUCTURAL—polycystic liver disease, granulomatous liver disease

BILIARY CIRRHOSIS—primary biliary cholangitis, primary sclerosing cholangitis, secondary biliary cirrhosis (recurrent pyogenic cholangitis, stones, strictures)

CARDIAC CIRRHOSIS—chronic right-sided heart failure

PATHOPHYSIOLOGY

CHILD-PUGH CLASSIFICATION OF LIVER CIRRHOSIS

Points	Encephalopathy	Ascites	Albumin	Total bili	INR
1	0	None	>35 g/L [>3.5 g/dL]	<34 μM [<2 mg/dL]	<1.7
2	1–2	Slight	28–35 g/L [2.8–3.5 g/dL]	34–51 μM [2–3 mg/dL]	1.7–2.3
3	3–4	Mod	<28 g/L [<2.8 g/dL]	>51 μM [>3 mg/dL]	>2.3

CP A=5–6, B=7–9, C=10–15; CP-C ≥12 associated with ≤6 month median survival.

PATHOPHYSIOLOGY (CONT'D)

MODEL FOR END-STAGE LIVER DISEASE

(MELD) SCORE—originally designed to predict survival in patients with portal hypertension undergoing elective TIPS, now used for organ allocation in patients with chronic liver disease (consider transplant if MELD ≥18). MELD range 6 to 40 (higher values = worse prognosis)

- **ORIGINAL MELD** = $9.57 \times \log_e(\text{Cr in mg/dL}) + 3.78 \times \log_e(\text{total bilirubin in mg/dL}) + 11.2 \times \log_e(\text{INR}) + 6.43$
- **UNITED NETWORK OF ORGAN SHARING MELD (UNOS-MELD)** = same formula but fixed lower limit of 1 for all variables and fixed upper limit of 4 mg/dL for Cr. Furthermore, Cr set at 4 for patients on renal replacement therapy
- **MELD-Na** = UNOS-MELD - Na - $[0.025 \times \text{MELD} \times (140 - \text{Na})] + 140$

For web-based calculator, please see MELD Score and 90-Day Mortality Rate for Alcoholic Hepatitis

CLINICAL FEATURES

HISTORY—symptoms of liver dysfunction (jaundice, bleeding, infections, ascites, confusion), weight change, risk factors of hepatitis (sexual activity, IDU, tattoos, piercing, healthcare worker, transfusions, dialysis), past medical history (alcohol, hereditary disorders), medication history (acetaminophen, other hepatotoxins)

PHYSICAL

- **STIGMATA OF CHRONIC LIVER DISEASE**—leukonychia, Terry nails, clubbing, Dupuytren contractures, palmar erythema, asterixis, scleral icterus, altered mental status, parotid enlargement, fetor hepaticus, spider angiomas, gynecomastia, ascites, splenomegaly, caput medusa, hemorrhoids, testicular atrophy, proximal muscle weakness, peripheral edema, petechiae

CLINICAL FEATURES (CONT'D)

- **CLUES TO ETIOLOGY**—obesity (fatty liver), excoriations (PBC), tattoos/needle tracks (viral hepatitis), bronze skin (hemochromatosis), Kayser-Fleischer rings (Wilson disease)

DISTINGUISHING LIVER FROM RIGHT KIDNEY

1. The liver has no palpable upper border and extends more laterally and medially
2. The liver is not usually ballotable, but the kidney is because of its retroperitoneal position
3. The percussion note is dull over the liver but is usually tympanic over the kidney
4. A friction rub may occasionally be heard over the liver, but never over the kidney because it is too posterior
5. The liver has a shaper edge, while kidney is usually more rounded

DISTINGUISHING FEATURES BETWEEN PORTAL HYPERTENSION AND VENA CAVA OBSTRUCTION

- **PORTAL HYPERTENSION**—caput medusa veins drain away from umbilicus. Stigmata of liver disease
- **IVC OBSTRUCTION**—veins prominent in the abdomen and drain up toward the superior vena cava system. No evidence of liver disease
- **SVC OBSTRUCTION**—veins prominent in the chest and drain down toward the inferior vena cava system. No evidence of liver disease

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HAV serology, HBsAg, HBsAb, anti-HBc, HCV, quantitative immunoglobulins

INVESTIGATIONS (CONT'D)

- **IMAGING**—US abd (with Doppler), Fibroscan*

SPECIAL

- **LABS**—ANA, ASMA (anti-actin antibodies), anti-liver-kidney-microsomal (LKM) antibody, AMA, ferritin, ceruloplasmin, α 1-antitrypsin, AFP, anti-TTG
- **GASTROSCOPY**—varices screening if platelets $<150 \times 10^9/L$ or liver stiffness ≥ 20 kPa
- **LIVER BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE—consideration for liver transplantation

PRIMARY VARICEAL BLEEDING PROPHYLAXIS

—prophylaxis if high risk (small varices with red wale sign or CP-B/C cirrhosis, medium/large varices); primary prophylaxis with non-selective β -blocker (*nadolol* 40–80 mg PO daily, *propranolol* 20 mg PO BID, or *carvedilol* 6.25 mg PO daily-BID) or endoscopic variceal ligation. Target HVPg reduction $\geq 10\%$ or ≤ 12 mmHg, HR 55–60 bpm if NSBB used. See UPPER GI BLEED (p. 134), HEPATIC ENCEPHALOPATHY (p. 152), and ASCITES (p. 153)

HEPATOMA SCREENING—for all patients with cirrhosis, and those with HBV and HCC risk factors, repeat abdominal US +/- AFP every 6 months for surveillance

SPECIFIC ENTITIES**CAUSES OF HEPATOMEGALY**

- **CONGESTIVE**—right heart failure, constrictive pericarditis, tricuspid regurgitation, IVC obstruction, hepatic vein obstruction
- **CHOLESTATIC LIVER DISEASE**—PBC, PSC
- **INFILTRATION**—malignancy, amyloidosis, hemochromatosis, fatty liver
- **REACTIVE**—acute viral or drug-induced hepatitis

WILSON DISEASE

- **ETIOLOGY**—autosomal recessive defect in copper excretion
- **DIAGNOSIS**—neurologic features (dysarthria, dystonia, choreoathetosis, cognitive impairment, cerebellar ataxia), Kayser–Fleischer ring, low serum ceruloplasmin, high 24-h urine for copper, associated with Coombs-negative hemolytic anemia
- **TREATMENTS**—**dietary restriction** (avoid shellfish, organs, chocolate, nuts, and mush-

SPECIFIC ENTITIES (CONT'D)

rooms), **chelating agent** (D-penicillamine or trientine), and zinc. Liver transplant for patients with Wilson related acute liver failure

AUTOIMMUNE HEPATITIS

- **DIAGNOSIS**—transaminitis, quantitative immunoglobulins (\uparrow IgG), ANA, ASMA, anti-LKM antibody (less common antibodies: anti-liver cytosol Ab-1, anti-soluble liver/liver pancreas Ab), liver biopsy (interface hepatitis), exclude viral hepatitis
- **CLINICAL FEATURES**—broad spectrum, from asymptomatic to acute hepatitis (including AHF), chronic hepatitis/cirrhosis. Associated autoimmune disorders (thyroiditis, RA, type 1 diabetes, ulcerative colitis, SLE, celiac)
- **TREATMENTS**—prednisone, azathioprine, or mycophenolate mofetil. For fulminant hepatitis or cirrhosis, consider liver transplantation

HEPATIC HYDROTHORAX

- **PATHOPHYSIOLOGY**—low oncotic pressure, diaphragmatic defects \rightarrow ascitic fluid moves to pleural space due to pressure gradient \rightarrow transudative pleural effusion \rightarrow decreased lung volumes \rightarrow V/Q mismatch \rightarrow hypoxemia
 - **DIAGNOSIS**—diagnostic paracentesis/thoracentesis. US abd to assess liver and ascites. CT chest and abd to rule out other lesions. Intraperitoneal injection of ^{99m}Tc -labeled serum albumin may be helpful to confirm diagnosis
 - **TREATMENTS**— O_2 , salt restriction, diuretics, therapeutic paracentesis, may need thoracentesis, TIPS. Avoid chest tube (high risk of SBP and hepatorenal syndrome)
- HEPATOPULMONARY SYNDROME**
- **PATHOPHYSIOLOGY**—portal hypertension \rightarrow \downarrow metabolism of vasodilating substance or \downarrow production of vasoconstricting substance \rightarrow pulmonary capillary dilatation \rightarrow diffusion-perfusion imbalance \rightarrow hypoxemia, dyspnea on exertion and/or at rest, orthodeoxia and platypnea, cyanosis, clubbing and spider nevi
 - **DIAGNOSIS**—contrast echo/bubble study (presence of microbubbles in the left atrium 3–6 cardiac cycles after IV injection of normal saline suggests dilated pulmonary capillaries), lung perfusion scan, pulmonary angiogram (if severe hypoxemia)
 - **TREATMENTS**— O_2 , liver transplant

SPECIFIC ENTITIES (CONT'D)

PORTOPULMONARY HYPERTENSION

- **PATHOPHYSIOLOGY**—portal hypertension → imbalanced vasoconstrictive and vasodilatory mediators +/- thromboembolism in pulmonary circulation through portosystemic shunting +/- hyperdynamic pulmonary circulation → findings similar to primary pulmonary hypertension (dyspnea, syncope, edema, chest pain)
- **DIAGNOSIS**—echocardiogram, right heart catheterization (mPAP >20 mmHg at rest, PCWP ≤15 mmHg, PVR ≥3 Wood units)
- **TREATMENTS**—O₂, diuretics, sildenafil, prostaglandins, calcium channel blockers, liver transplant

HEPATORENAL SYNDROME

- **PATHOPHYSIOLOGY**—liver failure with portal hypertension → dilated systemic circulation (low vascular resistance) → ↑ renin-aldosterone system with ↑ cardiac output but not enough to counter splanchnic arterial vasodilatation (especially nitric oxide) → reduced renal perfusion. Common precipitants: SBP, GI bleeding.
- **TYPES**—Type I more severe, >2 × increase in creatinine to >220 μmol/L [>2.2 mg/dL] in ≤2 weeks. Patients usually oliguric/anuric. Type II less rapidly progressive, characterized by ascites resistant to diuretics
- **DIAGNOSIS**—clinical diagnosis; rule-out other etiologies of AKI (including pre-renal causes,

SPECIFIC ENTITIES (CONT'D)

- ATN, infection, and GI bleed). Definition: AKI (increase in Cr >26.5 mmol/L within 48h or >50% from baseline within 7 days), urine Na <10 mM (<10 mEq/L), bland U/A, minimal proteinuria (<500 mg/day), and no improvement after volume expansion with IV albumin (1 g/kg/d and up to 100 g/d × 2 days)
- **TREATMENTS**—treat underlying liver disease, stop diuretics, fluid (usually no response). Albumin 1g/kg/day × 2 days minimum. Vasoconstrictors (norepinephrine or vasopressin in ICU setting; midodrine 7.5–15 mg TID + octreotide 50 mcg/h + albumin 1g/kg/day × 2 days, then 25–50 g/day if not in the ICU; terlipressin 1–2 mg IV q4–6 h if available as alternative to midodrine/octreotide). Refractory HRS: TIPS, renal replacement therapy (as bridge to liver recovery or transplant)

Ge et al. *NEJM* 2016;375(8)

Related Topics

Acute Hepatic Failure (p. 145)
 Ascites (p. 153)
 Encephalopathy (p. 152)
 Hemochromatosis (p. 482)
 Hepatitis B (p. 147)
 Hepatitis C (p. 148)
 Jaundice (p. 155)

Hepatic Encephalopathy

DIFFERENTIAL DIAGNOSIS

DRUGS

- **ALCOHOL**—acute intoxication, withdrawal, Wernicke-Korsakoff syndrome
- **PSYCHOACTIVE**—benzodiazepines, cocaine, heroin, ecstasy
- **OTHERS**—salicylates

INFECTIOUS—SBP, pneumonia, UTI, meningitis, encephalitis, abscess

METABOLIC

- **ORGAN FAILURE**—hepatic, azotemia, hypothyroidism, hypoxemia, CO₂ narcosis
- **ELECTROLYTES**—ketoacidosis, hyponatremia, hypomagnesemia, hypercalcemia, glucose (hypo, hyper)

STRUCTURAL

- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral
- **STROKE**—basilar

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **TUMOR**
- **EPILEPSY**

NEUROPSYCHIATRIC

PATHOPHYSIOLOGY

GRADING OF HEPATIC ENCEPHALOPATHY

- **MINIMAL**—psychometric/neuropsychological alterations but without clinical evidence of mental status changes
- **I**—altered sleep cycle, short attention span, mild confusion, tremor, incoordination
- **II**—lethargy or irritability, disoriented to time, personality change, asterixis, ataxia
- **III**—somnolence/stupor or agitation, disoriented to place and time, asterixis, hyperreflexia, positive Babinski
- **IV**—coma, decerebrate

PATHOPHYSIOLOGY (CONT'D)**PRECIPITANTS OF HEPATIC ENCEPHALOPATHY**

- ↑ **NH₄**—↑ dietary protein intake, constipation, GI bleed, transfusion, infection (spontaneous bacterial peritonitis), azotemia, hypokalemia
- ↑ **DIFFUSION ACROSS BLOOD-BRAIN BARRIER**—metabolic alkalosis
- ↓ **METABOLISM**—dehydration (vomiting, diarrhea), hypotension, hypoxemia, anemia, porto-systemic shunt, new HCC, progressive liver damage
- **DRUGS**—benzodiazepines, alcohol, narcotics, missed lactulose

CLINICAL FEATURES

HISTORY—characterize confusion (onset, duration, fluctuation), infectious symptoms, neurological symptoms, precipitants (diet, hydration, constipation, GI bleed, infection), past medical history (liver disease, alcohol and illicit drug use), medication history (sedatives, narcotics, missed lactulose)

PHYSICAL—vitals, signs of chronic liver disease, rectal examination (if suspect GI bleed), neurological examination, check for asterixis

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, TSH, AST, ALT, ALP, bilirubin, INR, PTT, NH₄ (poorly correlated with degree of encephalopathy), Ca, Mg, PO₄, osmolality, CK, troponin (as part of delirium workup), urinalysis
- **MICROBIOLOGY**—blood C&S, urine C&S, sputum Gram stain/C&S
- **IMAGING**—US abd, CT abd

INVESTIGATIONS (CONT'D)

- **ASCITIC FLUID ANALYSIS**—cell count and diff, C&S to rule out SBP

SPECIAL

- **CT HEAD**—delirium workup
- **ABG**—if critically ill
- **GASTROSCOPY**—to check for varices
- **LIVER BIOPSY**
- **EEG**—symmetric, high voltage, slow wave pattern

MANAGEMENT**ACUTE HEPATIC ENCEPHALOPATHY**

- **WORKUP FOR SEPSIS**
- **SYMPTOM CONTROL**—correct hypokalemia, if present. *Lactulose* 30 g PO BID–QID PRN titrate to 2–4 bowel movements/day; if patient obtunded and NPO, consider lactulose enema. Consider *rifaximin* 550 mg BID for patients not responsive to lactulose or as an alternative agent in patients intolerant of lactulose
- **TREAT UNDERLYING CAUSE**—liver transplant

CHRONIC HEPATIC ENCEPHALOPATHY

- **SYMPTOM CONTROL**—protein restriction not routinely recommended. *Lactulose* 30 g PO BID–QID PRN titrate to 2–4 bowel movements/day. Prophylaxis with *rifaximin* 550 mg PO BID (in high-risk patients with ≥2 episodes of hepatic encephalopathy in last 6 months). Others (neomycin but associated ototoxicity/nephrotoxicity, ornithine aspartate, oral branched-chain amino acids)
- **TREAT UNDERLYING CAUSE**—liver transplant
Wijdsicks NEJM 2016;375(17)

Ascites**DIFFERENTIAL DIAGNOSIS**↑ **HYDROSTATIC PRESSURE**

- **CARDIAC**—right heart failure, tricuspid regurgitation, constrictive pericarditis
- **HEPATIC**—**presinusoidal** (portal vein thrombosis, schistosomiasis), **sinusoidal** (cirrhosis), **postsinusoidal** (Budd–Chiari, veno-occlusive)

DIFFERENTIAL DIAGNOSIS (CONT'D)

↓ **ONCOTIC PRESSURE**—malnutrition, liver disease, nephrotic syndrome, protein-losing enteropathy

↑ **CAPILLARY PERMEABILITY/LYMPHATIC OBSTRUCTION**

- **INFECTIONS**—spontaneous bacterial peritonitis
- **MALIGNANCY**—ovarian, peritoneal metastasis
- **PANCREATITIS**

OTHERS—hypothyroidism

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ASCITES?

	Sens	SpC	LR+	LR-
History				
↑ abdominal girth	87%	77%	4.1	0.17
Recent weight gain	67%	79%	3.2	0.42
Ankle swelling	93%	68%	2.8	0.10
Hepatitis	67%	79%	3.2	0.42
Heart failure	47%	73%	2.0	0.73
Alcoholism	60%	58%	1.4	0.69
Hx of carcinoma	13%	85%	0.91	1.01
Physical				
Fluid wave	62%	90%	5.3	0.6
Shifting dullness	77%	72%	2.1	0.4
Flank dullness	84%	59%	1.7	0.4
Bulging flanks	81%	59%	1.8	0.5

APPROACH—the most useful finding for making a diagnosis of ascites is a positive fluid wave. The most useful findings to rule out ascites are a negative history of ankle swelling or increased abdominal girth. Puddle sign and auscultatory percussion not recommended

Williams et al. JAMA 1992;267(19)
Simel et al. The Rational Clinical Examination McGraw-Hill; 2009

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, amylase, lipase, TSH, urinalysis
- **IMAGING**—US abd, CT abd
- **PARACENTESIS**—cell count + diff, Gram stain, C&S, AFB, albumin, LDH, glucose, amylase, triglyceride, cytology

SPECIAL

- **LAPAROSCOPY WITH PERITONEAL BIOPSY**

DIAGNOSTIC ISSUES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE BACTERIAL PERITONITIS OR PORTAL HYPERTENSION? HOW DO I PERFORM A PARACENTESIS AND ANALYZE THE RESULTS?

PARACENTESIS TECHNIQUE—two studies showed that testing for coagulation prior to paracentesis was probably unnecessary; one study showed that a 15-gauge, 3.25-in. needle-cannula was associated with less multiple peritoneal punctures and termination due to poor

DIAGNOSTIC ISSUES (CONT'D)

fluid return as compared to a 14-gauge needle in therapeutic paracentesis; one study showed immediate as compared to delayed inoculation of culture bottles improved diagnostic yield (100% vs. 77%); nine studies examined therapeutic paracentesis with or without albumin or nonalbumin plasma expanders and found no consistent effect on morbidity or mortality

FEATURES SUGGESTIVE OF SPONTANEOUS BACTERIAL PERITONITIS

	LR+	LR-
Ascitic fluid WBC/PMN		
Ascitic fluid WBC >1000 cells/ μ L	9.1	0.25
Ascitic fluid WBC >500 cells/ μ L	5.9	0.21
Ascitic fluid WBC >250 cells/ μ L	0.9	1.1
Ascitic fluid PMN >500 cells/ μ L	10.6	0.16
Ascitic fluid PMN >250 cells/ μ L	6.4	0.20
Ascitic fluid pH and blood ascitic pH gradient		
Ascitic fluid pH <7.31	4.1	0.47
Ascitic fluid pH <7.32	4.8	0.65
Ascitic fluid pH \leq 7.31	5.8	0.43
Ascitic fluid pH <7.35	9.0	0.31
Ascitic fluid pH <7.40	2.5	0.23
Blood ascitic fluid pH gradient >0.11	4.6	0.47
Blood ascitic fluid pH gradient >0.10	7.1	0.30
Blood ascitic fluid pH gradient \geq 0.10	11.3	0.12

FEATURES SUGGESTIVE OF PORTAL HYPERTENSION

	LR+	LR-
Serum ascites albumin gradient (SAAG)		
Serum-ascites albumin gradient \geq 11 g/L (\geq 1.1 g/dL)	4.6	0.06

APPROACH—ascitic fluid should be inoculated into blood culture bottles at the bedside. Spontaneous bacterial peritonitis is more likely at predescribed parameters of ascitic WBC count (>1000 cells/ μ L), PMN count (>250 cells/ μ L) or blood-ascitic fluid pH (<7.35), and portal hypertension is less likely below a predescribed serum-ascites albumin gradient (<11 g/L [$<$ 1.1 g/dL])

Wong et al. JAMA 2008;299(10)

PARACENTESIS PROCEDURE

Thomsen et al. NEJM 2006;355(e21)

DIAGNOSTIC ISSUES (CONT'D)**SERUM-ASCITES ALBUMIN GRADIENT (SAAG)**

- **PORTAL HYPERTENSION OR CONGESTIVE HEART FAILURE**—(serum albumin – ascites albumin) ≥ 11 g/L [≥ 1.1 g/dL]. To distinguish between portal hypertension and HF, consider checking for ascitic fluid total protein level (generally >25 g/L [>2.5 g/dL] in cardiac ascites due to normal leaky hepatic sinusoid, while portal hypertension is associated with “capillarized” sinusoids that are less leaky)
- **INFLAMMATORY**—(serum albumin – ascites albumin) < 11 g/L [< 1.1 g/dL]

MANAGEMENT

SYMPTOM CONTROL—**Na restriction** (88 mmol/day or 2 g/day. Check urine Na for compliance, i.e. < 77 mmol/day). **Fluid restriction** (< 1.5 L/day only if Na < 120 mmol/L). **Diuretics** (*spironolactone* 100–400 mg PO daily and *furosemide* 40–160 mg PO daily, stepwise increase, monitor renal function). **Paracentesis. Albumin** (if > 5 L ascitic fluid removed, then replace with albumin. In general, give 100 mL of 25% albumin for every 3 L of ascites removed over 5 L), TIPS, liver transplant. Avoid NSBB if refractory ascites.

TREAT UNDERLYING CAUSE—stop alcohol consumption

Ginès et al. *NEJM* 2004;350(16)
Runyon *Hepatology* 2013;57(4)

SPECIFIC ENTITIES**DIFFERENTIAL DIAGNOSIS OF ANASARCA**

—renal (nephrotic syndrome), cardiac (HF, tricuspid regurgitation, constrictive pericarditis), liver (cirrhosis), thyroid (hypothyroidism), malignancy (venous/lymphatic obstruction)

SPONTANEOUS BACTERIAL PERITONITIS (SBP)**SPECIFIC ENTITIES (CONT'D)**

- **PATHOPHYSIOLOGY**—overgrowth of bacteria in bowel (usually *E. coli*) → bacterial translocation (migration) across bowel wall → infect ascites. Usually in patients with cirrhosis and large volume ascites with low ascites protein. Symptoms may be subtle as the visceral peritoneum is separated from the parietal peritoneum. Important to differentiate SBP from perforated bowel causing peritonitis
- **CLINICAL FEATURES**—may be asymptomatic if detected early. Common signs and symptoms include fever, abdominal pain and tenderness (diffuse, continuous), diarrhea, confusion, or renal deterioration. Sepsis with hypotension and paralytic ileus may develop later
- **DIAGNOSIS**—paracentesis (ascitic fluid PMN ≥ 250 cells/ μ L, fluid protein < 10 g/L [< 1.0 g/dL], Gram stain, C&S), blood cultures, urine cultures. (Note that in peritonitis secondary to perforated viscous, the ascitic fluid protein is usually > 10 g/L [> 1.0 g/dL], glucose < 2.8 mmol/L [< 51 mg/dL], and LDH $>$ upper limit of normal, and polymicrobial)
- **TREATMENTS**—*cefotaxime* 2 g IV q8h (preferred) or *ceftriaxone* 2 g IV q24h $\times 5$ –10 days, *albumin* 1.5 g/kg IV within 6 h of detection, then 1 g/kg IV on day 3 (reduces mortality and incidence of HRS). Discontinue non-selective beta-blockers
- **PROPHYLAXIS**—indicated in patients at high risk for SBP (cirrhosis + GI bleeding, ≥ 1 episode of SBP, cirrhosis + ascites with ascitic fluid protein < 15 g/L [1.5 g/dL] + impaired renal/liver function [$\text{Cr} > 106$ $\mu\text{mol/L}$, $\text{BUN} \geq 9$ mmol/L, $\text{Na} \leq 130$ mmol/L, Child-Pugh ≥ 9 + bilirubin > 50 $\mu\text{mol/L}$), hospitalized cirrhotic with ascitic protein < 1 g/L). Prophylaxis with *ciprofloxacin* 500 mg daily, *norfloxacin* 400 mg daily, or *trimethoprim-sulfamethoxazole* 1 DS tablet daily

Jaundice**DIFFERENTIAL DIAGNOSIS OF JAUNDICE/HYPERBILIRUBINEMIA****PRE-HEPATIC** (hemolysis)

- **RBC MEMBRANE**—spherocytosis, elliptocytosis
- **RBC ENZYMES**—G6PD, pyruvate kinase deficiency

DIFFERENTIAL DIAGNOSIS OF JAUNDICE/HYPERBILIRUBINEMIA (CONT'D)

- **RBC HEMOGLOBIN**—sickle cell
- **BLOOD**—toxins, drugs (fludarabine), infections (malaria), immune

DIFFERENTIAL DIAGNOSIS OF JAUNDICE/ HYPERBILIRUBINEMIA (CONT'D)

• **VASCULAR**—mechanical valve, vasculitis, HUS/TTP/DIC, HELLP, severe hypertension

• **INEFFECTIVE ERYTHROPOIESIS**—megaloblastic anemia

HEPATIC

• ↓ **UPTAKE**—Gilbert syndrome, drugs (rifampin, contrast)

• ↓ **CONJUGATION**—Gilbert syndrome, Crigler-Najjar I/II, hepatocellular diseases, drugs (chloramphenicol)

• ↓ **EXCRETION** (cholestasis)—Dubin-Johnson, Rotor, benign recurrent cholestasis, cholestasis of pregnancy, drug-induced cholestasis, PBC, PSC, TPN

• **MIXED**—hepatocellular disease, sepsis

POST-HEPATIC

• **GALLSTONES**

• **CANCER**—pancreas, bile ducts, ampulla

• **BILIARY STRUCTURES**—post-cholecystectomy, PSC, biliary atresia

PATHOPHYSIOLOGY

CHOLESTASIS—any condition in which bile excretion from the liver is blocked, which can occur either in the intrahepatic bile ducts (hepatic causes) or in the extrahepatic bile ducts (post-hepatic causes)

CLINICAL FEATURES

HISTORY—characterize jaundice (duration, previous episodes), abdominal pain, abdominal mass, stool color, urine color, pruritus, weight loss, past medical history (liver disease, hepatitis risk factors, IBD/PSC, hereditary disorders), medications

PHYSICAL—signs of chronic liver disease, liver and spleen examination

JAUNDICE—becomes clinically evident at levels of bilirubin $>70 \mu\text{mol/L}$ [$>41 \text{ mg/dL}$]

DARK URINE—suggests conjugated hyperbilirubinemia

PALE STOOL/PRURITUS—suggests cholestasis (bile cannot be secreted into the biliary system)

PAIN—painful jaundice suggests acute obstruction (by stones, masses); investigate with US abd/ERCP/MRCP/EUS. Painless jaundice suggests pancreatic cancer, infiltration, PSC, PBC, and drugs; investigate with imaging + biopsy

INVESTIGATIONS

BASIC

• **LABS**—CBC, peripheral smear, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin (conjugated and unconjugated), INR, albumin, HAV IgM, HAV IgG, HBsAg, HBsAb, HBcIgM, anti-HCV, ANA, ASMA, AMA, ferritin, ceruloplasmin, α 1-antitrypsin, AFP, LDH, haptoglobin, peripheral smear, reticulocyte counts

• **IMAGING**—US, CT abd

SPECIAL

• **ENDOSCOPIC US**

• **MRCP/ERCP**

• **LIVER BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

PRIMARY BILIARY CHOLANGITIS (PBC)

• **PATHOPHYSIOLOGY**—autoimmune destruction of intrahepatic bile ducts \rightarrow cholestasis \rightarrow inflammation and necrosis \rightarrow cirrhosis

• **CLINICAL FEATURES**—pruritus, fatigue, RUQ pain, xanthomas/xanthelasmas, sicca syndrome, hyperlipidemia. Females \gg males. Decreased bone mineral density. Cirrhosis and risk of HCC. Associated conditions: Sjögren, scleroderma/CREST, autoimmune thyroid disease

• **DIAGNOSIS**— ≥ 2 of: ALP $\geq 1.5 \times$ ULN, antimitochondrial (AMA) Ab $>1:40$, histologic evidence of PBC. AMA (sens 95%), ANA (70%), \uparrow bilirubin, \uparrow ALP, \downarrow C4, \uparrow IgM, hyperlipidemia (cholesterol, rather than TGL, is what classically becomes elevated). Liver biopsy can be helpful for staging but not essential for diagnosis, can evaluate overlap autoimmune hepatitis

• **TREATMENTS**—*ursodeoxycholic acid* (*ursodiol*, *UDCA*) 13–15 mg/kg/day PO in 2 divided doses. UDCA improves liver enzymes, slows disease progression, delays time to transplant. *Obeticholic acid* (farnesoid X receptor agonist) 5–10 mg PO daily in patients with inadequate response/intolerance of UDCA. Consider adding fibrates to UDCA for patients with incomplete biochemical response. For pruritus, consider *cholestyramine* (4–16 g daily), *rifampin* (150–300 mg BID), *naltrexone* (12.5–50 mg daily), *sertraline* (75–100 mg daily).

SPECIFIC ENTITIES (CONT'D)

Consider treating hyperlipidemia (despite hypercholesterolemia, risk of atherosclerotic death not increased). Prevent osteoporosis with calcium and vitamin D. Supplement fat-soluble vitamins (ADEK). Artificial tears, saliva substitutes for sicca. Consider liver transplant if progressive disease, hepatic decompensation, refractory pruritus, or severe bone disease

2018 AASLD Guideline Primary Biliary Cholangitis

PRIMARY SCLEROSING CHOLANGITIS (PSC)

- **PATHOPHYSIOLOGY**—cholangitis → fibrosis with intra- and extrahepatic duct strictures → cirrhosis; 75% associated with IBD, 10% with cholangiocarcinoma

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—can be asymptomatic; pruritus, episodic cholangitis, associated features of IBD, pANCA, hypergammaglobulinemia (high IgM, IgG4), cirrhosis/decompensated liver disease
- **DIAGNOSIS**—MRCP (beading, strictures), ERCP (especially for patients with dominant stricture ≤ 1.5 mm in CBD or ≤ 1 mm in hepatic duct, exclude cholangiocarcinoma), cholangiography, biopsy (small duct PSC)
- **TREATMENTS**—treatment of cholangitis (may require long-term prophylactic antibiotics), screening for hepatobiliary cancer (MRCP or US +/- CA19-9 q6–12 months), colon cancer screening (annual colonoscopy if IBD), liver transplant

Acute Pancreatitis**CAUSES****★BAD HITS★**

BILIARY OBSTRUCTION—gallstones, sludge

ALCOHOL

ANATOMIC—biliary cysts, annular pancreas, pancreas divisum

DRUGS—thiazides, furosemide, sulfonamide, tetracycline, calcium, estrogen, vinca alkaloids, antiretrovirals (didanosine, pentamidine)

HYPER—hypercalcemia, hypertriglyceridemia (>10 mmol/L)

INFECTIOUS—*E. coli*, *Legionella*, *Salmonella*, HIV, CMV, mumps, HBV, HSV, ascariasis, *Toxoplasma*, *Aspergillus*

IDIOPATHIC—25–30%

INHERITED—familial (*CFTR*, *SPINK1*, *PRSS1*)

TRAUMA—blunt

SURGERY—ERCP (\pm sphincterotomy, 5% risk), sphincter of Oddi dysfunction

PATHOPHYSIOLOGY**COMPLICATIONS OF ACUTE PANCREATITIS****★SCAR★**

- **SEPSIS**
- **CALCIUM** (hypocalcemia)
- **ABDOMINAL** (necrotizing pancreatitis \pm hemorrhage, pancreatic pseudocyst \pm hemorrhage [10–20%], pancreatic abscess, splenic vein thrombosis, fistula, cholangitis)
- **RESPIRATORY FAILURE (ARDS) AND ASPIRATION PNEUMONIA**
- **RENAL FAILURE**

CLINICAL FEATURES

HISTORY—abdominal pain, nausea and vomiting, fever, anorexia, past medical history (previous pancreatitis, recent ERCP, biliary stones, alcohol use, HIV), medication history (diuretics, antibiotics)

PHYSICAL—vitals (fever, hypotension, hypoxemia), volume status, abdominal examination (distention, ileus), Cullen sign (periumbilical ecchymoses suggestive of hemoperitoneum), Grey Turner sign (ecchymoses of the flanks suggestive of retroperitoneal hemorrhage)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, LDH, lipase, amylase, Ca, albumin, fasting lipid profile
- **IMAGING**—US abd, CT abd (+ contrast for necrotic pancreatitis)
- **ERCP**—both diagnostic and therapeutic to relieve obstruction

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIFFERENTIAL DIAGNOSIS FOR LIPASE ELEVATION—acute pancreatitis, pancreatic cancer, pancreatic duct obstruction, perforated peptic ulcer, bowel infarction, intestinal obstruction, renal failure

RANSON CRITERIA

- **ON ADMISSION**—age >55 , WBC $>16 \times 10^9/L$, glucose >11.1 mmol/L [>200 mg/dL], AST >250 U/L, LDH >350 U/L

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **48 H**—hematocrit ↓ >10%, urea ↑ >1.78 mmol/L [>5 mg/dL], base deficit >4 mEq/L, Ca <2 mmol/L [<8 mg/dL], sequestration of fluid >6 L
- **PROGNOSIS**—0–2 = 2% mortality, 3–4 = 15%, 5–6 = 50%, 7–8 = 100%

MANAGEMENT

ACUTE—ABC, O₂, **IV hydration**. NPO, NG if severe N&V or obstruction. *Morphine* 2.5–5 mg SC q4h PRN and 1–2 mg IV q1h PRN. **Antiemetics** (*dimenhydrinate* 50 mg IM/IV q4h, *metoclopramide* 10 mg IV q6h). Consider broad-spectrum **antibiotics** (*meropenem* 1 g IV q8h or *imipenem* 500 mg IV q6h) if infected necrosis suspected

NUTRITION SUPPORT—early oral or EN support; PN only if unable to tolerate EN within 72 hours

TREAT UNDERLYING CAUSE—**gallstone pancreatitis** (ERCP and biliary sphincterotomy within 72 h, cholecystectomy). **Necrotizing pancreatitis** (ICU admission, antibiotics, surgical debridement)

Forsmark et al. *NEJM* 2016;375(20)

SPECIFIC ENTITIES**CHRONIC PANCREATITIS**

- **PATHOPHYSIOLOGY**—inflammation and fibrosis leading to structural pancreatic damage, loss of pancreatic exocrine and endocrine function. Causes: toxic-metabolic (alcohol), genetic, autoimmune, recurrent acute pancreatitis, obstructions, idiopathic

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—chronic abdominal pain, steatorrhea, fat soluble vitamin deficiency, osteoporosis, radiographic evidence (XR, EUS, CT/MR) of structural changes to pancreatic parenchyma, elevated risk of pancreatic cancer
 - **TREATMENT**—pain control, pancreatic enzyme replacement (PPI if uncoated enzyme replacement to avoid gastric inactivation), fat restriction (<20 g/day), endocrine replacement, complication management (duct obstruction, pseudocyst)
- ASCENDING CHOLANGITIS**
- **PATHOPHYSIOLOGY**—biliary stones, post-ERCP, tumors, PSC, or benign stricture → biliary obstruction and stasis → bacterial colonization and infection (*E. coli*, *Klebsiella*, *Enterobacter*, *Enterococcus*, anaerobes) → sepsis
 - **CLINICAL FEATURES**—Charcot triad (fever, RUQ pain, jaundice); Reynold pentad (triad + hypotension and confusion)
 - **DIAGNOSIS**—↑ bilirubin, ALP, and potentially AST and ALT. Blood cultures essential. US abd to check for common bile duct dilatation and stones, ERCP (diagnostic and therapeutic)
 - **TREATMENTS**—**antibiotics** (*meropenem* 1 g IV q8h, *imipenem* 500 mg IV q6h, or ampicillin plus gentamicin). **Facilitate biliary drainage** (urgent ERCP with sphincterotomy for infection source control, stone extraction, stent insertion, percutaneous transhepatic cholangiogram [PTC] with stent drainage, and surgical decompression as last resort)



Polycythemia

DIFFERENTIAL DIAGNOSIS

SPURIOUS—stress (Gaisböck syndrome), decreased intravascular volume

PRIMARY—polycythemia vera

SECONDARY ★HERA★

- **HYPOXIA**—obstructive sleep apnea, COPD, smoking, high altitude
- **EPO-SECRETING TUMORS**—renal, hepatoma, cerebellar, pheochromocytoma
- **RENAL**—polycystic kidney disease, hydronephrosis, post-transplant
- **ADRENAL**—Cushing syndrome

PATHOPHYSIOLOGY

DEFINITION OF POLYCYTHEMIA—hematocrit >0.6 in ♂, hematocrit >0.5 in ♀

Related Topics

Hypoxemia (p. 110)

Myeloproliferative Disorders (p. 185)

CLINICAL FEATURES

HISTORY—hyperviscosity (headache, blurred vision, epistaxis), dyspnea, epigastric pain, early satiety, weight loss, fever, night sweats, pruritus, erythromelalgia, recent travel to high-altitude areas, past medical history (respiratory diseases, myeloproliferative disorders, myocardial infarction, stroke, pulmonary embolism, DVT, renal disorders, smoking), medications (androgens, EPO)

PHYSICAL—hypertension, oxygen saturation, facial plethora, conjunctival injections, engorgement of the veins of the optic fundus, abdominal mass, hepatomegaly, splenomegaly, excoriations, stigmata of a prior arterial or venous thrombotic event, gouty arthritis, and tophi

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, leukocyte alkaline phosphatase (LAP), vitamin B12, RBC mass (total blood volume × Hct, to rule out spurious causes), carboxyhemoglobin level, cortisol level, peripheral blood smear

SPECIAL

- **JAK2 MUTATION**—JAK2 is a cytoplasmic tyrosine kinase activated by EPO binding to its receptor; the V617F mutation activates JAK2 and thereby drives EPO-independent erythropoiesis. JAK2 mutation >95% sensitive for primary PV
- **EPO LEVEL**—low in PV, high if secondary causes
- **HYPOXIA WORKUP**—oximetry, ABG, CO-hemoglobin, high-affinity hemoglobin
- **SOLID TUMOR WORKUP**—targeted CT
- **BONE MARROW BIOPSY**—rule out myelofibrosis and CML

DIAGNOSTIC ISSUES

WHO CRITERIA FOR POLYCYTHEMIA VERA

- **MAJOR CRITERIA**
 - (1) Hemoglobin >165 g/L [>16.5 g/dL] in men or >160 g/L [>16.0 g/dL] in women, **or** hematocrit >49% in men or >48% in women, **or** increased red cell mass (>25% above mean normal predicted value)
 - (2) Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
 - (3) Presence of JAK2 (V617F) or JAK2 exon 12 mutation
- **MINOR CRITERIA**—subnormal serum erythropoietin level

DIAGNOSTIC ISSUES (CONT'D)

- **DIAGNOSIS**—requires meeting all 3 major criteria or the first 2 major criteria and the minor criterion. Note: criterion #2 (bone marrow biopsy) may not be required in cases with sustained absolute erythrocytosis: hemoglobin >185 g/L [>18.5 g/dL] or hematocrit >55.5% in men, or hemoglobin >165 g/L [>16.5 g/dL] or hematocrit >49.5% in women if major criterion #3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a bone marrow biopsy; this finding

DIAGNOSTIC ISSUES (CONT'D)

may predict a more rapid progression to overt myelofibrosis (post-PV myelofibrosis)

MANAGEMENT

TREAT UNDERLYING CAUSE—**relative** (hydration), **CO hemoglobinemia** (smoking cessation. See p. 490), **sleep apnea** (CPAP, see p. 113), **polycythemia vera** (cytoreduction with hydroxyurea ± phlebotomy target to keep hematocrit <0.45 in ♂ and <0.42 in ♀, ASA 81 mg PO daily prevents thrombosis but watch out for bleeding)

Microcytic AnemiaDeLoughery *NEJM* 2014;371(14)**DIFFERENTIAL DIAGNOSIS**

★TAILS★

THALASSEMIA

ANEMIA OF CHRONIC DISEASE—infection, malignancy, inflammatory disorders

IRON DEFICIENCY—blood loss (GI, GU, vaginal, trauma), iron-deficient diet, celiac disease, atrophic gastritis, renal failure on EPO, pulmonary hemosiderosis, intravascular hemolysis

LEAD POISONING**SIDEROBLASTIC****PATHOPHYSIOLOGY**

DEFINITION OF MICROCYTIC ANEMIA—Hb <135 g/L [<13.5 g/dL], MCV <80 fL

SEQUENCE OF IRON DEFICIENCY—↓ iron → ↑ TIBC → ↓ Hb → ↓ MCV → hypochromia

ANEMIA OF CHRONIC DISEASE—chronic inflammatory states such as malignancy, infection and rheumatologic diseases → ↑ IFN γ , TNF α , IL-1, IL-6, IL-10 → ↑ hepatic expression of hepcidin, which inhibits duodenal absorption of iron, ↑ uptake and storage of iron into monocytes and macrophages, ↓ production of EPO → ↓ availability of iron for erythrocytes → anemia (microcytic or normocytic)

CLINICAL FEATURES

HISTORY—shortness of breath, chest pain, dizziness, fatigue, bleeding (GI, menstrual), pica (ice, dirt), diet history, fever, night sweats, weight loss, past medical history (malignancy, chronic infections, rheumatologic disorders), medications (NSAIDs, ASA, anticoagulants), family history (thalassemia)

PHYSICAL—vitals, koilonychia (spoon nails), alopecia, blue sclerae, conjunctival pallor, angular

CLINICAL FEATURES (CONT'D)

cheilitis, atrophic glossitis, lymphadenopathy (anemia of chronic disease), rectal examination for occult blood and pelvic examination for blood loss

INVESTIGATIONS**BASIC**

- **LABS**—CBC, peripheral smear, reticulocyte count, serum iron, serum ferritin, TIBC (transferrin), % sat, Hb electrophoresis, fecal occult blood (if suspect GI bleed)

SPECIAL

- **ENDOSCOPY**—gastroscopy and/or colonoscopy targeting symptoms in any man or post-menopausal woman with iron deficiency or in anyone with suspected GI bleeding
- **SOLUBLE TRANSFERRIN RECEPTOR (sTfR)**—helps to distinguish between iron deficiency and anemia of chronic disease. Depleted iron store is associated with increased sTfR levels
- **BONE MARROW ASPIRATE AND BIOPSY WITH IRON STAIN**

DIAGNOSTIC ISSUES**IRON INDICES**

	Ferritin	Iron	TIBC	% sat
Iron deficiency	↓	↓	↑	↓
Anemia of chronic disease	↑/N	↓	N/↓	N/↓
Thalassemia	↑/N	↑	↓	↑
Sideroblastic	N/↑	N/↓	N/↓	N/↓

DIAGNOSTIC ISSUES (CONT'D)**DISTINGUISHING FEATURES BETWEEN IRON DEFICIENCY AND THALASSEMIA**

- **RDW**—red cells in thalassemia tend to have a narrower distribution than in iron deficiency
- **MCV**—red cells in thalassemia tend to be smaller than in iron deficiency
- **MCHC**—usually normal in thalassemia
- **RETICULOCYTE COUNT**—normal to elevated in thalassemia
- **RBC**—RBC high or normal if thalassemia but tend to decrease proportionally to Hb in iron deficiency
- **THALASSEMIA INDEX**—MCV/RBC. Suggests thalassemia if <13 and iron deficiency if >13
- **MORPHOLOGY**—thalassemia causes microcytic target cells

DISTINGUISHING FEATURES BETWEEN IRON DEFICIENCY AND ANEMIA OF CHRONIC DISEASE—ferritin is indicative of marrow iron stores and is key to the diagnosis of iron deficiency anemia as serum iron and TIBC levels may change with other diseases. Ferritin may be elevated as acute phase reactant

- **<30 ng/mL**—iron deficiency anemia (PPV 92–98%)
- **30–100 ng/mL**—combination of anemia of chronic disease and true iron deficiency if

DIAGNOSTIC ISSUES (CONT'D)

- (sTfR/log ferritin) > 2. Anemia of chronic disease alone if (sTfR/log ferritin) < 1
- **100 ng/mL**—anemia of chronic disease

MANAGEMENT

SYMPTOM CONTROL—**transfusion** 1–2 U PRBC IV over 2 h for severe symptomatic anemia

TREAT UNDERLYING CAUSE—**iron deficiency** (oral replacement: *iron gluconate* 300 mg PO, *iron sulfate* 325 mg PO, *ferrous fumarate* 360 mg PO; optimal oral dosing is every other day; parenteral replacement: *sodium ferric gluconate complex* in sucrose 125 mg IV for multiple doses, iron sucrose 200–400 mg IV for multiple doses, *ferumoxyl* 510 mg IV 2 doses given 3–8 days apart, *ferric carboxymaltose* 500 mg–1,000 mg IV for 1–2 doses, *ferric derisomaltose* 20 mg/kg IV for 1 dose. See package insert for dosing instructions)

SPECIFIC ENTITIES

PLUMMER-VINSON SYNDROME—iron deficiency anemia, atrophic glossitis and esophageal web. Increased risk of esophageal squamous cell carcinoma

Normocytic Anemia**DIFFERENTIAL DIAGNOSIS**

ACUTE BLOOD LOSS—GI, GU, pelvis/abdomen, skin, CNS

↓ PRODUCTION

- **PRIMARY MARROW DISORDERS**—bone marrow suppression from drugs (esp. chemotherapy), multiple myeloma, myelodysplasia, leukemia, myeloproliferative disorders, lymphoma, metastasis, infections (esp. TB)
- **DECREASED EPO**—renal failure
- **ANEMIA OF CHRONIC DISEASE**

SEQUESTRATION—splenomegaly

↑ DESTRUCTION

- **IMMUNE**—autoimmune hemolytic anemia (warm IgG antibody, cold IgM agglutinins)
- **NON-IMMUNE**
 - **RBC MEMBRANE**—spherocytosis
 - **RBC ENZYMES**—G6PD, pyruvate kinase deficiency
 - **RBC HEMOGLOBIN**—sickle cell anemia

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **MICROANGIOPATHIC**—DIC, HUS/TTP, prosthetic valve, hypertensive crisis
- **BLOOD**—toxins, infections (malaria), immune

MIXED PICTURE—combined microcytic and macrocytic anemia (e.g. gastric bypass causing iron deficiency and vitamin B12 deficiency)

PATHOPHYSIOLOGY

DEFINITION OF NORMOCYTIC ANEMIA—Hb <135 g/L [<13.5 g/dL], MCV 80–100 fL

CLINICAL FEATURES

HISTORY—shortness of breath, chest pain, dizziness, fatigue, bleeding, fever, night sweats, weight loss, diet history, past medical history (malignancy, chronic infections, rheumatologic disorders, liver disease, renal disease, alcohol, hypothyroidism, myelodysplasia), medications

CLINICAL FEATURES (CONT'D)

(NSAIDs, ASA, chemotherapy, antibiotics, antiepileptics), family history (sickle cell)

PHYSICAL—vitals, jaundice, conjunctival pallor, cardiac examination, liver examination. Check for macroglossia, subacute combined degeneration and peripheral neuropathy. Rectal examination for occult blood

INVESTIGATIONS**BASIC**

- **LABS**—CBC, peripheral smear, reticulocyte count, iron, ferritin, TIBC, % sat, Cr, TSH, AST, ALT, ALP, bilirubin, INR, PTT, haptoglobin, LDH, direct and indirect Coombs test, serum protein electrophoresis, fecal occult blood

SPECIAL

- **URINE TESTS**—urinalysis (hemoglobinuria)
- **BONE MARROW ASPIRATE AND BIOPSY**

DIAGNOSTIC ISSUES

MCHC—↑ MCHC suggests spherocytosis

MCV—a rise in MCV suggests reticulocytosis; ↑↑↑ MCV indicates the presence of cold agglutinins causing agglutination in the laboratory specimen before blood is run through the analyzer

COOMBS TEST

- **DIRECT COOMBS TEST (DAT)**—patient's washed RBC incubated with anti-IgG and anti-C3. A positive result (i.e. agglutination) indicates that IgG and/or C3 have bound to RBC surface *in vivo*. DAT positivity indicates immune rather than nonimmune causes of hemolysis
 - **IMMUNE HEMOLYTIC ANEMIA (DAT positive)**—autoimmune hemolytic anemia, drug-induced hemolytic anemia, alloimmune hemolytic anemia (acute hemolytic reaction)
 - **NON-IMMUNE HEMOLYTIC ANEMIA (DAT negative)**—TTP/HUS, DIC, hemoglobinopathies, hereditary spherocytosis
 - **INDIRECT COOMBS TEST**—normal RBCs incubated with patient's serum. It is mainly used to detect low concentrations of antibodies in a patient's serum prior to blood transfusion. If the antibody reacts with all red cells it is termed a "pan-agglutinin" and is an autoantibody. If the antibody reacts with some of the red cells it is termed an alloantibody and cross-matching must avoid donor red cells that express the protein recognized by the alloantibody
- RETICULOCYTE PRODUCTION INDEX (RPI, corrected reticulocyte count)**—more accurate

DIAGNOSTIC ISSUES (CONT'D)

than raw reticulocyte count to evaluate if bone marrow response to anemia is appropriate or hypoproliferative

- **RPI** = [retic count × (hematocrit in %/45)]/maturation factor

Maturation Factor	Hematocrit
1.0%	45%
1.5%	35%
2.0%	25%
2.5%	20%

- **INTERPRETATION**—RPI >2% suggests adequate marrow response, <2% suggests hypoproliferative (i.e. ↓ production)

MANAGEMENT**TREAT UNDERLYING CAUSE**

- **SYMPTOM CONTROL**—transfusion 2 U PRBC IV over 2 h. **Erythropoietin** (*epoetin alfa* 50–200 U/kg/week SC/IV div 2–3 ×/week, *darbepoetin alfa* 20–40 µg SC weekly) for anemia of chronic kidney disease or selected cancer patients on active chemotherapy (after ensuring iron stores replete)

SPECIFIC ENTITIES**AUTOIMMUNE HEMOLYTIC ANEMIA: WARM ANTIBODY—IgG**

- **CAUSES**—**neoplasia** (CLL, especially with fludarabine, pentostatin, cladribine), **autoimmune** (SLE), **infections** (viral), **drugs** (penicillins, fludarabine, methyl dopa)
- **CLINICAL FEATURES**—anemia, jaundice, splenomegaly, smear (microspherocytosis), ↑ reticulocytes, ↑ bilirubin, ↑ LDH, ↓ haptoglobin, direct Coombs test (IgG±, C3±)
- **TREATMENTS**—**symptom control** (transfusion with caution, difficult to cross-match due to autoantibodies reacting with antigens present on cells of almost all individuals). **Steroids** (*prednisone* 1 mg/kg PO daily, taper after stable). **Reduce antibody-mediated clearance** (IVIg, splenectomy). **Immuno-suppression** (*azathioprine* 100–150 mg PO daily, *cyclophosphamide* 100 mg PO daily). **Biological agents** (rituximab, alemtuzumab). **Treat underlying disease** (CLL, SLE, drugs)

SPECIFIC ENTITIES (CONT'D)

AUTOIMMUNE HEMOLYTIC ANEMIA COLD AGGLUTININS—IgM

- **CAUSES**—**neoplasia** (CLL, lymphoma, Waldenström macroglobulinemia, adenocarcinoma), **infections** (mycoplasma pneumonia, infectious mononucleosis, CMV, VZV)
- **CLINICAL FEATURES**—anemia, agglutination, jaundice, splenomegaly, smear (spherocytosis), ↑ reticulocytes, ↑ bilirubin, ↑ LDH, ↓ haptoglobin, direct Coombs test (IgG-, C3+), cold agglutinin screen

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—**symptom control** (avoidance of cold). **Steroids** (prednisone 1 mg/kg PO daily, taper after stable). **Chemotherapy** (bendamustine, cyclophosphamide, chlorambucil). **Biological agents** (rituximab). **Plasmapheresis**

Macrocytic Anemia

DIFFERENTIAL DIAGNOSIS

LIVER DISEASE

ALCOHOL

DRUGS—**chemotherapy** (hydroxyurea, cytosine arabinoside, methotrexate, azathioprine, cladribine, capecitabine), **antiepileptics** (phenytoin, phenobarbital), **antibiotics/antivirals** (trimethoprim-sulfamethoxazole, zidovudine)

VITAMIN B12 DEFICIENCY FROM PERNICIOUS ANEMIA

DIETARY FOLATE DEFICIENCY
MYELODYSPLASTIC SYNDROME

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

HYPOTHYROIDISM

RETICULOCYTOSIS

PATHOPHYSIOLOGY

DEFINITION OF MACROCYTIC ANEMIA—Hb <135 g/L [<13.5 g/dL], MCV >100 fL

Related Topics

Alcoholism (p. 478)

Chronic Liver Disease (p. 149)

Myelodysplastic Syndrome (p. 189)

Vitamin B12 Deficiency (p. 453)

CLINICAL FEATURES

HISTORY—shortness of breath, chest pain, dizziness, fatigue, bleeding, fever, night sweats, weight loss, diet history, past medical history (liver disease, alcohol, hypothyroidism, myelodysplasia), medications (chemotherapy, antibiotics, antiepileptics)

PHYSICAL—look for signs of hypothyroidism, vitamin B12 deficiency, and chronic liver disease. Vitals (bradycardia, hypoventilation, hypotension), leukonychia, clubbing, Dupuytren contractures, palmar erythema, asterixis, cool and dry

CLINICAL FEATURES (CONT'D)

skin, vitiligo, hair thinning, alopecia areata, periorbital edema, scleral icterus, conjunctival pallor, altered mental status, macroglossia, parotid enlargement, fetor hepaticus, goiter, lymphadenopathy, spider angiomas, gynecomastia, pericardial effusion, ascites, splenomegaly, caput medusa, hemorrhoids, testicular atrophy, proximal muscle weakness, hyporeflexia, edema (non-pitting), petechiae, subacute combined degeneration of the cord (B12 deficiency affecting dorsal columns and lateral corticospinal tracts, test for Romberg sign, vibration and proprioception), peripheral neuropathy

INVESTIGATIONS

BASIC

- **LABS**—CBC, peripheral smear, reticulocyte count, vitamin B12, RBC folate, methylmalonic acid, homocysteine, TSH, AST, ALT, ALP, bilirubin, INR, PTT

SPECIAL

- **UGI ENDOSCOPY**—to identify atrophic gastritis and survey for gastric cancer
- **BONE MARROW BIOPSY**

MANAGEMENT

SYMPTOM CONTROL—**transfusion** 2 U PRBC IV over 2 h in everyone except those with pernicious anemia. For patients with pernicious anemia, transfuse fewer units and transfuse each unit slowly over 3 h since an expanded intravascular volume puts patients at risk for transfusion-induced pulmonary edema

TREAT UNDERLYING CAUSE—**folate deficiency** (folate 0.4 mg PO/SC/IM daily \times 4–5 days).

Vitamin B12 deficiency (vitamin B12 1,000 μ g PO/SC/IM daily \times 5–10 days, then 1,000 μ g PO/SC/IM qweek \times 4 weeks, then every month).

Hypothyroidism (levothyroxine starting at 12.5–50 μ g PO daily, adjust every 2 weeks)

Sickle Cell Disease

Piel et al. *NEJM* 2017;376(16)

PATHOPHYSIOLOGY

β-CHAIN MUTATION—leads to formation of hemoglobin S ($\alpha\beta S_2$)→polymerization of hemoglobin S→elongated fibers that distort shape of RBC→vasoocclusive phenomena (infarctions, ischemia) and hemolysis. Subtypes include **sickle cell disease** (homozygous HbS, most severe), **hemoglobin SC disease** (heterozygous HbS and HbC, moderately severe) and **sickle cell trait** (heterozygous HbS, mild)

CLINICAL FEATURES

★ABCDEFHGH PAIN★

ANEMIA

- **CHRONIC HEMOLYSIS**—normo or macrocytic due to reticulocytosis, elevated bilirubin, LDH, low haptoglobin. There may be associated folate/iron deficiency from increased utilization
- **ACUTE ANEMIA**—may be due to splenic sequestration crisis (venooclusion of spleen leading to RBC pooling), aplastic crisis (transient arrest of erythropoiesis), and hyperhemolytic crisis (sudden onset of severe hemolysis). All of these may be triggered by viral infections such as parvovirus B19

BONES—bone infarction (pancytopenia), avascular necrosis, fat embolism, orbital compression syndrome

CARDIAC—myocardial infarction (due to increased oxygen demand from cardiac output)

DERMATOLOGIC—leg ulcers

EYES—proliferative retinopathy, retinal artery occlusion, retinal detachment and hemorrhage

FAIRLY BAD PAIN—back, chest, extremities and abdomen. May be associated with fever, swelling, tenderness, tachypnea, hypertension, nausea, and vomiting. May be precipitated by weather changes, dehydration, infection, stress, menses and alcohol. Multi-organ failure may develop in severe pain episodes

GENITAL—priapism

HEPATOSPLENIC—splenic infarction, acute hepatic ischemia, hepatic or splenic sequestration crisis, iron overload (transfusions)

PULMONARY—restrictive lung disease (chronic interstitial fibrosis), obstructive lung disease, hypoxemia, pulmonary hypertension, fat embolism

ANEMIA—remember that sickle cell disease is associated with both acute and chronic anemia

INFECTIONS—sepsis (particularly asplenic patients), meningitis, pneumonia, osteomyelitis

CLINICAL FEATURES (CONT'D)

(susceptible to *Salmonella* and Gram-negative osteomyelitis)

NEUROLOGIC—ischemic stroke, intracerebral hemorrhage, septic emboli, spinal cord infarction or compression, vestibular dysfunction, sensory hearing loss, cognitive failure

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, haptoglobin, smear (sickled red cells, polychromasia from reticulocytosis, Howell-Jolly bodies from hyposplenism), reticulocytes, RBC folate, Fe, ferritin, % saturation, transferrin, hemoglobin electrophoresis (identify subtypes), urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, *Clostridioides difficile* toxin A/B

MANAGEMENT

ACUTE—ABC, O₂, IV

- **VASOOCCLUSIVE PAIN CRISIS**—fluids, pain control (morphine, ketorolac)
- **APLASTIC CRISIS**—transfusions. Avoid GCSF
- **SEQUESTRATION CRISIS**—fluids, judicious transfusion if symptomatic anemia to avoid overload if trapped splenic blood re-enters circulation
- **HEMOLYTIC CRISIS**
- **ACUTE CHEST SYNDROME** (chest pain, pulmonary infiltrates, cough, progressive anemia, hypoxemia, with or without fever)—treat precipitating factor, fluids, pain control, transfusions (simple or exchange)
- **PRIAPISM**—hydration, analgesics, transfusions, urology consultation
- **PREOPERATIVELY**—transfuse to Hb 100 g/L [10 g/dL]

CHRONIC—interprofessional team, **immunizations** (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Nisseria meningitidis*, hepatitis B virus, and influenza), **exchange transfusion** (goal HbS <30%), **hydroxyurea** (increase levels of fetal Hb, decrease incidence of vasoocclusive pain), **folic acid** 1 mg PO daily; recent new FDA-approved treatments are **L-glutamine** (antioxidant), **crizanlizumab** (a monoclonal antibody to P-selectin that reduces leukocyte recruitment), and **voxelotor** (an anti-sickling compound)

SPECIFIC ENTITIES

ASPLENIC PATIENTS—particularly susceptible to encapsulated bacteria (*S. pneumoniae*, *H. influenzae*, and *N. meningitidis*), *Capnocytophaga canimorsus*, Gram-negative enteric organisms, and babesiosis

- **VACCINATIONS**—all patients should receive vaccinations against *H. influenzae*, pneumococcus, and meningococcus. Flu shot should be given annually and other immunizations repeated every 5 years

SPECIFIC ENTITIES (CONT'D)

- **ANTIBIOTICS WITH FEVER**—any fever in an asplenic patient should prompt self-administration of preprescribed antibiotics (*levofloxacin* 750 mg PO daily, *moxifloxacin* 400 mg PO daily, or *cefuroxime* 1 g PO daily). Patients should then seek medical advice urgently
- **MEDICAL ALERT BRACELET**

NeutropeniaGibson et al. *Blood* 2014;124(8)**DIFFERENTIAL DIAGNOSIS****★PANIC★**

POST-INFECTIOUS—sepsis

AUTOIMMUNE—drug induced, SLE, idiopathic

NEOPLASTIC—lymphoproliferative disorders, myelodysplasia, leukemias, myelophthisis

INFECTIONS—sepsis, HIV

INSUFFICIENCY—folate, vitamin B12

IATROGENIC—chemotherapy, chloramphenicol, trimethoprim-sulfamethoxazole, synthetic penicillins, phenytoin, carbamazepine, NSAIDs, gold, antithyroid medications, phenothiazines, clozapine

CONSUMPTION—hypersplenism

Related Topic

Febrile Neutropenia (p. 250)

PATHOPHYSIOLOGY

DEFINITION OF NEUTROPENIA—neutrophils $<1.5 \times 10^3/\mu\text{L}$, severe neutropenia if absolute neutrophil count (ANC) $<0.5 \times 10^3/\mu\text{L}$

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, peripheral smear, PTT, INR, AST, ALT, ALP

SPECIAL

- **FURTHER WORKUP**—bilirubin, fibrinogen, LDH, ANA, vitamin B12, RBC folate
- **BONE MARROW BIOPSY**

MANAGEMENT**TREAT UNDERLYING CAUSE**

GROWTH FACTORS—in some cases, the use of myeloid growth factors such as G-CSF or GM-CSF is appropriate

TREATMENT ISSUES

FEBRILE VS. NON-FEBRILE NEUTROPENIA—the presence of fever ($>38.3^\circ\text{C}$ [$>101^\circ\text{F}$] or $>38^\circ\text{C}$ [$>100.4^\circ\text{F}$] sustained >1 h) in a neutropenic patient is considered an emergency, as overwhelming sepsis can develop quickly. Patients with febrile neutropenia (see p. 250 for definition) require early evaluation, initiation of antibiotics, and potentially hospitalization. However, neutropenia alone without fever can usually be monitored on an outpatient basis. Isolation is usually not required, although patients should avoid the following: (1) being in contact with people with active infections, (2) consumption of uncooked meat/vegetables and unpasteurized dairy products and (3) exposure to fresh flowers or plants

SPECIFIC ENTITIES

BENIGN ETHNIC NEUTROPENIA—neutrophil counts in Africans, African Americans and middle-eastern Arabs are lower in a significant minority

Eosinophilia

Klion *Blood* 2015;126(9)

DIFFERENTIAL DIAGNOSIS

★ PAIN ★

PRIMARYLY ORGAN-SPECIFIC DISORDERS

- **PULMONARY**—interstitial lung disease, AIDS-related pneumonia, idiopathic eosinophilic pneumonia, drug-induced lung disease
- **GASTROINTESTINAL**—eosinophilic gastroenteritis, eosinophilic esophagitis, primary biliary cirrhosis, primary sclerosing cholangitis
- **GENITOURINARY**—acute interstitial nephritis, acute post-streptococcal glomerulonephritis, eosinophilic cystitis, eosinophilic prostatitis
- **RHEUMATOLOGIC**—eosinophilia—myalgia syndrome and idiopathic eosinophilic synovitis, eosinophilic granulomatosis with polyangiitis
- **DERMATOLOGIC**—eosinophilic panniculitis, episodic angioedema with eosinophilia, Kimura disease and angiolymphoid hyperplasia with eosinophilia, eosinophilic fasciitis, eosinophilic cellulitis, eosinophilic pustular folliculitis, recurrent cutaneous necrotizing eosinophilic vasculitis, eosinophilic ulcers of the oral mucosa

ALLERGIES

- **NASAL**—allergic rhinitis, asthma, nasal polyposis
- **MEDICATIONS**—cytokine mediated (GM-CSF, IL-2), pulmonary (NSAIDs), gastroenteritis (NSAIDs), interstitial nephritis (penicillins, cephalosporins), necrotizing myocarditis (ranitidine), vasculitis (phenytoin, allopurinol), asymptomatic (ampicillin, penicillins, cephalosporins)

ADRENAL—adrenal insufficiency

ATHEROEMBOLIC—cholesterol emboli

INFECTIONS

- **PARASITIC**—angiostrongyliasis, costaricensis, ascariasis, hookworm, strongyloidiasis, trichinosis
- **FUNGAL**—aspergillosis, coccidioidomycosis
- **OTHERS**—chronic TB, scarlet fever, HIV related

NEOPLASTIC

- **HEMATOLOGIC**—hypereosinophilic syndrome, Hodgkin lymphoma, non-Hodgkin lymphoma, mastocytosis
- **SOLID TUMOR**—large cell carcinoma (lung), squamous cell carcinoma (vagina, penis, skin, nasopharynx), adenocarcinoma (stomach, large bowel, uterine body), transitional cell carcinoma

PATHOPHYSIOLOGY

DEFINITION OF EOSINOPHILIA—eosinophils $>600/\mu\text{L}$

EOSINOPHIL FUNCTION—eosinophils play an important role in both combating infections (especially parasitic) and allergic response, through the release of cytotoxic molecules, reactive oxygen species, and cytokines. Thus, common causes of eosinophilia include infections and allergies

CLINICAL FEATURES

HISTORY—dyspnea, chest pain, cough, sputum, diarrhea, rash, fever, lymphadenopathy, weight loss, night sweats, infectious contact, travel history, past medical history (allergic rhinitis, asthma), medications (NSAIDs, antibiotics, phenytoin, allopurinol), allergies

PHYSICAL—vitals (hypotension, fever), rash, weight loss, nasal, lymphadenopathy, respiratory examination, abdominal examination

INVESTIGATIONS

BASIC

- **LABS**—CBC, peripheral smear, AST, ALT, ALP, bilirubin, CK, ESR, C3, C4, ANCA, serology for parasites
- **MICROBIOLOGY**—blood C&S, urine C&S, stool C&S, stool O&P
- **IMAGING**—CXR, CT chest

SPECIAL

- **BRONCHOSCOPY**—if pulmonary eosinophilia

DIAGNOSTIC ISSUES

PERIPHERAL EOSINOPHIL COUNTS—as eosinophils are primarily tissue dwelling, they are likely several hundred-fold more abundant in affected tissues than represented in peripheral blood. Furthermore, the development of an intercurrent bacterial or viral infection may lead to suppression of blood eosinophilia until the superimposed acute infection has resolved. Thus, elevated or even normal blood eosinophil counts in a febrile patient should prompt investigations for eosinophilia (e.g. adrenal insufficiency)

MANAGEMENT

SYMPTOM CONTROL

TREAT UNDERLYING CAUSE—**deworm** (if parasites), **stop offending drugs** (if suspect

MANAGEMENT (CONT'D)

medication induced), **prednisone** (if unknown cause), **hydroxyurea** or **imatinib** (for idiopathic hypereosinophilic syndrome)

SPECIFIC ENTITIES

PULMONARY EOSINOPHILIA

- **PATHOPHYSIOLOGY**—defined as ↑ eosinophils in blood with evidence of lung involvement, radiologically, through bronchoalveolar lavage or lung biopsy

SPECIFIC ENTITIES (CONT'D)

- **CAUSES**—**infectious** (Loeffler syndrome [*Ascaris*, hookworms, strongyloides], *Paragonimus* lung flukes, tropical pulmonary eosinophilia [*Wuchereria bancrofti*, *Brugia malayi*], coccidioidal), **medications** (NSAIDs, nitrofurantoin, ampicillin, minocycline, phenytoin, ranitidine), **idiopathic** (acute eosinophilic pneumonia, chronic eosinophilic pneumonia), **others** (eosinophilic granulomatosis with polyangiitis, allergic bronchopulmonary aspergillosis)

Thrombocytosis

Rumi et al. *Blood* 2016;128(20)
Rumi et al. *Blood* 2017;129(6)

DIFFERENTIAL DIAGNOSIS

PRIMARY (clonal thrombocytosis)—essential thrombocythemia, chronic myelogenous leukemia, polycythemia vera, myeloid metaplasia with or without myelofibrosis, prefibrotic myelofibrosis

SECONDARY (reactive)

- **MALIGNANCY**
- **INFECTIONS**
- **CONNECTIVE TISSUE DISEASE**
- **DRUG REACTIONS**—vincristine, all-trans-retinoic acid, cytokines, growth factors
- **OTHERS**—iron deficiency, acute blood loss, hemolytic anemia, rebound from thrombocytopenia, splenectomy

PATHOPHYSIOLOGY

DEFINITION—platelets $>450 \times 10^3/\mu\text{L}$

Related Topic

Myeloproliferative Disorders (p. 185)

CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY THROMBOCYTOSIS

	Primary	Secondary
Underlying disease	N	Y
Digital ischemia/CVA	Y	N
Thrombosis	Y	N
Bleeding	Y	N

CLINICAL FEATURES (CONT'D)

	Primary	Secondary
Splenomegaly	Y (40%)	N
Peripheral smear	Giant platelets	Normal platelets
Platelet function	Abnormal	Normal
BM megakaryocytes	↑, giant	↑, normal

INVESTIGATIONS

BASIC

- **LABS**—CBC, peripheral smear, PTT, INR, Fe, ferritin, TIBC, % sat, ESR (secondary cause), CRP (secondary cause)

SPECIAL

- **BONE MARROW ASPIRATE AND BIOPSY WITH MUTATION ANALYSES OF JAK, MPL AND CALRETICULIN**

DIAGNOSTIC ISSUES

IMPORTANT PEARL—remember that essential thrombocythemia often is a diagnosis of exclusion. Thus, it is important to consider and rule out iron deficiency, occult malignancy, and another myeloproliferative disorder before making this diagnosis

MANAGEMENT

ESSENTIAL THROMBOCYTHEMIA—observation if asymptomatic and low risk of thrombosis, defined as age <60 and no cardiovascular risk factors. For all others with platelet counts $>450 \times 10^3/\mu\text{L}$, use **ASA** 81 mg PO daily (low dose) plus **hydroxyurea** (or **anagrelide**) targeting normalization of the platelet count. When

MANAGEMENT (CONT'D)

the platelets are $>1,500 \times 10^3/\mu\text{L}$, **platelet-pheresis** must be started for active ischemia and can be considered for use in asymptomatic

MANAGEMENT (CONT'D)

patients at risk for coronary and/or cerebral ischemic events

SECONDARY CAUSES—treat underlying cause

Thrombocytopenia**DIFFERENTIAL DIAGNOSIS**

PSEUDOTHROMBOCYTOPENIA—platelet clumping (usually due to EDTA-induced platelet activation, recollect with citrate)

DILUTIONAL—PRBC transfusion (at least 15–20 units), pregnancy

↓ PRODUCTION

- **INFILTRATIVE**—leukemia, MDS, bone marrow metastasis
- **INFECTIONS**—HIV, rubella, mumps, varicella, parvovirus, HCV, EBV, fungi, mycobacteria
- **APLASIA**—aplastic anemia, Fanconi anemia
- **TOXINS**—chemotherapy, radiation, alcohol
- **B12/FOLATE DEFICIENCY**

HYPERSPLENISM—congestive, reactive, infiltrative (see SPLENOMEGALY p. 184)

↑ DESTRUCTION

- **IMMUNE THROMBOCYTOPENIC PURPURA**—primary, secondary (lymphoma, CLL, HIV, SLE, Evans syndrome)
- **ALLOIMMUNE**—neonatal, post-transfusion, post-transplantation
- **MICROANGIOPATHIC HEMOLYTIC ANEMIA**—disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), HELLP syndrome, antiphospholipid antibody syndrome
- **INFECTIONS**—HIV, HEPC, EBV, CMV
- **MEDICATIONS**—heparin, GPIIb/IIIa inhibitors, quinine, quinidine, valproic acid, thiazides, sulfonamides, rifampin, indomethacin, vancomycin, linezolid

PATHOPHYSIOLOGY

DEFINITION—platelets $<150 \times 10^3/\mu\text{L}$. However, an acute drop of 50%, even if the platelet count remains in the normal range, requires close monitoring and potential investigations

LIFE CYCLE—half-life of platelets is 8–10 days. One-third of the total body platelets is found in the spleen

PATHOPHYSIOLOGY (CONT'D)**BLEEDING RISK IN UNDER-PRODUCTION THROMBOCYTOPENIA****Platelet count**

($\times 10^3/\mu\text{L}$)	Bleeding risk
>100	Minimal symptoms
50–100	Minor symptoms
10–50	Prone to bruises
<10	Risk of spontaneous bleed (intracranial bleed)

NOTE—in destruction or sequestration thrombocytopenia, bleeding does not correlate with the magnitude of thrombocytopenia

CLINICAL FEATURES

HISTORY—mucocutaneous bleeding (epistaxis, petechiae, easy bruising), abdominal pain, bloody diarrhea, recent infections, fever, weight loss, past medical history (malignancy, HIV, ITP, alcohol), medications (heparin, GPIIb/IIIa inhibitors, quinine, ASA, NSAIDs)

PHYSICAL—vitals. Look for retinal bleed (fundoscopy), petechiae, and purpura. Check for lymphadenopathy and hepatosplenomegaly

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, peripheral smear, PTT, INR, AST, ALT, ALP, bilirubin, fibrinogen, LDH, ANA, vitamin B12, RBC folate, D-dimer, HIV serology, hepatitis serology, Coombs test

SPECIAL

- **HITT ASSAY**—heparin-induced platelet aggregation assay, heparin–PF4 solid phase immunoassay, serotonin release assay
- **BONE MARROW BIOPSY**

DIAGNOSTIC ISSUES**SMEAR**

- **LARGE PLATELETS**—destruction (ITP), sequestration
- **SCHISTOCYTES/FRAGMENTS**—microangiopathic hemolytic anemia (DIC, TTP)

BONE MARROW BIOPSY

- **DECREASED MEGAKARYOCYTES**—underproduction
- **INCREASED MEGAKARYOCYTES**—destruction/sequestration/MDS (5q- syndrome)

MANAGEMENT

SYMPTOM CONTROL—in under-production thrombocytopenia, **transfuse** 5 U platelets if platelets $<50 \times 10^3/\mu\text{L}$ and severe bleeding, platelets $<10 \times 10^3/\mu\text{L}$ in non-bleeding patient, and prior to certain procedures (expect platelet rise of $\sim 5/\text{unit}$). 1-h post-transfusion platelet count can help differentiate under-production vs. destructive causes. Note that platelet transfusions are not effective in ITP and may worsen TTP/HUS and HITT

TREAT UNDERLYING CAUSE—discontinue medications that may cause thrombocytopenia (platelets return to normal in 7–14 days). Please refer to specific disorders below for details regarding treatment of each disease

SPECIFIC ENTITIES

MICROANGIOPATHIC HEMOLYTIC ANEMIA (MAHA)—also called fragmentation hemolysis. Characterized by non-immune hemolytic anemia with schistocytosis. Causes include DIC, HELLP, TTP, HUS, malignancy, malignant hypertension, artificial heart valve, insertion of foreign bodies, and medications

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

- **PATHOPHYSIOLOGY**—damage to endothelium \rightarrow release of tissue factor \rightarrow activation of coagulation cascade \rightarrow intravascular coagulation and depletion of clotting factors
- **CAUSES**—trauma, shock, sepsis (*Escherichia coli*, *N. meningitidis*, malaria), neoplasm (lung, prostate, pancreatic), obstetrical (abruptio placentae, preeclampsia, amniotic fluid embolus)
- **CLINICAL FEATURES**—microangiopathic hemolytic anemia, thrombocytopenia, bleeding and/or thrombosis, ischemia. \uparrow INR, \uparrow PTT, \downarrow fibrinogen (although it can be normal or even elevated in acute phase), \uparrow D-dimers. Schistocytes on peripheral smear
- **TREATMENTS—treat underlying cause and complications** (hypoxia, dehydration, acidosis, acute renal failure). **Replete coagulation**

SPECIFIC ENTITIES (CONT'D)

factors (FFP) and fibrinogen (cryoprecipitate) **if deficient and bleeding**. **Anticoagulation if thrombosis** (consider IV heparin 200–500 IU/h infusion)

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- **PATHOPHYSIOLOGY**— \downarrow ADAMTS13 activity \rightarrow failure to degrade unusually large multimers of vWF \rightarrow agglutination of platelets \rightarrow arteriolar thrombi \rightarrow systemic ischemia of brain, kidneys, gut, and heart
- **CAUSE**—autoantibody to ADAMTS13
- **CLINICAL FEATURES**—MAHA (100%), thrombocytopenia (90%), renal dysfunction, fever (90–100%), neurologic abnormalities (90%) with delirium, focal neurological deficit, seizure, coma. Schistocytes on peripheral smear
- **TREATMENTS**—full volume plasma exchange (plasmapheresis + FFP infusions), steroids, and rituximab if not resolving. Avoid platelet transfusion, ASA and antiplatelet agents. High mortality without treatment

George et al. *NEJM* 2014;371(7)

HEMOLYTIC UREMIC SYNDROME (HUS)

- **PATHOPHYSIOLOGY**—exposure to Shiga toxin or defect in plasma factor H \rightarrow arteriolar thrombi \rightarrow predominantly renal involvement
- **CAUSES**—*E. coli* O157:H7
- **CLINICAL FEATURES**—MAHA (100%), thrombocytopenia (90%), renal dysfunction (90%). Schistocytes on peripheral smear
- **TREATMENTS**—supportive care only. Does not respond to plasma exchange. Avoid antibiotics unless patient septic

Related Topics

Anticoagulation Therapy (p. 179)
 Antiphospholipid Antibody Syndrome (p. 176)
 Thrombocytopenia in Pregnancy (p. 474)

HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS (HITT)

- **PATHOPHYSIOLOGY**—**type 1** (non-immune) happens within 2 days, mild drop in platelets, and return to normal by itself. **Type 2** (immune) starts between days 4 and 14 (can present earlier if recent heparin exposure in past 1–3 months). It is usually more severe (platelet drop $>50\%$) and has great clinical significance. Pathogenesis: heparin complexes with PF4

SPECIFIC ENTITIES (CONT'D)

(from platelets) → IgG against heparin–PF4 complex → these megacomplexes bind to platelets and activate them, producing more PF4 → platelet aggregation → thrombosis

- **CAUSES**—heparin, LMWH (much less likely)
- **CLINICAL FEATURES** (type II)—thrombocytopenia, thrombosis, ischemia
- **TREATMENTS** (type II)—**stop heparin immediately and treat with danaparoid, lepirudin, argatroban, or fondaparinux** until platelets return to normal. Begin warfarin when platelets $>150 \times 10^3/\mu\text{L}$ and overlap warfarin with the alternative anticoagulant for 5 days (this reduces risk of venous limb gangrene). Avoid future heparin exposure except during CABG (performed at least 3 months after heparin exposure)

IMMUNE THROMBOCYTOPENIA (ITP)

- **PATHOPHYSIOLOGY**—autoantibodies against platelets → isolated thrombocytopenia
- **ASSOCIATIONS**—neoplasm (CLL, lymphoma), infections (HIV), autoimmune (SLE)
- **DIAGNOSIS**—isolated thrombocytopenia with an otherwise normal CBC and no obvious causes
- **TREATMENTS**—should be started when platelets $<30 \times 10^3/\mu\text{L}$. The goal of treatment is to support platelet counts until spontaneous remission occurs
 - **URGENT SUPPORT**—given to patients with active bleeding. **IVIG** 1 g/kg IV daily $\times 1-2$ days, which may increase the platelet count within days and lasts for a few weeks.

SPECIFIC ENTITIES (CONT'D)

Dexamethasone 40 mg PO daily for 4 days (may require repeat course on day 10 if no improvement). **Platelet transfusions** are rarely effective, although they may provide temporary support for actively bleeding patients

- **FIRST LINE**—**prednisone** 1–2 mg/kg PO daily or **dexamethasone** 40 mg PO daily for 4 days (repeat on day 10 if no response). Platelet recovery occurs within 3 weeks in 2/3 of patients. If platelet count does not increase after 4 weeks of treatment, consider second line therapies
- **SECOND LINE**—**rituximab, thrombopoietic agents** (romiplostim, eltrombopag, avatrombopag), **splenectomy** (see p. 292)

Cooper et al. NEJM 2019;381(10)

EVANS SYNDROME—ITP and autoimmune hemolytic anemia

DRUG-INDUCED IMMUNE THROMBOCYTOPENIA—patients usually present with severe thrombocytopenia (platelets $<20 \times 10^3/\mu\text{L}$). With the exception of platelet inhibitors, there is usually 5–7 days between initiation of drug therapy and platelet drop if patient is receiving the medication for the first time. Treatment consists of discontinuation of offending (or all) drugs and platelet transfusions as needed

Aster et al. NEJM 2007;357(6)

Pancytopenia

DIFFERENTIAL DIAGNOSIS

★ PANIC ★

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- ↑ **COMPLEMENT-MEDIATED RED CELL LYSIS**

APLASTIC ANEMIA

- **IDIOPATHIC** (50%)
- **INFECTIONS**—EBV, CMV, parvovirus, hepatitis
- **FANCONI ANEMIA**
- **DRUG INDUCED**—chemotherapy, gold
- **TOXINS**—alcohol

NEOPLASTIC—leukemia (AML, CLL), MDS, bone marrow metastasis

INFECTIONS—sepsis, TB, parvovirus, fungal

INSUFFICIENCY—folate, vitamin B12

IATROGENIC—chemotherapy

CONSUMPTION—hypersplenism, immune-mediated destruction

INVESTIGATIONS

BASIC

- **LABS**—CBC, peripheral smear, B12, RBC folate, HIV test, Coombs test

SPECIAL

- **BONE MARROW BIOPSY**—if suspect aplastic anemia or malignancy
- **FLOW CYTOMETRY**—if suspect PNH. Historically, sucrose hemolysis test was used for screening, followed by Ham acid hemolysis test for diagnosis. Currently, blood flow cytometry is used to measure the expression of the complement regulatory proteins CD55 and CD59, which are deficient on blood cells in PNH

DIAGNOSTIC ISSUES

PRE-MEDS FOR BONE MARROW BIOPSY—morphine 2.5–5 mg IV, lorazepam 1 mg SL, lidocaine 2.5%/prilocaine 2.5% cream rarely needed

MANAGEMENT**TREAT UNDERLYING CAUSE****SPECIFIC ENTITIES****APLASTIC ANEMIA**

- **PATHOPHYSIOLOGY**—precipitants (e.g. parvovirus, drugs) → T-cell subsets produce local concentrations of INF γ → ↑ Fas on CD34+ cells (maturing stem cells) → apoptosis → severe

Bleeding Diathesis**DIFFERENTIAL DIAGNOSIS**

★**PVC**★ platelets, vessels, coagulopathy
EXTRINSIC PATHWAY (isolated PT/INR ↑)

- **FACTOR DEFICIENCY OR INHIBITOR**—VII or X
- **VITAMIN K DEFICIENCY**—malnutrition, pancreatic insufficiency, recent antibiotic use, warfarin use (early stage)
- **LIVER DISEASE**
- **EARLY DIC**

INTRINSIC PATHWAY (isolated PTT ↑)

- **FACTOR DEFICIENCY**—X-linked deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B). Autosomal deficiency of factor XI, especially among Ashkenazi Jews (8% are carriers)
- **VON WILLEBRAND DISEASE**
- **FACTOR INHIBITORS**—lupus anticoagulant due to APA; acquired hemophilia due to an inhibitor to factor VIII
- **HEPARIN USE**

COMMON PATHWAY (PT ↑, PTT ↑)

- **FACTOR DEFICIENCY**—X, V, II, I
- **VITAMIN K DEFICIENCY**—malnutrition, pancreatic insufficiency, recent antibiotic use
- **LIVER DISEASE**
- **DIC**

PLATELET DYSFUNCTION (mucocutaneous bleeding with normal PT, PTT, and platelet count; bleeding time sometimes ↑)

- **INHERITED**—Bernard–Soulier syndrome, Glanzmann thrombasthenia, storage pool disease

SPECIFIC ENTITIES (CONT'D)

pancytopenia and hypocellular marrow. Complications include paroxysmal nocturnal hemoglobinuria, acute leukemia, and MDS

- **TREATMENTS**—corticosteroids, antithymocyte globulin, cyclosporine, eltrombopag, stem cell transplant

Bacigalupo Blood 2017;129(11)

FANCONI ANEMIA—hereditary form of aplastic anemia that usually affects children but occasionally presents in adults. The main features include pancytopenia, hyperpigmentation, skeletal malformation, small stature, and hypogonadism

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **ACQUIRED**—renal failure, liver failure, myeloproliferative disorders, paraproteinemia, autoantibodies, DIC, acquired storage pool disease from extracorporeal circulation

VESSELS—collagen vascular disease, scurvy, hereditary hemorrhagic telangiectasia

NOTE—INR=international normalized ratio, helps to standardize interpretation of PT

PATHOPHYSIOLOGY**HEMOSTASIS**

- **PRIMARY HEMOSTASIS**—endothelium, platelets
- **SECONDARY HEMOSTASIS**—coagulation proteins

PLATELET ACTIVATION PATHWAY

1. Collagen binds to GPIIb/IIIa on platelet membrane, also binds to GPIb/IX via vWF
2. Platelet becomes activated by agonist binding (thrombin, adenosine diphosphate, epinephrine, collagen)
3. Secretion of δ granules (serotonin, ADP) and α granules (vWF, growth factors, factor V, factor X, fibrinogen)
4. Conformational change → phospholipids become available for factors V and VIII binding
5. Platelet aggregation (unstable) by vWF and fibrinogen binding to the activated GPIIb/IIIa complex
6. Platelet fibrin clot formation—fibrin–fibrin crosslinked by factor XIII and platelet–fibrin via GPIIb/IIIa

PATHOPHYSIOLOGY (CONT'D)

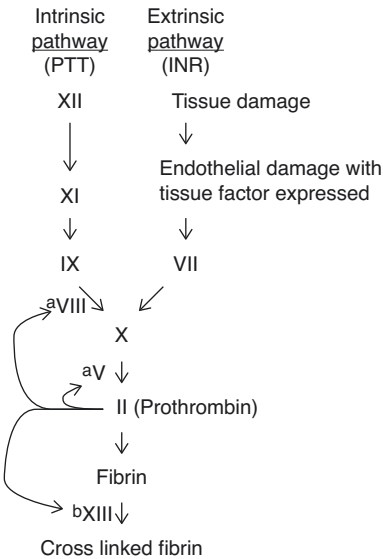
ANTICOAGULATION PATHWAYS

1. Antithrombin binds to thrombin and inhibits it
2. Thrombin binds to thrombomodulin, which activates protein C and S to cleave factors Va and VIIIa
3. Factor Xa → tPA (by endothelial cells) → plasmin → fibrinolysis

COAGULATION FACTOR PEARLS

- **SYNTHESIZED IN LIVER**—factors I, II, V, VII, VIII, IX, X, XI, XII, protein C, S, AT-III, plasminogen
- **VITAMIN K DEPENDENT**—factors II, VII, IX, X, protein C, S
- **SYNTHESIZED IN ENDOTHELIAL CELLS AND MEGAKARYOCYTES**—vWF

COAGULATION PATHWAY



^aNon-enzymatic cofactors; ^bFactor XIII is called "fibrin-stabilizing factor" because it covalently cross-links fibrin polymers and strengthens the clot

PATHOPHYSIOLOGY (CONT'D)

FACTORS VII AND VIII ARE SPECIAL

- **FACTOR VII**—shortest half-life (5–7 h). Decreased factor VII results in INR ↑. Thus, INR can help to detect *early* stages of liver failure, DIC, vitamin K deficiency, and warfarin use
- **FACTOR VIII**—part of coagulation cascade and has von Willebrand factor (vWF, synthesized by endothelial cells) as carrier in plasma. Thus, von Willebrand disease (vWD) leads to ↓ factor VIII

CLINICAL FEATURES

BLEEDING SYNDROMES

- **PLATELET DYSFUNCTION**—skin/mucous membrane (petechiae, purpura, small/superficial ecchymosis, epistaxis, gingival bleed, menorrhagia), immediate bleeding
- **COAGULATION FACTORS**—joints/muscles (hemarthroses, muscle hematomas, large/palpable ecchymosis), delayed bleeding

INVESTIGATIONS

BASIC

- **LABS**—CBC, peripheral smear, AST, ALT, ALP, bilirubin, albumin, PT/INR, PTT, D-dimer, fibrinogen

SPECIAL

- **HEPZYME STUDY**—to remove heparin from blood samples to distinguish if isolated elevation of PTT is spurious
- **50:50 MIXING STUDY**—to distinguish between factor deficiency vs. inhibitors (factor deficiency corrects with mixing study)
- **HEMOPHILIA WORKUP**—factors VIII, IX, XI
- **ANTIPHOSPHOLIPID ANTIBODY SYNDROME WORKUP**—lupus anticoagulant screen, anticardiolipin antibody, dilute Russell viper venom time, anti-β₂ glycoprotein 1 antibody
- **VON WILLEBRAND DISEASE WORKUP**—von Willebrand factor (vWF) antigen level, factor VIII level, ristocetin cofactor activity, ristocetin-induced platelet aggregation
- **PLATELET DISORDER WORKUP**—bleeding time, platelet aggregometry
- **MYELOMA WORKUP**—serum protein electrophoresis

MANAGEMENT

ACUTE—ABC, O₂, IV, **transfusion** 2 U **PRBC** IV over 2 h, transfusion **platelets** 6 U, **FFP** 15 mL/kg, **cryoprecipitate** 10–15 U q48h for fibrinogen deficiency

TREAT UNDERLYING CAUSE—**avoid** anticoagulants. **Vitamin K deficiency** (*vitamin K* 10 mg PO/IV daily × 3 days). **vWD type I** (*DDAVP* 0.3 µg/kg SC, intermediate purity factor VIII)

SPECIFIC ENTITIES

VON WILLEBRAND DISEASE (VWD)

- **PATHOPHYSIOLOGY**—vWF acts as a linker between platelets and endothelium and also serves as carrier for factor VIII. Thus, vWD deficiency may lead to decrease in factor VIII levels
- **CLINICAL FEATURES**—platelet disorder with bruising, skin or mucosal bleeding, and heavy menstrual cycles for most subtypes except type IIN, which manifests as hemophilia with soft tissue, joint, and urinary bleeding
- **DIAGNOSIS**—**Ristocetin cofactor activity** (RCo, assesses capacity of plasma vWF to sup-

SPECIFIC ENTITIES (CONT'D)

port ristocetin-induced aggregation of control platelets), **collagen binding activity** (assesses vWF binding to collagen), vWF antigen (non-functional assay that quantifies vWF), **vWF multimer assay** (agarose gel to determine the size of multimers), **ristocetin-induced platelet aggregation** (assesses vWF binding to platelets in patients' platelet-rich plasma)

- **TREATMENTS**—*DDAVP* 0.3 µg/kg by IV infusion or 300 µg one spray each nasal for type I patients. vWF concentrates containing all vWF multimers may be used for type II and III and for bleeding and surgical management of type I patients

BERNARD-SOULIER SYNDROME—mutation of GPIb/IX/V (platelet receptor for vWF)

GLANZMANN THROMBASTHENIA—mutation of GPIIb/IIIa (platelet receptor for fibrinogen)

STORAGE POOL DISEASE—defect in releasing platelet granules

VWD	Inheritance	Pathophysiology
I	Heterozygous mutations	Mild to moderate quantitative ↓ of all multimers
IIA	Autosomal dominant/ recessive	↓ activity of vWF due to decrease in large multimers of vWF (synthesis of active forms in platelet adhesion)
IIB	Autosomal dominant	Same as IIA except decrease due to large multimer vWF adherence to platelets
IIN	Autosomal recessive	↓ vWF affinity for factor VIII, similar to hemophilia
III	Homozygous mutations	Complete absence of vWF

VWD	vWF:Ag	vWF:RCo	vWF multimer	RIPA
I	↓	↓	↓ all multimers	↓
IIA	↓ or N	↓	↓ large multimers	↓ or N
IIB	↓ or N	↓	↓ large multimers	↑
IIN	Normal	↓	Normal	Normal
III	↓↓	↓↓	↓↓ undetectable	↓↓

Hypercoagulable States

DIFFERENTIAL DIAGNOSIS

COAGULATION FACTORS

- **INHERITED DEFICIENCY OF NATURAL ANTICOAGULANTS**—protein S, protein C, antithrombin III
- **INHERITED MUTATIONS THAT INCREASE PROCOAGULANT ACTIVITY**—factor V Leiden, prothrombin G20210A mutations
- **ACQUIRED EXCESSIVE PROTHROMBOTIC ACTIVITY**—HITT, DIC, TTP, HUS, PNH, APA, and nephrotic syndrome (reduced antithrombin III)

VASCULAR DAMAGE—vasculitis, sepsis, trauma, surgery, cancer (Trousseau syndrome, lymphoproliferative disease)

STASIS/IMMOBILITY—bed rest, pregnancy, air travel, leg cast

PATHOPHYSIOLOGY

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

- **COAGULATION FACTORS**—excess, mutation (factor V Leiden, prothrombin), deficiency (protein S, protein C, antithrombin III, plasminogen, tissue plasminogen activator)
- **NEOPLASTIC**—solid tumors, myeloproliferative, leukemia
- **OTHERS**—immobilization, surgery, congestive heart failure, oral contraceptives, hormone replacement therapy, pregnancy, nephrotic syndrome

RISK FACTORS FOR ARTERIAL THROMBOEMBOLISM

- **ATHEROSCLEROSIS**—hypertension, diabetes, smoking
- **EMBOLIC**—AF, atrial myxoma, endocarditis, cholesterol emboli, MI with ventricular thrombosis, paradoxical embolism
- **OTHERS**—SLE

RISK FACTORS FOR ARTERIAL AND VENOUS THROMBOEMBOLISM

- **FACTORS**—dysfibrinogenemia, plasminogen activator deficiency
- **PLATELET DEFECTS**—myeloproliferative disorders, HITT, PNH
- **HYPERVISCOSITY**—polycythemia vera, Waldenström macroglobulinemia, cryoglobulinemia, sickle cell disease

PATHOPHYSIOLOGY (CONT'D)

- **OTHERS**—antiphospholipid antibody syndrome, vasculitis, paradoxical embolism

Connors et al. NEJM 2017;377(12)

FACTOR V LEIDEN—mutation that resists cleavage by activated protein C. Most common hereditary form of thrombophilia (3–4% general population)

THROMBOPHILIC MUTATIONS—homozygous factor V Leiden or prothrombin gene mutation or combine heterozygous factor V Leiden/prothrombin mutations > antithrombin III, > protein S, protein C > heterozygous factor V Leiden > heterozygous prothrombin gene mutation in terms of risk of thrombosis

INVESTIGATIONS

BASIC

- **LABS**—CBC, PT, INR, activated protein C resistance, factor V Leiden, prothrombin G20210A, anticardiolipin antibody, anti-beta2 glycoprotein I antibody, lupus anticoagulant, homocysteine, protein C, protein S, antithrombin III, fibrinogen, urinalysis
- **IMAGING**—CXR

Related Topics

Anticoagulation Therapy (p. 179)

DVT (p. 177)

Pulmonary Embolism (p. 12)

DIAGNOSTIC ISSUES

INDICATIONS FOR HYPERCOAGULABILITY WORKUP—testing for inherited thrombophilia is not routinely warranted in a patient with first episode unprovoked VTE. However, there may be a benefit to investigating patients with a family history of VTE, unusual thrombosis (hepatic, portal, mesenteric, or cerebral veins), recurrent thromboembolism, or arterial thrombosis

THROMBOPHILIA WORKUP AFTER ACUTE THROMBOSIS OR DURING ANTICOAGULATION—acute VTE and anticoagulants can affect thrombophilia testing

DIAGNOSTIC ISSUES (CONT'D)

Hypercoagulable Disorder	Acute Thrombosis	Heparin Anticoagulation	Warfarin Anticoagulation	Direct Oral Anticoagulation
Anti-thrombin deficiency	↓	↓	–	–
Anti-phospholipid syndrome	–	–	–	–
Lupus anticoagulant	–	Cannot measure	False positive	False positive with direct Xa inhibitors
Factor V Leiden	–	–	–	–
Protein C and S	↓	–	Cannot measure	–
Prothrombin gene mutation	–	–	–	–
Draw protein C and S prior to warfarin therapy				

MANAGEMENT

ACUTE—ABC, O₂ to keep sat >94%, IV, consider thrombolysis for systolic BP <90 mmHg for >15 min

ANTICOAGULATION—see Approach to Anticoagulation Therapies Table (see p. 179). For cancer patients, extended anticoagulation is generally considered

IVC FILTER—when anticoagulation is contraindicated; use a retrievable filter if the contraindication is temporary

TREATMENT ISSUES

WARFARIN USE AND PROTEIN C DEFICIENCY—patients with protein C deficiency given warfarin may be susceptible to transient hypercoagulable state (coumadin necrosis). This can be avoided by overlapping heparin with warfarin for 5 days (with minimum 48 h therapeutic INR overlap)

PRIMARY PROPHYLAXIS OF THROMBOEMBOLISM IN HOSPITALIZED MEDICAL PATIENTS

- **INDICATIONS**—patients on the medical service >40-years old, have limited mobility for ≥3 days, and have at least one of following risk factors
 - **CONDITIONS**—acute infectious disease, congestive heart failure, acute myocardial infarction, acute respiratory disease, stroke, rheumatic disease, inflammatory bowel disease, cancer

TREATMENT ISSUES (CONT'D)

- **CLINICAL CHARACTERISTIC**—previous venous thromboembolism, older age (especially >75), recent surgery or trauma, immobility or paresis, BMI >30 kg/m², inherited or acquired thrombophilic states, varicose veins, estrogen therapy
- **INTERVENTIONS**—early ambulation and exercises involving foot extension for all patients. Specific prophylaxis regimens include *heparin* 5,000 U SC q8h, *enoxaparin* 40 mg SC daily, *dalteparin* 5,000 U SC daily, *tinzaparin* 75 units/kg SC daily, *fondaparinux* 2.5 mg SC daily, or *rivaroxaban* 10 mg PO daily. For patients at high risk for bleeding, consider non-pharmacologic measures such as graduated compression stockings and pneumatic compression devices

RISK REDUCTION BY ANTICOAGULATION

- **ACUTE VTE**—without anticoagulation, the risk for recurrent VTE in the next month is 50%. Anticoagulation ↓ risk to 8–10% during months 2 and 3 and 4–5% per month after 3 months
- **UNPROVOKED VTE**—recurrent DVT risk 10%/year during the first 2 years after stopping anticoagulation. Anticoagulation ↓ risk to <3%/year
- **VTE IN PATIENTS WITH CANCER**—risk of recurrence at 6 months on anticoagulation is 3–9%. Risk of recurrence for patients with active cancer and/

TREATMENT ISSUES (CONT'D)

or receiving therapy in the first year after stopping anticoagulation is about 20%

- **AF WITH PREVIOUS STROKE**—stroke risk 12%/year. Anticoagulation ↓ risk to <4%/year
- **AF WITH OTHER RISK FACTORS**—stroke risk ≤8%/year. Anticoagulation ↓ risk to <2%/year
- **LONE AF**—recurrent stroke risk 1–2%/year. Anticoagulation ↓ risk to <1%/year

MECHANICAL HEART VALVE—recurrent arterial embolic risk 4%/year. Warfarin ↓ risk to <1%/year. Mitral valve prostheses 2 × risk of aortic valve prostheses. INR 2–3 for bileaflet or tilting disc mechanical valves and 2.5–3.5 for caged-ball or caged-disc valves

SPECIFIC ENTITIES**ANTIPHOSPHOLIPID ANTIBODY SYNDROME (APS)**

- **PATHOPHYSIOLOGY**—antibody against phospholipids or cell surface proteins bound to anionic phospholipids. These include lupus anticoagulants, anticardiolipin antibody (false-positive VDRL), and anti-β₂-glycoprotein 1 antibody → hypercoagulable state by stimulating complement activation on endothelium
- **CAUSES**—primary APS, secondary APS (various rheumatic diseases such as SLE and infections such as HIV and drugs)
- **CLINICAL FEATURES**—venous and arterial thrombosis and rarely hemorrhage affecting the lungs, heart, CNS, GI, kidneys, skin, and eyes. Also recurrent fetal losses (recurrent first trimester or single late term), thrombocytopenia, and livedo reticularis
- **DIAGNOSIS**—**clinical criteria** include thrombosis (≥1 arterial, venous, or small-vessel thrombosis in any organ) or pregnancy complications (≥1 unexplained deaths of morphologically normal fetus at or after the 10th week of gestation, ≥1 premature births of morphologically normal neonate at or before the 34th week of gestation, or ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation). **Laboratory criteria** include anticardiolipin or anti-β₂-glycoprotein 1 antibodies (IgG or IgM at moderate or high levels on ≥2 occasions at least 6 weeks apart)

SPECIFIC ENTITIES (CONT'D)

or the presence of a lupus anticoagulant (≥2 occasions at least 6 weeks apart). Diagnosis requires at least one clinical and one laboratory criterion (sens 70%, spc 98%)

- **CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME**—acute and devastating syndrome with multiple simultaneous vascular occlusions throughout the body, affecting mainly small vessels of kidney, lungs, CNS, heart, and skin. May be associated with DIC, ARDS, cerebral and myocardial microinfarctions. May be precipitated by infections, surgery, and withdrawal of anticoagulation. Treatment consists of a combination of anticoagulation, steroids, plasmapheresis, and/or IVIG. Mortality rate is 50%
- **TREATMENTS**—primary prophylaxis for thrombosis is not indicated in persons with incidentally discovered antiphospholipid antibodies or lupus anticoagulants. Treatment of thromboses (both venous and arterial) is indefinite anticoagulation with warfarin (if high risk triple positive APS) or a direct acting oral anticoagulant or warfarin (all others). See p. 475 for management of APS in pregnancy

Garcia et al. NEJM 2018;378(21)

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)

- **PATHOPHYSIOLOGY**—mutation in PIG-A gene coding for GPI anchor → ↓ GPI-linked proteins such as CD59 (membrane attack complex inhibitory factor) and CD55 (decay accelerating factor) → complement-mediated lysis of RBC → acute renal failure due to hemoglobinuria, chronic renal failure due to iron deposits. Also ↑ platelet activation and endothelial injury due to complement activation, ↑ tissue factor, ↓ fibrinolysis → ↑ thrombosis
- **CLINICAL FEATURES**—hemolysis, venous thrombosis (hepatic vein, portal vein, splenic vein, renal vein), arterial thrombosis (rarer), marrow aplasia, MDS, leukemia, infections, esophageal spasm, sexual dysfunction
- **DIAGNOSIS**—flow cytometry, historically, Ham test (RBC sensitivity to acidity)
- **TREATMENTS**—steroids, eculizumab (anti-complement factor 5a), stem cell transplant

Deep Vein Thrombosis

Kearon et al. *Blood* 2020;135(5)

PATHOPHYSIOLOGY

LOCATION—DVT typically originates in the venous sinuses of the calf muscles and occasionally the proximal veins. While most calf vein thrombi lyse spontaneously, ~15% extend into proximal veins within 2 weeks

COMPLICATIONS—clot extension, pulmonary embolism, recurrent thrombosis, post-thrombotic syndrome, chronic thromboembolic pulmonary hypertension

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, PTT, INR, D-dimer, fibrinogen, AST, ALT, ALP, bili
- **IMAGING**—Doppler/compression US (sens 95%, spc 95%)

SPECIAL

- **THROMBOPHILIA WORKUP**—if there is a family history of thrombosis, consider activated protein C resistance, factor V Leiden, prothrombin G20210A, antithrombin III, protein C, and protein S
- **PREGNANCY TEST**—in female <50
- **VENOGRAM**—gold standard

DIAGNOSTIC ISSUES

COMPRESSION US—high sensitivity (95%) and specificity (95%) for DVT. US of calf veins is not routinely performed because of lower sensitivity (70%). Rather, US of thigh (deep veins) is usually repeated in 2 weeks after a normal test to detect the possible extension of DVT from calf into proximal veins

Related Topics

- Anticoagulation Therapy (p. 179)
- Hypercoagulable States (p. 174)
- Pulmonary Embolism (p. 12)

DIAGNOSTIC ISSUES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES DOES THIS PATIENT HAVE DEEP VEIN THROMBOSIS?

WELLS CRITERIA FOR DVT—alternative diagnosis more or as likely (−2), recent paralysis/paresis/plaster immobilization (+1), recent bedridden >3 days or major surgery <4 weeks (+1), localized tenderness along deep venous system (+1), calf swelling by more than 3 cm at 10 cm below tibial tuberosity (+1), pitting edema greater in symptomatic leg (+1), collateral non-varicose superficial veins (+1), active cancer (+1)

D-DIMER UTILITY FOR DVT BASED ON WELLS CRITERIA

	Sens	Spc	LR+	LR−
Low risk	88%	72%	3.3	0.18
Moderate risk	90%	58%	2.1	0.19
High risk	92%	45%	1.6	0.16

POST-TEST PROBABILITY OF DVT USING HIGH SENSITIVITY D-DIMER ASSAY

- **LOW RISK** (0 or less points)—0.5% chance of DVT. If age-adjusted D-dimer (for patients >50 years, a D-dimer that is less than 10 × the patient's age) is negative, can exclude DVT
- **MODERATE RISK** (1–2 points)—1% chance of DVT. Workup may or may not be needed
- **HIGH RISK** (3 or greater points)—8.6% chance of DVT. D-dimer testing not useful. Proceed to compression US or impedance plethysmography → serial studies → venogram
- **APPROACH**—"Diagnostic accuracy for DVT improves when clinical probability is estimated before diagnostic tests. Patients with low clinical probability on the predictive rule have prevalence of DVT of less than 5%. In low-probability patients with negative D-dimer results, diagnosis of DVT can be excluded without ultrasound; in patients with high clinical suspicion for DVT, results should not affect clinical decisions."

Wells et al. *JAMA* 2006;295(2)
Simel et al. *The Rational Clinical Examination*. McGraw-Hill; 2009
Le Gal et al. *JAMA* 2015;313(16)

DIAGNOSTIC ISSUES (CONT'D)

THROMBOPHILIA WORKUP—testing for antiphospholipid syndrome should be done in all patients with unprovoked VTE as it will be a predisposing factor in ~10% of these patients. Routine testing for inherited thrombophilias of hypercoagulable states (e.g. protein S, C, antithrombin, factor V Leiden, prothrombin mutations) is not recommended; however, if there is a family history, a hereditary cause should be tested for. Other alarm features that warrant testing include age <45 years or clot in an unusual location (mesenteric vessels, brain).

MALIGNANCY WORKUP—basic screening includes history and physical, CXR, CBC, LFTs, calcium, and U/A. Consider CT abdomen and pelvis for those >40 years. Consider mammography for women >40 years.

PROTEIN S AND PROTEIN C DEFICIENCY WHILE ANTICOAGULATED—when anticoagulated, these levels decrease by similar proportion to II, VII, IX and X.

MANAGEMENT

ANTICOAGULATION—see Approach to Anticoagulation Therapies Table (p. 179).

IVC FILTER—if anticoagulation contraindicated.

THROMBOLYSIS—*alteplase* 100 mg infused over 2 h is the default intervention for hemodynamically unstable pulmonary embolism (SBP <90 mmHg for 15 min). Do not use systemic thrombolytic therapy for patients with a history of stroke, recent surgery, recent bleeding, thrombocytopenia or coagulopathy. For these patients, try to arrange mechanical thrombectomy.

TREATMENT ISSUES**ANTICOAGULATION DURATION**

- **3-6 MONTHS**—first DVT with reversible or time-limited risk factor removed (i.e. estrogen therapy, pregnancy, surgery)
- **6-12 MONTHS**—unprovoked or idiopathic VTE
- **INDEFINITE**—recurrent idiopathic DVT or continuing major risk factor (malignancy, antithrombin III deficiency, homozygous factor V Leiden, homozygous prothrombin G20210A, heterozygous factor V Leiden plus prothrombin G20210A)

CONTRAINDICATIONS TO ANTICOAGULATION THERAPY

- **ABSOLUTE**—neurosurgery, ocular surgery, or intracranial bleeding within the past 5 days,

TREATMENT ISSUES (CONT'D)

active bleeding, severe bleeding diathesis, thrombocytopenia (<20,000/ μ L)

- **RELATIVE**—mild–moderate bleeding diathesis, brain metastases from melanoma, renal cell carcinoma, choriocarcinoma and thyroid cancers, recent major trauma, major abdominal surgery <2 days, GI or GU bleeding <2 weeks, endocarditis, severe hypertension (>200/120 mmHg)

SPECIFIC ENTITIES

SUPERFICIAL THROMBOPHLEBITIS—characterized by painful, erythematous, palpable cord along a superficial vein usually in the lower extremity, can be associated with hypercoagulable states. 25% will have synchronous ipsilateral DVT and a new DVT develops within 3 months in 10%; treat with prophylactic dose anticoagulation for 45 days.

CATHETER RELATED THROMBOSIS

- **INCIDENCE**—approximately 5% for symptomatic CRT and 15% for asymptomatic CRT; usually within the first 100 days after placement
- **RISK FACTORS**—in addition to traditional risk factors (e.g. cancer), left subclavian vein placement, positioning of catheter tip too high in the superior vena cava and previous catheter infections
- **CLINICAL FEATURES**—often asymptomatic. However, patients may experience arm swelling, erythema, pain, warmth, development of collateral vessels and fever. Acute PE, post thrombotic syndrome and persistent vascular compromise represent potential complications
- **DIAGNOSIS**—ultrasound (sens 78–100%, spc 86–100%). Venogram is gold standard but rarely done
- **TREATMENTS**—if catheter is still needed (e.g. for chemotherapy administration), consider continuing anticoagulation for at least 3 months after catheter removal. Note that in serious cases in which the limb may be threatened or if anticoagulation is contraindicated, catheter may need to be removed regardless. If no need for catheter, consider anticoagulation for 3–5 days, then remove catheter, and then anticoagulate for up to 3 months. Primary prophylaxis is not indicated.

Rajasekhar et al. *Blood* 2017;129(20)

Approach to Anticoagulation Therapies

Please refer to manufacturer insert for dosing instructions

Class/Drugs	Mechanism	Indications	Usual dose	Complications/ monitoring
Warfarin	Inhibition of gamma carboxylation by inhibition of the vitamin K-dependent epoxide reductase. Inhibits hepatic synthesis of vitamin K-dependent factors (II, VII, IX, X, protein S, protein C)	DVT/PE Atrial fibrillation Prosthetic valves	<i>Warfarin</i> 5 mg PO daily overlapping with heparin for 5 days, then adjust based on INR target of 2–3	COMPLICATIONS —bleeding (may be reversed with vitamin K), coumadin-induced skin necrosis MONITOR —INR
Unfractionated heparin	INDIRECT THROMBIN AND FACTOR Xa INHIBITOR (NONSELECTIVE) . Binds to antithrombin (AT) and converts it from a slow form to fast-acting form, which binds and inactivates thrombin and factors Xa, IXa, XIa, XIIa Heparin resistance is usually due to AT deficiency and could be treated with AT concentrates	Acute DVT/PE Arterial embolism Prosthetic valves ACS DVT prophylaxis	For acute DVT/PE, <i>unfractionated heparin</i> 80 U/kg or 5,000 U IV bolus, then 18 U/kg/h or 1,000 U/h, and adjust to 1.5–2.5 × normal PTT For DVT prophylaxis, <i>unfractionated heparin</i> 5,000 U SC 2 h before surgery, then 5,000 U SC TID	COMPLICATIONS —bleeding (may be reversed by <i>protamine</i> 1 mg/100 U UFH), HITT, osteoporosis MONITOR —aPTT (1.5–2.5 × normal) and platelets. Narrow therapeutic window and highly variable dose–response curve
Low molecular weight heparin: <i>Enoxaparin</i> <i>Dalteparin</i> <i>Tinzaparin</i>	INDIRECT FACTOR Xa INHIBITOR (RELATIVELY SELECTIVE) . Binds to AT and converts it from a slow form to fast acting form, which binds and inactivates factor Xa, and to a smaller extent, thrombin. Inactivation of thrombin specifically requires heparin binding to <i>both</i> AT and thrombin. This complex only forms with heparin chains ≥18-saccharide long. Thus, LMWH is not as effective in inhibiting thrombin and does not prolong aPTT	Acute DVT/PE Maintenance DVT/PE in cancer patients Arterial embolism Prosthetic valves ACS DVT prophylaxis	For acute DVT/PE, <i>enoxaparin</i> 1 mg/kg SC BID or 1.5 mg/kg SC daily, <i>dalteparin</i> 200 U/kg SC daily, <i>tinzaparin</i> 175 U/kg SC daily. For DVT prophylaxis, <i>enoxaparin</i> 40 mg SC daily × 7–14 days starting 12 h pre-op, <i>dalteparin</i> 2500 U SC 1 h pre-op, then 5000 U SC daily × 5–14 days	COMPLICATIONS —bleeding (may be reversed partially with <i>protamine sulfate</i> 1 mg/100 anti-Xa U of LMWH), HITT, avoid in spinal surgery MONITOR —anti-factor Xa activity and platelets. Anticoagulant response correlates well with body weight, allowing fixed dosing without monitoring usually. Less likely to induce HITT but still requires platelet monitoring

Class/Drugs	Mechanism	Indications	Usual dose	Complications/ monitoring
Heparinoids: <i>Danaparoid</i> (<i>organon</i>)	INDIRECT FACTOR Xa INHIBITOR (SELECTIVE). Mixture of heparin sulfate, dermatan sulfate, and chondroitin sulfate. Inhibits thrombin via a combination of AT (heparin cofactor I), heparin cofactor II, and some undefined mechanism. aPTT not useful for monitoring	HITT Acute DVT	For HITT, <i>danaparoid</i> 2,000 anti-factor Xa U IV bolus, then 200 U/h, titrate to plasma anti-Xa level of 0.5–0.8 U/mL. For acute DVT, if thrombosis <5 days old, IV bolus of 1,250–1,500 U if ≤55 kg, 2,250–2,500 U if 55–90 kg, and 3,750 U if >90 kg; if thrombosis ≥5 days old, IV bolus 1250 U. After IV bolus, give maintenance IV infusion or SC injections	COMPLICATIONS —bleeding MONITOR —anti-factor Xa activity. Particularly important in renal failure. 10% cross-reactivity between <i>danaparoid</i> and the antibody responsible for HITT, but clinical significance is uncertain
Fondaparinux	INDIRECT FACTOR Xa INHIBITOR (HIGHLY SELECTIVE). Similar to LMWH, but only a pentasaccharide that binds strongly to AT and inactivates factor Xa. Complex does not bind thrombin due to short length	DVT prophylaxis Acute DVT/PE Acute coronary syndrome HITT (no cross reactivity with heparin-dependent anti-platelet antibodies)	For DVT prophylaxis, <i>fondaparinux</i> 2.5 mg SC daily (start 6–8 h after surgical hemostasis). For acute DVT/PE, <i>fondaparinux</i> 5 mg SC daily for weight <50 kg, 7.5 mg SC daily for weight 50–100 kg, 10 mg SC daily for weight >100 kg	COMPLICATIONS —bleeding; avoid in spinal surgery MONITOR —anti-factor Xa activity
Oral direct factor Xa inhibitor: <i>Rivaroxaban</i> <i>Apixaban</i> <i>Edoxaban</i>	DIRECT FACTOR Xa INHIBITOR (HIGHLY SELECTIVE). Inhibits factor Xa by binding to its active site without interacting with AT	DVT prophylaxis VTE treatment (except if hemodynamically unstable or massive PE) Atrial fibrillation	For DVT prophylaxis, <i>rivaroxaban</i> 10 mg PO daily or <i>apixaban</i> 2.5 mg PO BID; For acute VTE, <i>rivaroxaban</i> 15 mg PO BID for 3 weeks followed by 20 mg PO daily, <i>apixaban</i> 10 mg PO BID for 7 days followed by 5 mg PO BID; or <i>edoxaban</i> 60 mg PO daily for 5 days after LMWH induction. For atrial fibrillation, <i>rivaroxaban</i> 20 mg PO daily, <i>apixaban</i> 5 mg PO BID, or <i>edoxaban</i> 60 mg PO daily	COMPLICATIONS —bleeding MONITOR —no routine monitoring assay is available

Class/Drugs	Mechanism	Indications	Usual dose	Complications/ monitoring
Direct thrombin inhibitors: <i>Desirudin</i> <i>Bivalirudin</i> <i>Argatroban</i> <i>Dabigatran</i>	DIRECT THROMBIN INHIBITORS (HIGHLY SELECTIVE). AT independent. In contrast to heparin, LMWH, and heparinoid, direct thrombin inhibitors can inhibit clot-bound thrombin because their sites for binding (active site ± exosite I) are not masked by fibrin. Does not depend on AT for action and thus unaffected by AT deficiency	HITT (<i>argatroban</i> , <i>bivalirudin</i>) ACS (<i>bivalirudin</i>) DVT prophylaxis (<i>desirudin</i>) VTE treatment (<i>dabigatran</i>) Atrial fibrillation (<i>dabigatran</i>)	For HITT, <i>argatroban</i> 2 µg/kg/min infusion; For DVT prophylaxis, <i>desirudin</i> 15 mg SC BID or <i>dabigatran</i> 220 mg PO daily; For VTE treatment, <i>dabigatran</i> 150 mg PO BID after 5 days of heparin. For atrial fibrillation, <i>dabigatran</i> 150 mg PO BID	COMPLICATIONS —bleeding MONITOR —aPTT is unreliable DOSE ADJUST DABIGATRAN —CrCl <30 mL/min

Related Topics
 DVT (p. 177)
 Hypercoagulable States (p. 174)
 Pulmonary Embolism (p. 12)

WARFARIN-INDUCED SKIN NECROSIS

CLINICAL FEATURES—usually within first few days of warfarin therapy (especially large loading doses) → significantly decreases protein C levels → transient hypercoagulable → erythematous macule → purpuric zone → necrotic lesion. Occurs over extremities, breast, trunk, and penis
TREATMENTS—immediately stop warfarin, give vitamin K, heparin IV, consider FFP or protein C concentrate. Lesion may continue to progress despite adequate anticoagulation

CORRECTION OF SUPRATHERAPEUTIC INR DUE TO WARFARIN USE

INR < 5—if no significant bleeding, rapid reversal is not indicated. Reduce warfarin dose or hold the next warfarin dose

CORRECTION OF SUPRATHERAPEUTIC INR DUE TO WARFARIN USE (CONT'D)

INR 5–9—if no significant bleeding, hold the next 1–2 doses of warfarin or omit the next dose of warfarin ± administer *vitamin K1* 2.5 mg PO. If rapid reversal required (e.g. bleeding or urgent surgery), FFP 10–20 mL/kg + *vitamin K1* 2–4 mg PO (↓ INR within 24 h), if INR remains high at 24 h, give additional *vitamin K1* 1–2 mg PO. May also consider prothrombin complex concentrate in selected cases

INR > 9—if no significant bleeding, hold warfarin and administer *vitamin K1* 2.5–5 mg PO. Use additional vitamin K1 if indicated by frequent INR monitoring. If serious bleeding, hold warfarin, administer FFP 20–30 mL/kg + *vitamin K1* 10 mg by slow IV infusion. Also can use unactivated prothrombin complex concentrate depending on volume status. If life-threatening or intracranial bleeding, hold warfarin therapy and administer unactivated prothrombin complex and *vitamin K1* 10 mg by slow IV infusion. Monitor INR and repeat as necessary

Transfusion Reactions

COMPLICATIONS OF TRANSFUSIONS

Adverse Effect	Pathophysiology	Onset and Symptoms	Treatments
Anaphylaxis	Recipient Ab against donor IgA, 1/40,000	Immediate. ↓ BP, bronchospasm, no fever	Stop transfusion, epinephrine, corticosteroids
ABO incompatibility	Recipient Ab against donor RBC major antigen, 1/40,000	Immediate. Fever, ↓ BP, CP, lumbar pain, hemoglobinuria, and bleeding	Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis
Acute hemolytic transfusion reaction (AHTR)	Recipient Ab against donor RBC minor antigen, 1/600,000	Acute/delay. Milder form of above	Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis
Delayed hemolytic transfusion reaction	Recipient Ab against donor RBC minor antigen, 1/2,500	Days after transfusion	Avoid donor red cells with minor antigens that recipient's alloantibodies recognize
Febrile reaction	Recipient Ab against donor WBC in transfused PRBC, 1/300; or transfused platelets (5 U), 1/10	End of transfusion. Fever, chills without other systemic symptoms	Antihistamine (<i>diphenhydramine</i> 50 mg IV × 1 dose), acetaminophen
Post-transfusion purpura (PTP)	Recipient Ab against donor platelets, 1/50,000	7–10 days after. Consumptive thrombocytopenia and purpura	Steroids, plasmapheresis
Urticarial transfusion reaction	Recipient IgE against donor antigens, 1/100 plasma-containing products	Acute. Pruritic rash	Antihistamine (<i>diphenhydramine</i> 50 mg IV × 1 dose)
Transfusion-related acute lung injury (TRALI)	Donor Ab against recipient WBC, 1/5,000 plasma-containing products	Acute. Hypoxemic, pulmonary edema	Supportive measures
Transfusion-associated circulatory overload (TACO)	Hypervolemia, 1/700	Acute/delay. Pulmonary edema	Diuresis, supportive measures
Septic transfusion	Platelets (5 U), 1/10,000 risk of symptomatic sepsis and 1/40,000 chance of death PRBC (1 U), 1/100,000 risk of symptomatic sepsis and 1/500,000 chance of death	Acute. Fever, ↓ BP	Stop transfusion, empiric antibiotics (vancomycin + broad spectrum beta-lactam or aminoglycoside)

Adverse Effect	Pathophysiology	Onset and Symptoms	Treatments
Air embolism	Venous air embolism, rare but may occur with complex transfusions such as apheresis	Acute. SOB, ↓ BP	Supportive measures
Transfusion associated graft vs. host disease (GVHD)	Donor lymphocytes against recipient tissue, very rare	Delay (up to 30 days post transfusion). Rash, hepatitis, diarrhea	Use irradiated blood products
Infection risk	HIV 1/10 million, HCV 1/3 million, HBV 1/72,000, HTLV1 1/2 million, West Nile virus < 1/1 million		

INVESTIGATIONS

BLOOD TESTS—CBC, peripheral smear, urea, Cr, LDH, indirect bilirubin, serum hemoglobin, Coombs test, PTT, INR, fibrinogen, blood C&S, send blood product for culture/typing

URINE TESTS—urinalysis

IMAGING—CXR

INDICATIONS FOR SPECIALLY PREPARED BLOOD PRODUCTS

WASHED TRANSFUSION PRODUCT (removes almost all serum proteins and most leukocytes)—IgA deficiency, previous anaphylactic transfusion reaction, febrile reactions not prevented by leukocyte reduction, severe urticarial reactions not prevented by the antihistamines

LEUKOCYTE-DEPLETED TRANSFUSION PRODUCT (removes most leukocytes)—preven-

INDICATIONS FOR SPECIALLY PREPARED BLOOD PRODUCTS (CONT'D)

tion of febrile reactions or TRALI, prevention of HLA alloimmunization (leukemia, aplastic anemia, chronic hemolytic anemia, MDS, MPS), transplant candidates, substitute for CMV-negative blood

IRRADIATED TRANSFUSION PRODUCTS (inhibits lymphocyte proliferation and prevents transfusion-associated graft vs. host disease [GVHD])—stem cell transplant recipients, recipients of directed donor transfusions from blood relatives, Hodgkin lymphoma

CMV-NEGATIVE TRANSFUSION PRODUCTS (screened)—CMV-negative transplant recipients (solid organ or bone marrow from CMV negative donors), antepartum transfusions for CMV-negative women

Approach to the Peripheral Blood Smear

Bain *NEJM* 2005;353(5)

TERMS

ANISOCYTOSIS—varying sizes of RBC
POIKILOCYTOSIS—varying shapes of RBC
HYPOCHROMIA—present when the central pale area >1/3 diameter. Occurs in iron deficiency, thalassemia, and lead poisoning

RBC INTRACELLULAR INCLUSIONS

BASOPHILIC STIPPLING—β-thalassemia, lead, or arsenic poisoning
HEINZ BODIES—G6PD deficiency, alpha thalassemia

RBC INTRACELLULAR INCLUSIONS (CONT'D)

PAPPENHEIMER BODIES—non-nucleated RBC containing such inclusions are called siderocytes, due to hyposplenism, thalassemia, and sideroblastic disorders. Nucleated RBC are termed sideroblasts

NUCLEATED RBC—acute systemic hypoxia, intense erythropoietin stimulation, infiltrative narrow processes (myelophthisis), extramedullary erythropoiesis

HOWELL-JOLLY BODIES—asplenia, megaloblastic hematopoiesis

RBC INTRACELLULAR INCLUSIONS (CONT'D)

POLYCHROMASIA—RBC with diffuse bluish discoloration due to the presence of RNA. Increased number of cells showing polychromasia indicates reticulocytosis

TELLTALE MORPHOLOGIES

TARGET CELLS—liver disease (especially obstructive jaundice, hepatitis), thalassemia, post-splenectomy, hemoglobinopathies (hemoglobin C and E), lecithin-cholesterol acyltransferase deficiency

FRAGMENTED CELLS (schistocytes, helmet cells)—microangiopathic hemolytic anemia (DIC, TTP, HUS), aortic valve prosthesis

TEAR DROP CELLS (dacrocytes)—myelophthisis, myelofibrosis with myeloid metaplasia (MMM), severe iron deficiency, thalassemia major. Disappear after splenectomy

TELLTALE MORPHOLOGIES (CONT'D)

BURR CELLS (echinocytes)—uremia, artifact
SPUR CELLS (acanthocytes)—chronic liver disease, abetalipoproteinemia, malabsorption, anorexia nervosa

SPHEROCYTES—due to loss of membrane surface area. Associated with autoimmune hemolytic anemia (microspherocytes), hereditary spherocytosis, and *Clostridium* infections

ELLIPTOCYTOSIS (ovalocytosis)—hereditary elliptocytosis, megaloblastosis

STOMATOCYTES—acute alcoholism, chronic liver disease, artifact

ROULEAUX—stacking of RBC suggestive of high ESR or hypergammaglobulinemia. Causes include malignancies (myeloma), infections, and connective tissue disease

SplénomegalyPozo et al. *Blood Rev* 2009;23(3)**DIFFERENTIAL DIAGNOSIS**

CONGESTIVE—right heart failure, constrictive pericarditis, tricuspid regurgitation, IVC obstruction, hepatic/splenic vein obstruction, cirrhosis with portal hypertension

INFILTRATIVE

- **MALIGNANCY**—lymphoma (Hodgkin, non-Hodgkin, hairy cell leukemia), leukemia (CLL, CML), myeloproliferative disorders (PV, CML, ET, MF), splenic tumor, metastasis
- **AMYLOIDOSIS**
- **SARCOIDOSIS**
- **CONGENITAL STORAGE DISEASES**—Gaucher, Niemann-Pick

REACTIVE

- **INFECTIONS**—**bacterial** (endocarditis, sepsis, TB, MAC), **viral** (mononucleosis, hepatitis), **fungal** (*Histoplasma*), **parasitic** (malaria, *Leishmania*, trypanosomiasis)
- **INFLAMMATORY**—rheumatoid arthritis (Felty syndrome), SLE, Still disease
- **SICKLE CELL, HEMOGLOBIN C, THALASSEMIA, IgG-mediated autoimmune hemolytic anemia**

CLINICAL FEATURES**SIX WAYS TO DISTINGUISH SPLEEN FROM LEFT KIDNEY**

1. Spleen has no palpable upper border
2. Spleen has a notch
3. Spleen moves inferomedially on inspiration while the kidney moves inferiorly

CLINICAL FEATURES (CONT'D)

4. Spleen is not usually ballotable unless gross ascites is present, but the kidney is because of its retroperitoneal position
5. The percussion note is dull over the spleen but is usually resonant over the kidney
6. A friction rub may occasionally be heard over the spleen, but never over the kidney because it is too posterior

RATIONAL CLINICAL EXAMINATION SERIES DOES THIS PATIENT HAVE SPLENOMEGALY?

NORMAL SPLEEN—<250 g [<0.55 lb] or 250 cm³, 12 cm by 7 cm [4.7 in. by 2.8 in.]. Anatomically, the spleen lies below the left diaphragm. It follows the curvature of left 10th rib and points anteriorly toward, the left colic flexure

	LR+	LR-
PERCUSSION		
Nixon method (right lateral decubitus position; percuss from lower level of pulmonary resonance in posterior axillary line downward obliquely to lower mid-anterior costal margin; >8 cm suggests splénomegaly)	3.6	0.41
Traube space (percuss space 6 th rib superiorly, mid-axillary line laterally and costal margin inferiorly; dullness suggests splénomegaly)	2.3	0.48

CLINICAL FEATURES (CONT'D)

	LR+	LR-
Castell method (percuss lowest intercostal space in the left anterior axillary line during both expiration and full inspiration; dullness suggests splenomegaly)	1.2	0.45
PALPATION		
One-handed palpation with patient supine	8.2	0.41
Middleton hooking maneuver	6.5	0.16

INVESTIGATIONS**BASIC**

- **LABS**—CBC, peripheral smear, AST, ALT, ALP, bili
- **MICROBIOLOGY**—blood C&S
- **IMAGING**—US abd

INVESTIGATIONS (CONT'D)**SPECIAL**

- **CT ABD**—weight = $0.43 \times \text{length} \times \text{width} \times \text{thickness}$
- **SCINTIGRAPHY**
- **MALIGNANCY WORKUP**—bone marrow biopsy, lymph node biopsy, laparoscopy/laparotomy

MANAGEMENT**TREAT UNDERLYING CAUSE**

SPLENECTOMY—see p. 292 for more details

SPECIFIC ENTITIES

CAUSES OF MASSIVE SPLENOMEGALY—lymphoma, hairy cell leukemia, CML, myelofibrosis, malaria, MAC in HIV, thalassemia major, sarcoidosis, Gaucher disease

Myeloproliferative NeoplasmsSpivak *NEJM* 2017;376(22)**DIFFERENTIAL DIAGNOSIS**

ESSENTIAL THROMBOCYTOSIS (ET)
POLYCYTHEMIA VERA (PV)
CHRONIC MYELOGENOUS LEUKEMIA (CML)
MYELOFIBROSIS (MF)

OTHERS—chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, systemic mastocytosis

PATHOPHYSIOLOGY

MYELOPROLIFERATIVE NEOPLASMS—associated with increased red blood cells (especially PV), white blood cells (especially CML), and/or platelets (especially ET). MPN should not be confused with myelodysplastic syndrome (MDS), which is associated with a decreased production of dysplastic blood cells. Both MPN and MDS can eventually lead to AML.

POLYCYTHEMIA VERA—see POLYCYTHEMIA (p. 159)

CHRONIC MYELOGENOUS LEUKEMIA (CML)—a stem cell disease with Philadelphia chromosome t(9;22) leading to fusion gene *bcr-abl*, found in erythroblasts, megakaryocytes, granulocytes, monocytes, and most lymphocytes. ↓ LAP. Chronic phase → accelerated phase → blast crisis, 2/3 myeloid, 1/3 lymphoid

PATHOPHYSIOLOGY (CONT'D)

- **CHRONIC PHASE** (5–6 years)—<15% blasts, <20% basophils, and <30% blasts plus promyelocytes
- **ACCELERATED PHASE** (6–9 months)—15–29% blasts, ≥20% basophils, ≥30% blasts + promyelocytes or platelets $<100 \times 10^3/\mu\text{L}$
- **BLAST CRISIS** (3–6 months)—≥30% blasts or extramedullary involvement (chloroma). Usually constitutional symptoms, worsening blood counts, and may have extra Ph chromosome, inv(17q), trisomy 8, and trisomy 19

CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)—also known as smoldering leukemia with persistent unexplained monocytosis. Classified as “MDS/MPS.” Clinical features include leukocytosis (monocytosis $>1.0 \times 10^3/\mu\text{L}$ for at least 6 months), anemia, thrombocytopenia, and splenomegaly

ESSENTIAL THROMBOCYTOSIS—see THROMBOCYTOSIS (p. 167)

MYELOFIBROSIS—↑ fibroblasts, massive spleen, teardrop RBC, nucleated RBC, large platelets

Related Topics

Polycythemia (p. 159)

Thrombocytosis (p. 167)

CLINICAL FEATURES

HISTORY—B symptoms (fever, night sweats, weight loss, pruritus), hyperviscosity symptoms (facial plethora, headache, visual or mental status changes, stroke, or another ischemic/thrombotic event)

PHYSICAL—splenomegaly

INVESTIGATIONS**BASIC**

- **LABS**—CBC, peripheral smear, reticulocyte count, uric acid
- **BONE MARROW BIOPSY**—always perform cytogenetic studies and stains for fibrosis (reticulin and collagen)

SPECIAL

- **GENETIC TESTING**—JAK2 mutation (sensitivity ~100% for PV and specific for other myeloproliferative disorders), calreticulin and cMPL mutations (ET), *bcr-abl* testing (CML), and NGS of hematopoietic genes to establish prognosis
- **EPO**—↓ in PV

DIAGNOSTIC AND PROGNOSTIC ISSUES

POLYCYTHEMIA VERA—median survival 20 years; ~14/100 transform to AML over 2 decades

CHRONIC MYELOGENOUS LEUKEMIA—median survival is now decades and risk of blast crisis is declining with *bcr-abl* tyrosine kinase inhibitors

ESSENTIAL THROMBOCYTOSIS—median survival 20 years; ~25/1,000 transform to AML over 3 decades

MYELOFIBROSIS—median survival 5 years; ruxolitinib improves symptoms, including painful splenomegaly; ~1/10 transforms to AML

MANAGEMENT

POLYCYTHEMIA VERA—phlebotomy 1–2/week, aspirin, hydroxyurea

CHRONIC MYELOGENOUS LEUKEMIA

- **CHRONIC PHASE**—tyrosine kinase inhibitors (imatinib, dasatinib, bosutinib, nilotinib, ponatinib). Imatinib is typically used in first line; consider other TKIs and stem cell transplant if imatinib-resistant CML
- **ACCELERATED PHASE**—allogeneic stem cell transplant is associated with 30–45% cure rate

MANAGEMENT (CONT'D)

- **BLAST CRISIS**—TKIs. Acute leukemia treatment
- ESSENTIAL THROMBOCYTOSIS**—aspirin, hydroxyurea, anagrelide
- MYELOFIBROSIS**—hydroxyurea, ruxolitinib, splenectomy, interferon α , thalidomide

TREATMENT ISSUES**RESPONSE CRITERIA FOR CML**

- **HEMATOLOGICAL RESPONSE**
 - **COMPLETE RESPONSE**—WBC $<10 \times 10^3/\mu\text{L}$ with no immature granulocytes and $<5\%$ basophils, platelet $<450 \times 10^3/\mu\text{L}$, and non-palpable spleen
 - **PARTIAL RESPONSE**—persistence of immature cells in peripheral blood, platelets $>450 \times 10^3/\mu\text{L}$ but $<50\%$ of pre-treatment levels, or persistent splenomegaly but $<50\%$ of pre-treatment size
- **CYTOGENIC RESPONSE** (FISH detection of the Philadelphia chromosome)
 - **MAJOR COMPLETE**—0% Ph+ cells
 - **MAJOR PARTIAL**—1–35% Ph+ cells
 - **MINOR**—36–65% Ph+ cells
 - **MINIMAL**—66–95% Ph+ cells
- **MOLECULAR RESPONSE** (*bcr-abl* transcript detection by RT-PCR)
 - **MR^{4.5}**—detectable disease with ratio of BCR-ABL1 to ABL1 (or other housekeeping genes) $\leq 0.0032\%$ (≥ 4.4 log reduction) on the international scale (IS) or undetectable disease in cDNA with $\geq 32,000$ ABL1 transcripts
 - **MR⁴**—detectable disease with ratio of BCR-ABL1 to ABL1 $\leq 0.01\%$ (≥ 4 log reduction) or undetectable disease in cDNA with $\geq 10,000$ ABL1 transcripts
 - **MR³**—detectable disease with ratio of BCR-ABL1 to ABL1 $\leq 0.1\%$ (≥ 3 log reduction)
 - **EARLY MOLECULAR RESPONSE**—BCR-ABL1 $\leq 10\%$ at 3 months

MONITORING FOR CHRONIC MYELOGENOUS LEUKEMIA—bone marrow annually, quantitative PCR every 3 months (repeat test in 4 weeks if >0.5 log increase)

IMATINIB RESISTANCE—*bcr-abl* mutations (T315I mutation confers tyrosine kinase inhibitor resistance), overexpression or amplification of *bcr-abl*

TREATMENT ISSUES (CONT'D)

DEFINITION OF TREATMENT FAILURE FOR CML PATIENTS ON IMATINIB THERAPY

Time	Suboptimal	Failure
3 months	BCR-ABL1 >10% or Ph+ >36–95%	No complete hematologic response or Ph+ >95%
6 months	BCR-ABL1 1–10% or Ph+ 1–35%	BCR-ABL1 >10% or Ph+ >35%
12 months	BCR-ABL1 >0.1–1%	BCR-ABL1 >1% or Ph+ >0
Anytime	Clonal chromosome abnormalities in Ph– cells	Loss of complete hematologic response, loss of complete cytogenetic response, loss of any molecular response, mutations, clonal chromosome abnormalities in Ph+ cells

Acute Myelogenous Leukemia

Döhner et al. *NEJM* 2015;373(12)

2017 European LeukemiaNet (ELN) Recommendations AML

HEMATOLOGIC MALIGNANCIES OVERVIEW

MYELO—bone marrow. Myeloproliferative disorders (PV, CML, ET, and MF) involve cell accumulation, while myelodysplastic disorders involve abnormal bone marrow cell growth. Both disorders have risk of transformation to acute myeloid leukemia

MYELOID—neutrophils, monocytes, macrophages, eosinophils, basophils, mast cells, erythrocytes, platelets, and their precursors. Myeloid malignancies include AML and CML

LYMPOID—B cells, T cells, natural killer cells. Lymphoid malignancies include ALL, CLL, and all lymphomas

LEUKEMIA—malignant cells in blood and/or bone marrow. May be myeloid (AML, CML) or lymphoid* (LL/ALL, SLL/CLL) in origin. Myeloid leukemia seldom presents in lymph nodes

- **ACUTE LEUKEMIA**—involves immature blast cells occupying ≥20% of the marrow cellularity. Aggressive course
- **CHRONIC LEUKEMIA**—involves mature differentiated cells. Indolent course

LYMPHOMA—malignancy of lymphoid origin and presents more in lymphoid organs

- **HODGKIN LYMPHOMA**—B cell (Reed–Sternberg cell)
- **NON-HODGKIN LYMPHOMA**—B, T, or NK cells

*lymphoblastic lymphoma (LL) = acute lymphoblastic leukemia (ALL). Small lymphocytic lymphoma (SLL) = chronic lymphocytic leukemia (CLL)

PATHOPHYSIOLOGY

EPIDEMIOLOGY

- **INCIDENCE**—1–2% of all cancers, 90% of all acute leukemias in adulthood, mean age 65
- **MORTALITY**—1.5% of all cancers

PATHOPHYSIOLOGY (CONT'D)

RISK FACTORS

- **FAMILY HISTORY**—family history (3 ×), Down syndrome Klinefelter, Fanconi syndrome, Bloom, ataxia telangiectasia, neurofibromatosis
- **ENVIRONMENTAL**—previous chemotherapy (alkylating agents [melphalan, cyclophosphamide, chlorambucil, temozolomide], topoisomerase II inhibitors [anthracyclines, etoposide]), radiation, benzene
- **DISEASES**—MDS, MPS (PV, CML, ET, MF), PNH, aplastic anemia

DISTINGUISHING FEATURES BETWEEN THERAPY-RELATED AMLs

	Alkylating agents	Topoisomerase II inhibitors
Latency	5–7 years	2–3 years
MDS pre-AML	Yes	No
AML types	All, M1–2	M4–5
Karyotype	–5, –7	11q23, 21q22, inv16
Prognosis	Poor	Poor except for Inv16 karyotype

CLINICAL FEATURES

PANCYTOPENIA—weakness, fatigue, infections, gingival bleed, ecchymosis, epistaxis, menorrhagia

BONE PAIN—ribs, sternum, long bones

CUTANEOUS LESIONS—leukemic cutis (especially M4, M5), chloromas (skin local collection of

CLINICAL FEATURES (CONT'D)

blasts, granulocytic sarcoma especially M2), gum hypertrophy (M5)

CNS LEUKEMIA (especially M4, M4EO, and M5)

DIC—associated with M3 subtype

NOTE—lymphadenopathy, hepatosplenomegaly not common

INVESTIGATIONS**BASIC**

- **LABS**—CBC, smear (Auer rods), lytes, urea, Cr, Ca, PO₄, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen
- **BONE MARROW BIOPSY (>20% BLASTS)**—with flow cytometry and cytogenetic / molecular analyses

SPECIAL

- **LUMBAR PUNCTURE**—CSF for cytology (risk of CNS involvement greatest with high circulating blasts, elevated LDH, and monocytic variants of AML) and flow cytometry
- **HLA TESTING**—to assist in obtaining HLA-matched platelets if needed during treatment and to find HLA-matched allogeneic bone marrow

MANAGEMENT**AGE 16–60**

- **INDUCTION CHEMOTHERAPY**—3+7 induction consisting of an anthracycline (daunorubicin, idarubicin or mitoxantrone) × 3 days and continuous infusion cytarabine × 7 days. 60–80% achieve remission (only ~30% cured). If no complete remission, repeat induction chemotherapy and proceed as high risk disease
- **CONSOLIDATION TREATMENT (AFTER COMPLETE REMISSION)**
 - **FAVORABLE GENETIC RISK**—2–4 cycles of intermediate dose cytarabine
 - **INTERMEDIATE OR ADVERSE RISK**—allogeneic stem cell transplant (SCT). Autologous SCT may be considered for selected patients without high risk features. If SCT not possible, consolidation therapy with 2–4 cycles of intermediate dose cytarabine or combination chemotherapy (mitoxantrone-cytarabine) for adverse risk AML
- **RELAPSE**—SCT if donor available (preferred); otherwise, salvage chemotherapy

AGE >60

- **INDUCTION CHEMOTHERAPY**—for patients with favorable or intermediate risk AML and no co-existing conditions, 3+7 induction regimen as in younger patients with or without dose reduction. 40–50% achieve remission.

MANAGEMENT (CONT'D)

Otherwise, consider low intensity therapies, hydroxyurea cytoreduction, or no further treatment

- **CONSOLIDATION TREATMENT (AFTER COMPLETE REMISSION)**
 - **FAVORABLE GENETIC RISK AND NO CO-EXISTING CONDITIONS**—2–3 cycles of intermediate dose cytarabine
 - **INTERMEDIATE, ADVERSE RISK OR CO-EXISTING CONDITIONS**—clinical trials or no treatment

Related Topics

Febrile Neutropenia (p. 250)

Tumor Lysis Syndrome (p. 244)

TREATMENT ISSUES

COMPLETE REMISSION—normal BM cellularity, <5% blasts in BM, none with leukemic phenotype or abnormal cytogenetics. Lumbar puncture after complete remission with induction chemotherapy, especially those with monoblastic phenotype

SPECIFIC ENTITIES**ACUTE PROMYELOCYTIC LEUKEMIA (APL)**

- **PATHOPHYSIOLOGY**—a unique sub-type of AML characterized by a translocation between chromosomes 15 and 17 (*t(15;17)*) that creates a new fusion gene combining the retinoic acid receptor α (*RAR\alpha*) gene with the promyelocytic leukemic (*PML*) gene. This codes for a new protein that blocks myeloid differentiation
- **TREATMENTS**—relieving this block with all-trans retinoic acid (ATRA) is a critical therapeutic intervention, usually begun with merely the suspicion of APL in order to minimize the bleeding and thrombotic complications that are the hallmark of APL. All-trans retinoic acid is always combined with another agent (often an anthracycline or non-myelosuppressive arsenic trioxide). APL is the most curable AML, with almost 90% of those affected cured with chemotherapy

Jimenez et al. *Oncotarget* 2020;11(11)

CLONAL HEMATOPOIESIS OF INDETERMINATE PROGNOSIS (CHIP)

—mutations in hematopoietic regulating genes are a natural effect of aging, affecting perhaps 90% of those >70 years. CHIP is defined as specific mutations in DNMT3A, TET2, and/or ASXL1 occurring at a variant allele frequency of >2%. CHIP patients will progress to myelodysplastic syndrome (MDS) at a

SPECIFIC ENTITIES (CONT'D)

rate of 0.5% to 1% per year. CHIP is a risk factor for cardiovascular diseases; 30–40% of these patients die from heart disease and this mortality greatly exceeds mortality from MDS

Jaiswal et al. *Science* 2019;366(6465)

MYELODYSPLASTIC SYNDROME—opposite of myeloproliferative disorders, decreased cell counts

- **SUBTYPES**—refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with multilineage dysplasia, refractory anemia with multilineage dysplasia and ringed sideroblasts, refractory anemia with excess blasts (RAEB) 5–10% blasts, refrac-

SPECIFIC ENTITIES (CONT'D)

tory anemia with excess blasts in transformation (RAEB-t) 10–19% blasts, MDS unclassified. RA and RARS are at low risk of transforming to AML (i.e. >20% blasts), while the rest are at high risk

- **DIAGNOSIS**—peripheral blood smear (RBC with abnormal morphologic features, dysgranulopoiesis with Pelger-Huët deformity, nuclear atypia and hypogranulation, monocytosis), bone marrow biopsy
- **PROGNOSIS**—the revised international prognostic scoring system (IPSS-R) is based on hemoglobin, neutrophil count, platelets, bone marrow blasts and cytogenetic category

Risk group	Score	% of patients	Median survival (years)	Median time to 25% AML evolution (years)
Very low	≤1.5	19%	8.8	14.5
Low	>1.5–3	38%	5.3	10.8
Intermediate	>3–4.5	20%	3.0	3.2
High	>4.5–6	13%	1.6	1.4
Very high	>6	10%	0.8	0.7

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—transfusions, erythropoietin/darbepoetin (for patients with serum EPO <500 ng/mL and low transfusion requirement), treat infections early, lenalidomide (deletion 5q low-

SPECIFIC ENTITIES (CONT'D)

intermediate MDS), 5-azacytidine, decitabine, combination chemotherapy, allogeneic stem cell transplant

Acute Lymphoblastic Leukemia

Bassan et al. *J Clin Oncol* 2018;36(35)
Malard et al. *Lancet* 2020;395(10230)

PATHOPHYSIOLOGY

RISK FACTORS FOR ALL—age, previous chemotherapy or radiation, Down syndrome

CLINICAL FEATURES

PANCYTOPENIA—weakness, fatigue, infections, gingival bleed, ecchymosis, petechiae, epistaxis, menorrhagia

ORGAN INVOLVEMENT—lymphadenopathy, hepatomegaly, splenomegaly, bone pain, cranial nerve palsies, headaches

CLINICAL FEATURES (CONT'D)**DISTINGUISHING FEATURES BETWEEN AML AND ALL**

	AML	Precursor ALL
Blasts	Larger	Small
Auer rods	+	–
TdT	–	+
Myeloperoxidase	+	–

INVESTIGATIONS**BASIC**

- **LABS**—CBC, smear, lytes, urea, Cr, Ca, PO₄, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen, flow cytometry of peripheral blood (immunophenotyping)
- **BONE MARROW BIOPSY**—>20% blast, flow cytometry for immunophenotyping, cytogenetic analysis, next generation sequencing
- **LUMBAR PUNCTURE**—CSF for cytology
- **TISSUE BIOPSY**—lymph node, skin, mediastinal mass

SPECIAL

- **IMAGING**—evaluate cardiac function prior to anthracycline therapy
- **HLA TESTING**—to assist in obtaining HLA-matched platelets if needed during treatment and to find HLA-matched allogeneic bone marrow
- **FERTILITY**—testing and preservation for young adults and adults who are still planning a family

PROGNOSTIC ISSUES

PROGNOSIS—while childhood ALL is curable in 85% of cases, adult ALL has a worse prognosis, with a 5-year survival of 40%

PROGNOSTIC FACTORS—unfavorable risk factors include minimal residual disease post induction therapy (most important), time to response >4 w, age >35, WBC >30 × 10⁹/L, CNS involvement, and cytogenetic abnormalities such as hypodiploidy (<45 chromosomes/cell), t(9;22) [BCR-ABL fusion, 20–50% of adults], t(4;11) [MLL-AF4 fusion, 5–6% of adults], KMT2A (MLL-r fusion at 11q23)

MANAGEMENT

INDUCTION THERAPY—combination chemotherapy with high-dose cyclophosphamide, prednisone, vincristine, anthracycline ± asparaginase. Complete response 80–90%. Management of specific subgroups with worse prognosis include

- **PH + ALL**—add imatinib, dasatinib, nilotinib or ponatinib
- **CD20+ ALL**—add rituximab
- **T-CELL ALL**—treat with cyclophosphamide-containing regimens

CNS PROPHYLAXIS—to start after remission with intrathecal methotrexate or high-dose intravenous methotrexate. Consider cranial radiation for patients at high risk of CNS relapse

INTENSIFICATION/CONSOLIDATION THERAPY

- **GOOD RISK**—consolidation chemotherapy with various combinations of cyclophosphamide, 6-mercaptopurine, cytarabine, vincristine, and doxorubicin
- **POOR RISK**—allogeneic SCT if donor available; otherwise, consolidation chemotherapy

MAINTENANCE THERAPY—combination of glucocorticoids, methotrexate, 6-mercaptopurine, vincristine, and intrathecal chemotherapy

TREATMENT ISSUES

SURVIVORSHIP ISSUES—risk of secondary malignancies, neurologic sequelae, cardiotoxicity, infertility, depression, anxiety, and fatigue

Related Topics

- Febrile Neutropenia (p. 250)
- Tumor Lysis Syndrome (p. 244)

Chronic Lymphocytic Leukemia

Strati et al. *Blood* 2015;126(4)
2018 iwCLL Guidelines CLL

DIFFERENTIAL DIAGNOSIS OF LYMPHOCYTOSIS**NEOPLASTIC**

- **BENIGN MONOCLONAL LYMPHOCYTOSIS** (presence of a clonal B-cell population in the peripheral blood with fewer than 5 × 10⁹/L B-cells and no other signs of a lymphoproliferative disorder)
- **CHRONIC LYMPHOCYTIC LEUKEMIA (CLL, most common cause)**

DIFFERENTIAL DIAGNOSIS OF LYMPHOCYTOSIS (CONT'D)

- **PROLYMPHOCYTIC LEUKEMIA (B and T cells)**
- **LEUKEMIC PHASE OF LYMPHOMAS**—mantle cell lymphoma, lymphoplasmacytic lymphoma, follicular lymphoma, marginal zone lymphoma, hairy cell leukemia
- **LARGE GRANULAR CELL LYMPHOCYTE LEUKEMIA**
- **INFECTIONS**—pertussis, infectious mononucleosis, CMV, hepatitis, toxoplasmosis

PATHOPHYSIOLOGY

WHO CLASSIFICATION—CLL is identical to small lymphocytic lymphoma (SLL, mature B-cell non-Hodgkin lymphoma). Traditionally, CLL diagnosis is made from peripheral blood, while SLL diagnosis is made from lymph node biopsy

TRANSFORMATION OF CLL—prolymphocytic leukemia 10%, diffuse large B-cell lymphoma (Richter transformation) 3–10%, Hodgkin disease 0.5%, multiple myeloma 0.1%

CLINICAL FEATURES

ORGAN INFILTRATION—lymphadenopathy (80%), splenomegaly (50%), hepatomegaly, skin and lung infiltration, gastric erosions

PERIPHERAL BLOOD—lymphocytosis with smudge cells, anemia, thrombocytopenia

CONSTITUTIONAL—weight loss, fever, night sweats, fatigue, anorexia

ASSOCIATED SYNDROMES—ITP, hemolytic anemia, pure red cell aplasia, cryoglobulinemia, MPGN, hypogammaglobulinemia, monoclonal gammopathy

SECOND MALIGNANCIES—non-melanoma skin cancer 4.7%, sarcomas 3.3%, kidney 2.8%, lung 2%, prostate 1.5%

INVESTIGATIONS**BASIC**

- **LABS**—CBC, smear (smudge cells), lytes, urea, Cr, Ca, PO₄, Mg, uric acid, LDH, β₂ microglobulin, albumin, quantitative immunoglobulin, serum protein electrophoresis, urinary protein electrophoresis
- **PERIPHERAL BLOOD FLOW CYTOMETRY FOR SURFACE MARKERS**

SPECIAL

- **BONE MARROW BIOPSY WITH CYTOGENETICS, FISH AND NEXT GENERATION SEQUENCING**
- **LYMPH NODE BIOPSY**
- **MICROBIOLOGY**—monospot test, hepatitis serology if need to rule out other causes

DIAGNOSTIC AND PROGNOSTIC ISSUES**NCI WORKING GROUP DIAGNOSTIC CRITERIA**

- **PERIPHERAL BLOOD**—absolute lymphocyte count in the $>5 \times 10^3/\mu\text{L}$, with ≥ 1 B-cell marker (CD19, CD20, CD23) and CD5; $>55\%$ atypical cells
- **BONE MARROW**—a normocellular to hypercellular marrow with $>20\%$ clonal lymphocytes. Interstitial/nodular pattern (70%) has a better prognosis than diffuse/extensive pattern (30%)

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **IMMUNOPHENOTYPE**—CD5+, CD19+, CD20+ dim, CD23+, CD43+, CD10–, SIg+ dim
- **NOTE**—for patients with lymphocyte count $5\text{--}10 \times 10^3/\mu\text{L}$, lymphocyte phenotyping is required

RAI STAGING

- 0** lymphocytosis in blood or bone marrow. Median survival >150 months
- I** lymphocytosis + lymphadenopathy. Median survival 101 months
- II** lymphocytosis + organomegaly. Median survival 71 months
- III** lymphocytosis + anemia (<110 g/L [<11 g/dL]). Median survival 19 months
- IV** lymphocytosis + thrombocytopenia ($<100 \times 10^3/\text{mL}$). Median survival 19 months

BINET STAGING

- A** <3 lymphoid-bearing sites enlarged. Median survival >10 years
- B** ≥ 3 lymphoid-bearing sites enlarged. Median survival 5 years
- C** anemia (<100 g/L [10 g/dL]) or thrombocytopenia ($<100 \times 10^3/\mu\text{L}$). Median survival 2 years

ADVERSE PROGNOSTIC FACTORS OF CLL—higher Rai stage, high Binet stage, diffuse pattern on bone marrow biopsy, lymphocyte doubling time <1 year (5-year survival vs. 12-year survival), CD38+, unmutated IgV_H genes, ZAP70 positive, 17p deletion, 11q deletion, trisomy 12, mutated TP53

FEATURES SUGGESTIVE OF TRANSFORMATION—*new onset* localized lymph node enlargement, B symptoms (without obvious increase in tumor burden), hypercalcemia, elevation in LDH, or extranodal disease other than bone marrow and liver, rapid increase of splenomegaly, rapid elevation of lymphocytosis

MANAGEMENT

YOUNGER AND RELATIVELY HEALTHY—ibrutinib \gg bendamustine + anti-CD20 therapy, or fludarabine, cyclophosphamide and rituximab

MANAGEMENT (CONT'D)

OLDER AND FAVORABLE PROGNOSIS—ibrutinib >> bendamustine + anti-CD20 therapy, or obinutuzumab (anti-CD20) ± ibrutinib

UNFAVORABLE PROGNOSIS (del(17p) or *TP53* mutated)—ibrutinib > alemtuzumab (anti-CD52) ± rituximab or obinutuzumab or clinical trial

SPECIFIC ENTITIES**HAIRY CELL LEUKEMIA**

- **PATHOPHYSIOLOGY**—rare indolent non-Hodgkin lymphoma with mononuclear cells displaying cytoplasmic projections giving a hairy appearance. Secretes fibronectin, cytokines, and TNF-causing bone marrow fibrosis
- **DIAGNOSIS**—based on morphological evidence of hairy cells, an HCL immunologic score of three or four based on the CD11C, CD103,

SPECIFIC ENTITIES (CONT'D)

CD123, and CD25 expression. Also, the bone marrow biopsy, which makes it possible to specify the degree of tumoral medullary infiltration and the presence of BRAF V600E somatic mutation

- **CLINICAL FEATURES**—splenomegaly (90%), tricytopenia (fatigue, recurrent infections, thrombocytopenia), and lymphocytosis. Lymphadenopathy is uncommon
- **TREATMENTS**—treat only if symptomatic (cytopenia, splenomegaly, B symptoms). Either cladribine (2-CdA) or pentostatin monotherapy as standard first-line treatment. Second-line therapy includes rituximab plus an alternative purine analogue, or vemurafenib (if *B-raf* mutant)

Maitre et al. *Am J Hematol* 2019;94(12)

Hodgkin Lymphoma

Connors et al. *Nat Rev Dis Primers* 2020;6(1)

PATHOPHYSIOLOGY**HISTOLOGIC TYPE**

- **CLASSICAL HODGKIN LYMPHOMA** (95%)—B-cell lymphoma characterized by the presence of Reed–Sternberg cells. CD15 and CD30 positive. Spreads in orderly fashion to contiguous nodal regions
 - **NODULAR SCLEROSIS** (70%)—more common in females, above diaphragm involvement (mediastinal mass). Three grades include lymphocyte predominant (G1), mixed (G2), and syncytial (G3)
 - **MIXED CELLULARITY** (20–25%)—more common in men. Tend to be EBV+. Retroperitoneal disease. Worse prognosis
 - **LYMPHOCYTE RICH** (5%)—more common in older males, peripheral lymph nodes. Excellent prognosis
 - **LYMPHOCYTE DEPLETED** (2%)—liver and marrow involvement with relative sparing of lymph nodes. Worse prognosis
- **NODULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA** (5%)—males, upper neck involvement. Characterized by popcorn cells. Slow progression, excellent prognosis. CD20 positive. Late relapse more common

RISK FACTORS

- **FAMILY HISTORY**
- **ENVIRONMENTAL**—wood workers, farmers, meat workers

PATHOPHYSIOLOGY (CONT'D)

- **DISEASES**—mononucleosis (EBV infection 3 ×), AIDS, bone marrow transplant

CLINICAL FEATURES**SYMPTOMS**

- **MASS EFFECT**—lymphadenopathy, hepatosplenomegaly, mediastinal/abdominal/pelvic masses may cause local destruction, obstruction, and compression
- **HEMATOLOGIC**—anemia, thrombocytopenia, lymphocytosis, eosinophilia
- **CONSTITUTIONAL**—B-symptoms specifically refer to weight loss >10% over 6 months, fever >38 °C [>100.4 °F], and drenching night sweats. Other constitutional symptoms include fatigue, anorexia, pruritus
- **PARANEOPlastic SYNDROMES**—**alcohol-induced pain, skin** (skin infiltration, erythema multiforme, erythema nodosum, necrotizing lesions, ichthyosis, acrokeratosis, urticaria), **neurologic** (paraneoplastic cerebellar degeneration, chorea, limbic encephalitis, subacute sensory neuropathy, subacute lower motor neuropathy, stiff man syndrome), **renal** (minimal change disease, FSGS), **hypercalcemia**

CLINICAL FEATURES (CONT'D)**DISTINGUISHING FEATURES BETWEEN MALIGNANT AND NON-MALIGNANT LYMPHADENOPATHY**

	Malignancy	Benign
Size	Larger, grows	Smaller (<1 cm)
Consistency	Rubbery, firm	Soft
Mobility	Immobile	Mobile
Matted	Yes	No
Tenderness	No	Yes

STAGING**COTSWOLDS STAGING (MODIFIED FROM ANN ARBOR STAGING)**

- I** Single node region or lymphoid structure (spleen, thymus, Waldeyer ring)
- II** Two or more node regions on the same side of diaphragm. All nodal disease within the mediastinum is considered to be a single lymph node region, and hilar involvement constitutes an additional site of involvement.
- The number of anatomic regions should be indicated by a subscript (e.g. II₂)
- III** Involvement on both sides of diaphragm. III₁ indicates involvement of the spleen or splenic hilar, celiac, or portal nodes. Stage III₂ indicates involvement of the paraaortic, iliac, inguinal, or mesenteric nodes
- IV** Diffuse or disseminated foci of involvement of one or more extralymphatic sites (e.g. bone marrow, extranodal sites that cannot be included in one radiation field)

DESIGNATIONS

- E**—extralymphatic site (i.e. involvement outside of lymph nodes, spleen, thymus, and Waldeyer ring) or involvement by direct extension
- X**—bulky disease defined as mediastinal mass >1/3 of internal transverse diameter of the thorax at the level of T5/6 interspace or >10 cm [>3.9 in.] maximum dimension of a nodal mass
- A**—no B symptoms
- B**—weight loss >10% over 6 months, fever >38 °C [>100.4 °F], drenching night sweats

INVESTIGATIONS**BASIC**

- LABS**—CBC, peripheral smear, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, LDH, ESR, albumin, quantitative immunoglobulin, serum protein electrophoresis, HCV, HBV, and HIV serology
- IMAGING**—CXR, CT chest/abdomen/pelvis, PET scan
- LYMPH NODE BIOPSY**—referral to surgery

SPECIAL

- BONE MARROW BIOPSY**—if B symptoms, Hb <120 g/L [<12 g/dL] in women, Hb <130 g/L [<13 g/dL] in men, WBC <4 × 10³/μL, platelets <125 × 10³/μL
- ENT EXAMINATION**—stage IA or IIA with upper cervical lymph node involvement
- MRI SPINE**—if suspect spinal cord compression
- MUGA SCAN OR ECHOCARDIOGRAM**—evaluate cardiac function prior to anthracycline therapy
- GALLIUM SCAN**—stage IA or IIA without intrathoracic involvement

PROGNOSTIC ISSUES

PROGNOSTIC FACTORS FOR EARLY STAGE DISEASE—age >50, bulky disease, ESR >50 mm/h without B symptoms or ESR >30 mm/h with B symptoms, anemia

INTERNATIONAL PROGNOSTIC FACTOR PROJECT SCORE FOR ADVANCED HODGKIN LYMPHOMA (HASENCLEVER SCORE)

- FACTORS**—age >45, male gender, Ann Arbor clinical stage IV, albumin <40 g/L [<4 g/dL], hemoglobin <105 g/L [<10.5 g/dL], WBC >15 × 10³/μL, lymphocyte <0.6 × 10³/μL, or <8% of total WBC count
- SCORING**—1 point per factor, with a score of 0–7
- UTILITY**—the 5-year progression-free survival was 84%, 77%, 67%, 60%, 51%, 42% for scores of 0, 1, 2, 3, 4, and 5–7, respectively

MANAGEMENT**CLASSICAL HODGKIN LYMPHOMA**

- LIMITED STAGE** (stage IA, IIA, or IB with mass <10 cm)—ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) × 2–3 cycles followed by involved field radiotherapy
- ADVANCED STAGE** (all other stages)—ABVD (doxorubicin, bleomycin, vinblastine,

MANAGEMENT (CONT'D)

dacarbazine) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) \times 6 cycles. Reassess with PET-CT. If residual disease, consider involved field irradiation

- **REFRACTORY OR RELAPSED DISEASE**—BEAM (BCNU, etoposide, cytarabine, melphalan) or CBV (cyclophosphamide, BCNU, etoposide) followed by autologous stem cell transplant and brentuximab maintenance. For frail patients, consider brentuximab (anti-CD30 antibody conjugated to auristatin), or immune checkpoint inhibitors should be considered. Overall, 40–50% with refractory disease and 60–70% with first relapse can be cured

NOULAR LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA

- **LIMITED STAGE** (stage IA)—involved field radiotherapy

Non-Hodgkin Lymphoma**DIFFERENTIAL DIAGNOSIS OF LYMPHADENOPATHY****INFECTIONS**

- **BACTERIAL**—local infections, brucellosis, leptospirosis, lymphogranuloma venereum, typhoid fever
- **ATYPICAL**—TB, syphilis, Lyme disease
- **VIRAL**—HIV, EBV, HSV, CMV, HBV, mumps, measles, rubella, dengue fever
- **FUNGAL**—histoplasmosis, coccidioidomycosis, cryptococcosis
- **PARASITIC**—toxoplasmosis

NEOPLASTIC

- **LYMPHOMA**—Hodgkin, non-Hodgkin
- **LEUKEMIA**
- **METASTATIC CANCER**
- **LYMPHOPROLIFERATIVE**—Castleman disease, angioimmunoblastic lymphadenopathy, autoimmune lymphoproliferative disease

INFLAMMATORY—RA, SLE, dermatomyositis, Still disease, eosinophilic granulomatosis with polyangiitis

INFILTRATIVE—sarcoidosis, amyloidosis, histiocytosis, chronic granulomatous disease

OTHERS—**medications** (phenytoin), **endocrine** (hypothyroidism, Addison disease), serum sickness

PATHOPHYSIOLOGY**HISTOLOGIC TYPE (WHO CLASSIFICATION)**

- **INDOLENT B-CELL LYMPHOMAS**
 - **FOLLICULAR LYMPHOMA** (FL, 25%)—grade I (0–5 centroblasts/high power field), II

MANAGEMENT (CONT'D)

- **LIMITED STAGE** (IB, IIA or IIB)—ABVD \times 2 cycles followed by involved field radiotherapy
- **ADVANCED STAGE** (all other stages)—ABVD or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) \times 6 cycles. Reassess with PET-CT. If residual disease, consider involved field irradiation

TREATMENT ISSUES

FOLLOW-UP—every 3 months for the first 2 years, every 6 months for the next 3 years, then annually. Pay particular attention to relapse (10–30%), hypothyroidism (50%), dental caries, and second malignancies (breast, lung, esophageal, stomach, thyroid, melanoma, cervical, AML)

PATHOPHYSIOLOGY (CONT'D)

(6–15 centroblasts/high power field), IIIA (>15 centroblasts/high power field, centrocytes present)

- **MARGINAL ZONE LYMPHOMA** (MZL, 5%)—MALT, nodal, splenic
- **MANTLE CELL LYMPHOMA** (MCL, 7%)—mantle zone, nodular, diffuse, blastoid variant
- **SMALL LYMPHOCYTIC LYMPHOMA** (SLL, 5–10%)—identical to chronic lymphocytic leukemia in pathologic characteristics, but treated as low grade B-cell lymphoma
- **HAIRY CELL LEUKEMIA** (HCL)
- **LYMPHOPLASMACYTIC LYMPHOMA** (LPL, 2–3%)—also called Waldenström macroglobulinemia
- **PLASMA CELL MYELOMA/PLASMACYTOMA** (MM)
- **AGGRESSIVE B-CELL LYMPHOMAS**
 - **FOLLICULAR LYMPHOMA** (FL)—grade IIIB (sheets of centroblasts)
 - **DIFFUSE LARGE B-CELL LYMPHOMA** (DLBCL, 30–40%)—clinical subtypes include primary mediastinal B-cell lymphoma, primary effusion lymphoma (HHV8), and intravascular B-cell lymphoma. Pathologic subtypes include T-cell-rich B-cell lymphoma, anaplastic large cell lymphoma, centroblastic, and immunoblastic
 - **DOUBLE-HIT DLBCL** (both *c-myc* and either *bcl2* or *bcl6* translocations)
- **LEUKEMIC B-CELL LYMPHOMAS**
 - **BURKITT LYMPHOMA** (BL)

PATHOPHYSIOLOGY (CONT'D)

- PRECURSOR B LYMPHOBLASTIC LYMPHOMA (ALL)
- **INDOLENT T-CELL LYMPHOMAS**
 - MYCOSIS FUNGOIDES (MF)
 - PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL (PCALC)
 - LYMPHOPROLIFERATIVE DISEASE OF LARGE GRANULAR LYMPHOCYTES (LGL)
- **INDOLENT NATURAL KILLER CELL LYMPHOMAS**
 - NATURAL KILLER CELL LARGE GRANULAR LYMPHOCYTE LEUKEMIA (NK-LGL)
- **AGGRESSIVE T-CELL LYMPHOMAS**
 - PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED (PTCL-NOS)
 - PERIPHERAL T-CELL LYMPHOMA, SPECIFIED—angiimmunoblastic (AILD++ type), nasal T/NK-cell type, subcutaneous panniculitic, intestinal enteropathy associated, hepatosplenic, anaplastic large cell including null cell
- **LEUKEMIC T-CELL LYMPHOMAS**
 - ADULT T-CELL LYMPHOMA/LEUKEMIA (HTLV)
 - PRECURSOR T LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

RISK FACTORS

- **FAMILY HISTORY**
- **ENVIRONMENTAL**—previous immunosuppressive therapy, radiation, allogeneic stem cell transplant, pesticides, agricultural chemicals, smoking, hair dyes, geography (e.g. risk of Burkitt lymphoma is 50 × higher in Africa than in the USA)
- **DISEASES**—infections (HIV, EBV, HHV8, HCV, HTLV, *Helicobacter pylori*), inflammatory disorders (RA, SLE, Sjögren syndrome, mixed cryoglobulinemia, inflammatory bowel disease), inherited immune defects

CLASSIC TRANSLOCATIONS IN LYMPHOMA

- **MANTLE CELL LYMPHOMA**—t(11;14) in 95%, cyclin D1 (bcl1)
- **FOLLICULAR LYMPHOMA**—t(14;18) in 85%, anti-apoptotic protein (bcl2)
- **DIFFUSE LARGE CELL LYMPHOMA**—t(3;14) in 40%, zinc finger transcription factor (bcl6)
- **MALT**—t(1;14) in < 5%, bcl10
- **BURKITT LYMPHOMA**—t(8;14), t(2;8), or t(8;22) in 100%, c-myc overexpression

INFECTIONS AND LYMPHOMA

- **EBV**—Hodgkin lymphoma, Burkitt lymphoma, post-transplant lymphoproliferative disorders, primary CNS lymphoma
- **HCV**—splenic marginal zone lymphoma
- **HHV8** (also known as Kaposi sarcoma herpes virus)—Castleman disease, primary effusion lymphoma
- **HIV**—primary CNS lymphoma

PATHOPHYSIOLOGY (CONT'D)

- **HTLV**—adult T-cell leukemia/lymphoma
- **BORRELIA BURGDORFERI**—cutaneous marginal zone lymphoma
- **CAMPYLOBACTER JEJUNI**—small bowel marginal zone lymphoma
- **CHLAMYDIA PSITTACI**—eye marginal zone lymphoma
- **H. PYLORI**—gastric MALT

TRANSFORMATION OF INDOLENT LYMPHOMA

—10% of SLL, MZL, and LPL and 60% of FL eventually transform into aggressive DLBCL. Features suggestive of transformation include rapid local progression, progression at unusual extranodal sites (CNS, lungs, soft tissue), acute rise in LDH, hypercalcemia, and new onset B symptoms

CLINICAL FEATURES**SYMPTOMS**

- **MASS EFFECT**—lymphadenopathy (occipital, posterior auricular, preauricular, mandibular, submental, cervical, supra- and infraclavicular, Waldeyer ring [tonsils, base of tongue, nasopharynx], epitrochlear, axillary, inguinal, popliteal); hepatosplenomegaly; mediastinal/abdominal/pelvic/testicular/CNS masses may cause local destruction, obstruction, and compression
- **HEMATOLOGIC**—anemia, thrombocytopenia, neutropenia, lymphocytosis
- **CONSTITUTIONAL**—B-symptoms. Other constitutional symptoms include fatigue, anorexia, pruritus
- **PARANEOPLASTIC SYNDROMES**

NOTE—lymphoma can mimic many diseases. Always have a high index of suspicion for lymphoma, particularly if B symptoms or multisystem involvement

STAGING

TUMOR BURDEN—a combination of stage, bulkiness (>10 cm in greatest diameter), B symptoms

ANN ARBOR STAGE

- I Single node region
- II Two or more node regions on same side of diaphragm
- III Involvement on both sides of diaphragm
- IV Diffuse or disseminated foci of involvement of one or more extralymphatic sites (e.g. bone marrow, extranodal sites that cannot be included in one radiation field)

STAGING (CONT'D)**DESIGNATIONS**

- E**—single extralymphatic site (i.e. involvement outside of lymph nodes, spleen, thymus, and Waldeyer ring) or involvement by direct extension
- S**—splenic involvement
- A**—no B symptoms
- B**—weight loss >10% over 6 months, fever >38 °C [100.4 °F], drenching night sweats

INVESTIGATIONS**BASIC**

- LABS**—CBC, peripheral smear, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, PO₄, Mg, uric acid, LDH, albumin, quantitative immunoglobulin, serum protein electrophoresis, HBV, HCV, and HIV serology
- IMAGING**—CXR, CT chest/abdomen/pelvis, PET scan
- LYMPH NODE BIOPSY (EXCISIONAL OR CORE) WITH FLOW CYTOMETRY FOR LYMPHOID SURFACE MARKERS, CYTOGENETICS AND NEXT GENERATION SEQUENCING**

BONE MARROW BIOPSY SPECIAL

- MRI SPINE**—if suspect spinal cord compression
- MUGA SCAN OR ECHOCARDIOGRAM**—evaluate cardiac function prior to anthracycline therapy for patients with significant cardiac risk factors

DIAGNOSTIC AND PROGNOSTIC ISSUES**LYMPH NODE BIOPSY**

- EXCISIONAL OR CORE BIOPSY**—consider if lymphoma is suspected based on clinical presentation, or in patients age <50 with lymphadenopathy >1 cm that persists for at least 3 months or is enlarging
- FINE NEEDLE ASPIRATE**—consider if infection is suspected, or in patients age >50 with any cervical lymphadenopathy >1 cm

IMMUNOPHENOTYPE OF SELECTED LYMPHOMAS

	CLL	MCL	FL	MZL
CD20	+ dim	+	+	+
CD5	+	+	–	–
CD23	+	–	–	–
CD43	+	+	–	+
CD10	–	–	+	–

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)**INTERNATIONAL PROGNOSTIC INDEX (IPI)**

- FACTORS**—age >60, serum LDH > normal, ECOG performance status ≥2, Ann Arbor clinical stage III or IV, extranodal disease sites ≥2 (defined as involvement of organs other than lymph nodes, spleen, thymus, and Waldeyer ring)
- SCORING**—1 point per factor, with a score of 0–5
- UTILITY**—5-year overall survival approximately 73%, 51%, 43%, and 26% for IPI of 0–1, 2, 3, and 4–5, respectively. With the new revised IPI (post-rituximab era), 5-year overall survival 94%, 79%, and 55% for IPI of 0, 1–2, and 3–5, respectively

FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI)

- FACTORS**—age >60, serum LDH > normal, hemoglobin <120 g/L [<12 g/dL], Ann Arbor clinical stage III or IV, involved nodal sites >4
- SCORING**—1 point per factor, with a score of 0–5
- UTILITY**—for follicular lymphoma patients specifically; 5-year survival approximately 91%, 78%, and 52% for FLIPI of 0–1, 2 and 3–5, respectively

MANAGEMENT**FOLLICULAR LYMPHOMA**

- LIMITED STAGE (IA or IIA, 10%)**—radiation (10-year survival 50%)
- ADVANCED STAGE (IB, IIB, III, IV, or any bulky disease, 90%)**—if asymptomatic (40%), watchful waiting. If symptomatic or threatening disease (60%), start bendamustine + rituximab, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or CVPR × 8 cycles (cyclophosphamide, vincristine, prednisone, and rituximab). Consider maintenance rituximab for 2 years if partial response.
- SALVAGE**—ibrutinib (BTK inhibitor), idelalisib (PI3K inhibitor), copanlisib (PI3K inhibitor), venetoclax (BCL2 inhibitor), lenalidomide, fludarabine, cyclophosphamide, I¹³¹-tositumomab, and Y⁹⁰-ibrutinomab. Obinutuzumab may be used if rituximab resistance (<6 months). Evaluation for SCT is appropriate

DIFFUSE LARGE B-CELL LYMPHOMA

- LIMITED STAGE (IA or IIA, 30%)**—R-CHOP × 3 cycles. PET scan afterwards, if complete remission, one more cycle; otherwise, give involved field radiation
- ADVANCED STAGE (IB, IIB, III, IV, or any bulky disease, 70%)**—R-CHOP or dose adjusted

MANAGEMENT (CONT'D)

R-EPOCH $\times 6$. PET scan afterwards; if local residual disease, give involved field radiation; if diffuse residual disease, consider **salvage therapy** (see below). For patients at high risk of CNS involvement (bone marrow, epidural, paranasal sinus, testicular, breast or ovarian involvement, high IPI scores or B symptoms), **CNS prophylaxis** with intrathecal methotrexate or Ara-C should be considered

- **SALVAGE**—**RICE** (rituximab, ifosfamide, carboplatin, etoposide), **R-GDP** (gemcitabine, dexamethasone, cisplatin, rituximab), **R-DHAP** or **R-ESHAP**, followed by **autologous stem cell transplant**. If chemotherapy resistant disease, consider **CD19-directed chimeric antigen receptor (CAR)-T cell therapy** (axicabtagene ciloleucel, tisagenlecleucel) or allogeneic stem cell transplant

HIGHLY AGGRESSIVE LYMPHOMAS

- **BURKITT LYMPHOMA OR DOUBLE-HIT LYMPHOMA**—expedited staging (within 1–2 days). For **low-risk disease** (stage I or II, non-bulky <5 cm, no bone marrow/blood/CNS disease and normal LDH), give CODOX-MR (cyclophosphamide, doxorubicin, vincristine, methotrexate, rituximab) $\times 1$, then restage. If CR/PR, give IVAC-R (ifosfamide, etoposide, cytarabine) $\times 1$, then CODOX-MR $\times 1$; otherwise, give IVAC-R $\times 1$, then proceed to stem cell transplant. For **high-risk disease**, give CODOX-MR $\times 1$, IVAC-R $\times 1$, then restage. If CR/PR and no marrow infiltration at diagnosis, then autologous stem cell transplant; otherwise, individualized higher intensity treatment. Allogeneic transplant may be considered (balance between time to find allogeneic donor and use of contaminated stem cells). A total of 8 doses of intrathecal chemotherapy should be given during treatment course. All patients should receive tumor lysis syndrome prophylaxis (hydration, allopurinol, rasburicase). Cure rate ~60% for Burkitt lymphoma
- **ACUTE LYMPHOBLASTIC LYMPHOMA**—expedited staging (within 1–2 days). For most patients, allogeneic/autologous stem cell transplant plus intrathecal chemotherapy (allogeneic if leukemic, otherwise, autologous). Another option is the hyper-CVAD/methotrexate/cytarabine regimen. All patients should receive tumor lysis syndrome prophylaxis (hydration, allopurinol)

SPECIFIC ENTITIES**PRIMARY CNS LYMPHOMA**

- **PATHOPHYSIOLOGY**—usually multifocal but confined to CNS. May have leptomeningeal or intraocular involvement. Frequently aggressive B-cell lymphoma
- **CLINICAL FEATURES**—focal neurological deficit, personality change, mild dementia, persistent headache
- **DIAGNOSIS**—CT or MRI head, lumbar puncture, slit lamp examination. If CNS lymphoma in the differential, try to avoid giving steroids before biopsy. Always check HIV
- **TREATMENTS**—high-dose corticosteroid with high-dose methotrexate is preferred. Whole brain radiation represents an alternative. Prognosis is 60% 2-year survival and 30–40% 5-year survival

LEPTOMENINGEAL MENINGITIS

- **RISK FACTORS**—aggressive lymphomas (lymphoblastic lymphoma, DLBCL, Burkitt lymphoma, MCL), extranodal site involvement (bone marrow, testicular, paranasal, retroperitoneal lymph nodes), any of the five IPI prognostic factors
- **CLINICAL FEATURES**—jaw pain and numbness, radicular pain, back pain, neck pain/rigidity, confusion, cranial nerve deficits (especially II, III, V, VI, VII), focal weakness, sensory changes, headaches
- **DIAGNOSIS**—lumbar puncture with positive cytology (sens 60% with single attempt, 3 attempts for increased yield), gadolinium-enhanced MRI showing enhancement and enlargement of one or more cranial nerves due to tumor infiltration
- **TREATMENTS**—high-dose steroid (dexamethasone 12–20 mg PO/IV daily), radiation to the site of disease, intrathecal methotrexate, or cytarabine. Important to treat underlying systemic disease. Highly selected patients may benefit from high-dose chemotherapy with stem cell transplantation with better outcomes. Median survival after CNS recurrence is 3 months

MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT)

- **PATHOPHYSIOLOGY**—extranodal marginal zone B-cell lymphomas that present with localized disease involving the GI tract, salivary glands, thyroid, orbit, conjunctiva, breast, and lung. Note that diffuse large cell lymphoma and mantle cell lymphoma also commonly involve GI mucosa

SPECIFIC ENTITIES (CONT'D)

- **ASSOCIATIONS**—*H. pylori*-associated chronic gastritis, celiac disease, Crohn disease, gastrointestinal nodular lymphoid hyperplasia
- **DIAGNOSIS**—for gastric MALT, need to determine presence of *H. pylori* by biopsy (gastroscopy) ± urea breath test
- **TREATMENTS**—for *H. pylori*-positive gastric MALT, triple therapy may be adequate. Need to confirm eradication of *H. pylori*. Follow closely with gastroscopy. If MALT persists for over 8–12 months, should consider single-agent chemotherapy (cyclophosphamide, chlorambucil) or involved-field radiation. Partial gastrectomy may be needed for hemorrhage or perforation

ACUTE LYMPHOBLASTIC LYMPHOMA

- **PATHOPHYSIOLOGY**—continuum of presentation with acute lymphoblastic leukemia. Consider lymphoma if < 5% blasts in bone marrow; otherwise, consider leukemia
- **CLINICAL FEATURES**—usually mediastinal mass in young males

BURKITT LYMPHOMA

- **PATHOPHYSIOLOGY**—t(8;14, 2;8, 8;22) leading to c-myc overexpression
- **CLINICAL FEATURES**—usually advanced stage (80–90%). Abdominal mass, CNS, breast/ovarian involvement, and nodal sites, but mediastinum usually spared

TESTICULAR LYMPHOMA

- **PATHOPHYSIOLOGY**—60% primary testicular lymphoma, 40% spread from other sites. Frequently DLBCL or immunoblastic subtype
- **CLINICAL FEATURES**—painless testicular mass in older man. High risk for recurrence, particularly CNS relapse
- **DIAGNOSIS**—scrotal US
- **TREATMENTS**—unilateral orchiectomy + R-CHOP + involved field radiation to scrotum + intrathecal chemotherapy if stage III/IV disease

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

- **PATHOPHYSIOLOGY**—mostly of host origin and usually EBV positive (LMP-1 oncogene). EBV-negative PTLD present later and are more aggressive than EBV-positive PTLD. Mostly B-cell non-Hodgkin lymphoma and very rarely T-cell or NK cell lymphomas
- **RISK FACTORS**—high degree of immunosuppression, pre-transplant EBV negativity. Risk highest in the first year, then reduces by 80%
- **CLINICAL FEATURES**—clinical spectrum includes reactive plasmacytic hyperplasia (55%, infectious mononucleosis-like illness with no malig-

SPECIFIC ENTITIES (CONT'D)

- nant transformation), polymorphic B-cell hyperplasia (30%, polyclonal cytogenetic abnormalities, immunoglobulin gene rearrangements, and disruption of underlying tissue architecture), and B- or T-cell lymphomas (15%, monoclonal malignancy)
- **TREATMENTS**—reduction in immunosuppression (may be sufficient for hyperplasia without monoclonal component), rituximab, chemotherapy (CHOP), antiviral agents, IVIG, surgical resection, radiation, interferon α , adoptive immunotherapy (cytotoxic T-cells specific for EBV). Overall survival 25–35%. Prognostic factors include advanced age, performance status >1, involved site >1

MYCOSIS FUNGOIDES

- **PATHOPHYSIOLOGY**—indolent cutaneous T-cell lymphoma. Stages include premycotic, plaque, and tumor stage. Sézary syndrome is a systemic variant of mycosis fungoides with a triad of erythroderma, lymphadenopathy, and leukemia
- **CLINICAL FEATURES**—localized patches or plaques evolving into nodules and diffuse exfoliative erythroderma associated with abnormal circulating cells. Poor prognostic factors include extensive cutaneous disease (erythroderma), nodal spread, and extracutaneous involvement (liver, spleen, lung, GI tract)
- **TREATMENTS**—topical corticosteroids, topical nitrogen mustard, psoralen with UVA/UVB, bexarotene, radiation. Systemic treatments include CHOP, pentostatin, cladribine, fludarabine, IL-2, IFN α , alemtuzumab, liposomal doxorubicin

SYSTEMIC ANAPLASTIC LARGE CELL LYMPHOMA

- **PATHOPHYSIOLOGY**—may be T-cell, B-cell, or null cell type. Uniform expression of CD4, CD30, clusterin and epithelial membrane antigen (EMA). Anaplastic lymphoma kinase (ALK) overexpression associated with t(2;5) is a key prognostic marker (ALK+ 65–90% 5-year survival vs. ALK– 30–40% 5 year survival)
- **CLINICAL FEATURES**—ALK+ cases usually present at younger age with early disease. ALK– cases usually present at older age with advanced stage, elevated LDH, B symptoms, and extranodal sites
- **TREATMENTS**—CHOP-based regimens or brentuximab-vedotin, crizotinib (if ALK+), romidepsin, pralatrexate. Consider allogeneic stem cell transplant

SPECIFIC ENTITIES (CONT'D)**CASTLEMAN DISEASE**

- **PATHOPHYSIOLOGY**—lymphoid proliferation associated with POEMS syndrome, lymphomas (Hodgkin, non-Hodgkin), and Kaposi sarcoma. HIV and HHV8 common in multicentric subtype
- **CLINICAL FEATURES**—unicentric (isolated lymphadenopathy, benign, HHV8 negative).

Multiple Myeloma**TYPES OF PLASMA CELL DYSCRASIAS**

MULTIPLE MYELOMA (75%)—malignant clone extends from pre-B-cell to plasma cell stage of differentiation. May produce IgG (60%), IgA (20%), or light chains (15%)

WALDENSTRÖM MACROGLOBULEMIA (20%)—proliferation of plasmacytoid lymphocytes (cell type that occurs earlier than plasma cell). Produces IgM. Now classified as lymphoplasmacytic lymphoma

HEAVY-CHAIN DEPOSITION DISEASE—IgA, IgG, or IgM heavy chain

LIGHT-CHAIN DEPOSITION DISEASE— κ or λ light chain

AL (PRIMARY) AMYLOIDOSIS— λ or κ light chain

PATHOPHYSIOLOGY

MGUS—occurs in 2% of population over age 50 and 3% over age 70. Rate of transformation to malignant plasma cell disorder (multiple myeloma, Waldenström macroglobulinemia, primary amyloidosis, B-cell lymphoma, or chronic lymphocytic leukemia) is about 1% per year

RISK FACTORS

- **PERSONAL**—old age, Black race
- **DISEASES**—chronic polyclonal hypergammaglobulinemia
- **TREATMENT**—radiation

CLINICAL FEATURES**SYMPTOMS**

- **PANCYTOPENIA**—weakness, fatigue, infections, gingival bleed, ecchymosis, epistaxis, menorrhagia
- **INCREASED POLYCLONAL PROTEIN**—infections due to ↓ normal Ig, hyperviscosity syndrome
- **LYTIC BONE LESIONS**—pain, fractures
- **HYPERCALCEMIA**—weakness, nausea, abdominal pain, polyuria, altered mental status
- **NEUROLOGIC**—peripheral neuropathy from amyloidosis, plasma cell infiltration of the

SPECIFIC ENTITIES (CONT'D)

Multicentric (fever, night sweats, fatigue, lymphadenopathy, pulmonary infiltrates, frequently HHV8 and HIV positive)

- **TREATMENTS**—unicentric (resection with high chance of cure, radiation, rituximab). Multicentric (rituximab, steroid, antivirals, anti-IL-6, CHOP)

CLINICAL FEATURES (CONT'D)

meninges, cord compression, or radiculopathy from vertebral osteolytic lesions ± plasmacytoma

- **RENAL FAILURE**
 - **PRE-RENAL**—N&V, renal vein thrombosis
 - **RENAL**—myeloma kidney (tubulointerstitial damage from increased light chain absorption at proximal tubule), plasma cell infiltration, Bence Jones/cast nephropathy, amyloidosis (λ), light-chain deposition disease (κ), hypercalcemia (nephrogenic DI), cryoglobulinemia, pyelonephritis, sepsis
 - **POST-RENAL**—renal stones (uric acid), neurogenic bladder
- **CONSTITUTIONAL**—anorexia, fatigue, weight loss

INVESTIGATIONS**BASIC**

- **LABS**—CBC, peripheral smear, lytes, urea, Cr, Ca, β_2 microglobulin, serum viscosity, quantitative immunoglobulin, albumin, serum protein electrophoresis (reciprocal depression), urinary protein electrophoresis, 24 h urinary collection for Bence Jones protein
- **IMAGING**—MRI or PET-CT; if not available use a skeletal survey (NB: standard bone scan does **not** play a role in routine myeloma staging)
- **BONE MARROW BIOPSY**
- **NOTE**—light chain myeloma (20%) may have normal serum protein electrophoresis. Urinary Bence Jones protein (urine protein electrophoresis) is required to detect paraproteinemia; non-secretory myeloma (3%) requires bone marrow biopsy for diagnosis

Related Topics

Amyloidosis (p. 483)
Renal Failure (p. 84)

DIAGNOSTIC AND PROGNOSTIC ISSUES**REVISED INTERNATIONAL MYELOMA WORKING GROUP CRITERIA FOR MGUS, SMOLDERING MYELOMA (SMM), AND MULTIPLE MYELOMA (MM)**

	MGUS	SMM	MM
Criteria	1. Serum monoclonal protein (IgG or IgA) <3 g/dL [<30 g/L] and 2. Clonal bone marrow plasma cells <10% and 3. Absence of myeloma defining events or amyloidosis or Waldenström macroglobulinemia in the case of IgM MGUS	1. Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL [≥ 30 g/L] and/or 2. Urine monoclonal protein ≥ 500 mg/24 hours and/or 3. Clonal bone marrow plasma cells ≥ 10 –60% and 4. Absence of myeloma defining events or amyloidosis	1. Clonal bone marrow plasma cells $\geq 10\%$ or biopsy proven bony or soft tissue plasmacytoma and either #2 or #3 2. End-organ disease with at least one of ★CRAB★ a) Calcium (>2.75 mmol/L [>11 mg/dL] or >0.25 mmol/L [>1 mg/dL] above upper limit of normal) b) Renal insufficiency (Cr >177 μ mol/L [>2 mg/dL]) c) Anemia (Hb <100 g/L [<10 g/dL] or >20 g/L [2 g/dL] below lower limit of normal) d) Bone lesions (one or more osteolytic lesions. If bone marrow has $<10\%$ clonal plasma cells, >1 bone lesion is required to distinguish it from solitary plasmacytoma) 3. Biomarkers of malignancy a) Clonal bone marrow plasma cells $\geq 60\%$ b) An involved serum free light chain (κ or λ) >100 mg/L with the ratio of the involved/uninvolved free light chains also ≥ 100 mg/L c) From MRI imaging, there must be more than one lesion of >5 mm in size

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)**DIAGNOSTIC CLUES**

- **SYMPTOMS**—the presence of tissue impairment suggests either multiple myeloma (usually high M-protein) or amyloidosis (usually low M-protein). AL amyloidosis is characterized by insoluble, toxic amyloid precursor (light chains) aggregates that deposit in tissues in antiparallel β -pleated sheet configuration. The absence of symptoms suggests MGUS or SMM
- **QUANTITATIVE IG**—typically decreased serum levels of normal polyclonal immunoglobulins in multiple myeloma. However, this may also occur in MGUS
- **SERUM M PROTEIN LEVEL**—the higher the level (e.g. >30 g/L [>3 g/dL]), the higher the likelihood of multiple myeloma

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **SERUM LIGHT CHAIN LEVELS**—multiple myeloma will have a serum involved/uninvolved free light chain (κ or λ) ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100 mg/L; a free light chain ratio (FLC ratio) <0.26 or >1.65 predicts high risk MGUS
- **BENCE JONES PROTEINURIA**—the presence of monoclonal light chains (especially >1 g/day) in the urine suggests multiple myeloma. However, small amounts (<50 mg/day) may also occur in MGUS
- **IMAGING**—to assess bony involvement for patients suspected of multiple myeloma. Patients with SMM may require imaging including PET-CT, low-dose whole-body CT, or MRI of whole body or spine/pelvis

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

DURIE-SALMON STAGING FOR MULTIPLE MYELOMA

- **STAGE I** (low tumor burden, $<0.6 \times 10^{12}/m^2$)—all of Hb >100 g/L [>10 g/dL], $Ca^{2+} \leq 2.6$ mmol/L [≤ 10.4 mg/dL], bones normal or solitary bone plasmacytoma only, IgG <50 g/L [<5 g/dL], IgA <30 g/L [<3 g/dL], and urinary λ or κ chains <4 g/day. Median survival ~ 60 months
- **STAGE II** (intermediate burden, $0.6-1.2 \times 10^{12}/m^2$)—between stages I and III. Median survival ~ 30 months
- **STAGE III** (high tumor burden, $>1.2 \times 10^{12}/m^2$)—any of Hb <85 g/L [<8.5 g/dL], $Ca^{2+} >2.6$ mmol/L [>10.4 mg/dL], >3 lytic lesions, plus one of IgG >70 g/L [>7 g/dL], IgA >50 g/L [>5 g/dL], or urinary λ or κ chains >12 g/day. Median survival ~ 15 months
- **SUBSTAGES**—A (Cr <175 μ mol/L [<1.9 mg/dL]) and B (renal failure with Cr >175 μ mol/L [>1.9 mg/dL])

PROGNOSTIC FACTORS FOR MULTIPLE MYELOMA— β_2 microglobulin, albumin, platelet, creatinine, and age. The international staging system for multiple myeloma is particularly useful. The revised version incorporates cytogenetic markers

- **STAGE I**— β_2 microglobulin <3.5 mg/L, albumin ≥ 35 g/L [≥ 3.5 g/dL]. Median survival 62 months
- **STAGE II**—neither stage I nor III. Median survival 44 months
- **STAGE III**— β_2 microglobulin ≥ 5.5 mg/L. Median survival 29 months

MANAGEMENT

MULTIPLE MYELOMA

- **AGE <65 AND OTHERWISE HEALTHY** (curative intent)—**induction chemotherapy** carfilzomib + lenalidomide + dexamethasone, or bortezomib + lenalidomide + dexamethasone. If good response, then proceed to **high-dose melphalan followed by autologous SCT**. Post-SCT maintenance therapy with lenalidomide is recommended
- **AGE >65 OR COMORBIDITIES** (palliative intent)—carfilzomib + lenalidomide + dexamethasone, bortezomib + lenalidomide + dexamethasone, ixazomib + lenalidomide + dexamethasone. If bony disease, add **bisphosphonate** (alendronate, zoledronate)
- **SUPPORTIVE MEASURES**—**hydration** (>3 L/day), **hypercalcemia** (hydration, prednisone

MANAGEMENT (CONT'D)

25 mg PO QID, pamidronate), **renal insufficiency** (treat underlying cause), **infections** (antibiotics, consider IVIG as last resort if recurrent infections despite prophylactic antibiotics), **skeletal lesions** (pamidronate 90 mg IV over 2 h q3-4weeks, radiation, vertebroplasty), **anemia** Hb <90 g/L [<9 g/dL] (transfusions, usually respond to an erythropoiesis stimulating agent, although one should exercise caution given the increased risk of thromboembolism and death), **hyperviscosity syndrome** (Ostwald viscosimeter >5 , plasmapheresis), **prophylactic anticoagulation** (if on thalidomide/lenalidomide and chemotherapy)

SMM—no treatment or clinical trial. Follow clinically

MGUS—no treatment. Follow clinically

TREATMENT ISSUES

INDICATIONS FOR TREATING MULTIPLE MYELOMA— \rightarrow stage I, increasing level of M-protein in serum or urine, significant hypercalcemia, anemia, renal insufficiency, lytic bone lesions, extramedullary plasmacytoma

SPECIFIC ENTITIES

SOLITARY PLASMACYTOMA OF BONE—single osteolytic bone lesion with limited amount of monoclonal protein in the serum or urine and absence of tissue impairment. Radiation is usually treatment of choice and may result in a cure. 80% chance of developing multiple myeloma

AMYLOIDOSIS—See p. 483 for more details. Workup includes abdominal fat biopsy, abd US, and echocardiogram

POEMS SYNDROME—osteosclerotic myeloma with Polyneuropathy, Organomegaly, Endocrine (diabetes, hypothyroidism, parathyroid, hypogonadism), Monoclonal protein, Skin changes (hyperpigmentation, hypertrichosis, acrocyanosis, plethora, hemangioma/telangiectasia). Polyneuropathy and monoclonal plasma cell disorder most important

HYPERVISCOSITY SYNDROME—IgG >70 g/L [>7 g/dL] or IgA >50 g/L [>5 g/dL]. Symptoms include fatigue, changes in mental status, focal or non-focal neurologic changes, visual changes along with retinopathy, angina pectoris, bleeding disorder, cryoglobulin, Raynaud phenomenon, or purpuric eruptions on exposure to the cold

Febrile Neutropenia

See FEBRILE NEUTROPENIA (p. 250)

Hematopoietic Stem Cell Transplant

TERMINOLOGIES

ALLOGENEIC TRANSPLANTATION (40%)—stem cells from HLA-matched sibling donor (25%) or unrelated donor (75%). The main advantage is graft vs. leukemia effect (GVL), while the main disadvantage is graft vs. host effect (GVHD)

AUTOLOGOUS TRANSPLANTATION (60%)—stem cells from self. The main advantage is lesser toxicity compared to allogeneic transplant, while the main disadvantage is possible contamination of the graft with malignant cells

HAPLOIDENTICAL TRANSPLANTATION (increasing use in adults)—stem cells from parent, child or sibling. Main advantage is the relative ease of identifying a donor, while the main disadvantage is graft rejection and GVHD

DONOR SOURCE—peripheral blood (10–20 L of blood, mobilization with GCSF, venipuncture, leukapheresis [up to 3 times for autologous stem cell transplant], faster engraftment, and improved overall survival [for autologous stem cell transplant and matched sibling allogeneic transplant]), **bone marrow**, **umbilical cord blood** (expands supply of donors, although limited amount of stem cells in cord blood can affect engraftment and directs frequent use of “dual cord” transplantation; less GVHD with mismatches)

COMMON INDICATIONS

DECIDING BETWEEN ALLOGENEIC AND AUTOLOGOUS STEM CELL SOURCE—dependent on age, underlying disease, donor availability, institutional preference. In general, allogeneic transplant is more suitable for younger, healthier adults as it is more toxic but potentially more effective than autologous transplant

ALLOGENEIC—acute leukemia (50–70% cure if first remission, 10–30% cure if relapse), myelodysplastic syndrome (40–50% cure rate), chronic myeloid leukemia (50–70% cure if chronic phase, 10–30% cure if blast phase), chronic lymphocytic leukemia, indolent lymphoma, severe immunodeficiency syndromes, hemoglobinopathies

AUTOLOGOUS—progressive Hodgkin lymphoma (60–70% cure if relapse, 40–50% cure if

COMMON INDICATIONS (CONT'D)

refractory disease), multiple myeloma, relapsed and progressive large cell lymphoma, relapsed germ cell cancer

ALLOGENEIC TRANSPLANTATION

HUMAN LEUKOCYTE ANTIGEN MOLECULES—responsible for displaying endogenous and exogenous peptides to T-cells. Mismatch between host and donor HLA type could result in GVHD, graft failure, or death. Note that transplant is not affected by differences in ABO blood groups

- **HLA CLASS I**—HLA-A, HLA-B, HLA-C
- **HLA CLASS II**—HLA-DR, HLA-DQ, HLA-DP

MATCHING PROCESS—ensure good match of HLA-A, HLA-B, HLA-C, DRB1, and DQB1. The chance of finding a sibling match is $1-0.75^n$, where n = number of siblings. The chance of finding a matched unrelated donor is >60%, higher for Caucasians and lower for other races. Search for a match typically takes 3–4 months

CONDITIONING—goal is to eradicate malignancy and suppress recipient's immune system to minimize rejection of donor's stem cells. Myeloablative regimens include cyclophosphamide plus total body irradiation (TBI) or high-dose busulfan. Reduced intensity regimens include fludarabine plus busulfan. Reduced intensity (also known as non-myeloablative or “mini” transplant) regimens use a milder conditioning regimen more tolerable for older patients (e.g. fludarabine plus cyclophosphamide, melphalan). Monitor toxicities closely during this time

- **HEMATOLOGIC**—pancytopenia, febrile neutropenia
- **EARLY NON-HEMATOLOGIC**—alopecia, N&V, oropharyngeal mucositis, diarrhea, sinusoidal obstruction syndrome (previously known as hepatic venoocclusive disease with tender hepatomegaly, jaundice and ascites), seizures, parotitis, pericarditis, cardiomyopathy, interstitial pneumonitis, hemorrhagic cystitis, rash
- **LATE NON-HEMATOLOGIC**—hypothyroidism, sterility or premature menopause, growth impair-

ALLOGENEIC TRANSPLANTATION (CONT'D)

ment, dry eyes or mouth, cataracts, osteopenia or osteoporosis

- **FERTILITY**—infertility is almost certain in both men and women after TBI regimens, but not definite with non-TBI regimens. Consider oocyte/sperm/embryo cryopreservation
- **SECOND MALIGNANCIES**—increased incidence of solid tumors (bone, oropharynx, connective tissue, CNS, thyroid, melanoma), myelodysplastic syndrome, acute myelogenous leukemia, and lymphoproliferative disorders. Highest risks in patients with TBI

TRANSPLANTATION—infusion of stem cells over 30 min to 2 h

ENGRAFTMENT—typically happens between days +10 and +20. Defined as ANC $>0.5 \times 10^3/\mu\text{L}$, with platelet and RBC engraftment following. G-CSF may be used in non-leukemic patients to accelerate engraftment by up to 1 week. Patient is supported with blood products and antimicrobial prophylaxis (e.g. ciprofloxacin for Gram-negatives, trimethoprim-sulfamethoxazole for PJP, acyclovir for HSV, fluconazole for fungal agents) until engraftment occurs. Failure to engraft (primary graft failure) and irreversible decline of blood counts (secondary graft failure) are serious complications (<5%). For non-myeloablative transplant, perform chimerism analysis and consider either donor leukocyte infusion (DLI) or reducing immunosuppression to improve disease control

IMMUNE RECONSTITUTION—restoration of T-cell and B-cell immunity takes up to 12 months. Immunosuppressive treatment can usually be stopped within 1–3 years post-allogeneic transplant. GVHD is a donor T-cell-mediated process. Overall transplant-related mortality is approximately 20–25%

GRAFT VS HOST DISEASE

- **ACUTE GVHD** (<100 days)—occurs in 40% of matched sibling and 80% of unrelated donor transplant. Symptoms include rash, hepatic dysfunction, diarrhea, vomiting. Mortality up to 80% in grade III and IV acute GVHD. Prophylaxis consisting of methotrexate and cyclosporine is usually used for anyone other than identical twins. Treatments include corticosteroids, cyclosporine, mycophenolate mofetil, tacrolimus, and antithymocyte globulin

ALLOGENEIC TRANSPLANTATION (CONT'D)

- **CHRONIC GVHD** (>100 days)—an autoimmune syndrome occurs in up to 50% of matched sibling and >50% of unrelated donor transplant. Symptoms include oral and ocular changes (sicca), alopecia, cholestatic hepatic dysfunction, polyserositis, cutaneous scleroderma, and bronchiolitis obliterans. Treatments include corticosteroids and cyclosporine or tacrolimus for at least 6 months

INFECTIONS

- **PRE-ENGRAFTMENT** (<30 days)—HSV, Gram-negative bacteria, Gram-positive *Streptococcus*, fungal, central line infections (*Staphylococcus epidermis*)
- **EARLY INFECTIONS** (30–100 days)—CMV, some fungal, PJP, central line infections (*S. epidermis*)
- **LATE INFECTIONS** (>100 days)—VZV, encapsulated bacteria, PJP, *Aspergillus*

AUTOLOGOUS TRANSPLANTATION

MATCHING PROCESS—not applicable

CONDITIONING—similar to allogeneic transplant. Regimens include CBV (cyclophosphamide, BCNU, etoposide), cyclophosphamide plus total body irradiation, and BEAM (BCNU, etoposide, cytosine arabinoside, melphalan)

TRANSPLANTATION—similar to allogeneic transplant, except stem cells obtained from patient pretransplant and cryopreserved

ENGRAFTMENT—similar to allogeneic transplant

IMMUNORECONSTITUTION—more rapid immune recovery and no GVHD. Overall transplant-related mortality is approximately 2%

LATE EFFECTS—MDS and AML in at least 10% of patients 5–10 years after autologous transplant

Related Topics

- Acute Leukemia (p. 187)
- Non-Hodgkin Lymphoma (p. 194)
- Febrile Neutropenia (p. 250)
- Fungal Infections (p. 286)
- Multiple Myeloma (p. 199)
- Sepsis (p. 118)
- Tumor Lysis Syndrome (p. 244)



Lung Cancer

 Reck et al. *NEJM* 2017;377(9)
 NCCN Guidelines v6.2020

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **SMALL CELL (SCLC, 15%)**—mainly seen in smokers, central lesions, early metastasis compared to NSCLC
- **NON-SMALL CELL (NSCLC, 85%)**
 - **ADENOCARCINOMA (50–60%)**—women, may develop in nonsmokers (account for 25%), peripheral lesions
 - **SQUAMOUS (25%)**—mainly seen in smokers, central, cavity lesions
 - **LARGE CELL (15%)**—peripheral lesions with prominent necrosis, slightly worse prognosis than squamous and adenocarcinoma, diagnosis of exclusion
- **CARCINOID (2%)**—neuroendocrine origin. May cause airway obstruction, ectopic Cushing, and carcinoid syndrome
- **CYSTIC ADENOID CARCINOMA**—locally invasive but may also metastasize
- **CARCINOSARCOMA**—localized lesion usually

RISK FACTORS

- **SMOKING**—30 × increased risk compared to nonsmokers. Smokers have 30% lifetime risk of developing lung cancer. 85–90% of all lung cancers are related to smoking. Polymorphisms in carcinogen activating enzymes (*N-acetyltransferase* [NAT1 and NAT2], CYP

PATHOPHYSIOLOGY (CONT'D)

- 1A1 and 2A6) and inactivating enzymes (glutathione S-transferase S1 and M1) may contribute to individual susceptibility. The duration of smoking is a stronger risk factor than the number of cigarettes smoked. Cigar/pipe smoking (2 ×) and second-hand smoke (1.3 ×) are also risk factors
- **ENVIRONMENTAL**—asbestos (7 ×), arsenic, silica, chromium, nickel, polycyclic hydrocarbons, radon (10 ×), β-carotene supplements (in heavy smokers, 2–3 ×)
 - **DISEASES**—tuberculosis, COPD, pulmonary fibrosis, previous radiation
 - **FAMILY HISTORY**

CLINICAL FEATURES

LOCOREGIONAL—cough, sputum, hemoptysis, dyspnea, chest pain, wheezing, dysphagia, brachial plexus (Pancoast tumor), hoarseness, Horner syndrome (miosis, ptosis, anhidrosis), superior vena cava syndrome (dilated neck veins, facial edema, plethoric appearance)

METASTATIC—bone pain, jaundice, seizures, headaches, adrenal lesions, skin lesions

CONSTITUTIONAL—weight loss, anorexia, fatigue

PARANEOPlastic SYNDROMES

	SCLC	Squamous	Adenocarcinoma	Large cell
SIADH	✓			
Ectopic Cushing syndrome	✓			
Neurological syndromes ^a	✓			
Hypercalcemia		✓	✓	
Clubbing or hypertrophic osteoarthropathy		✓	✓	

CLINICAL FEATURES (CONT'D)

	SCLC	Squamous	Adenocarcinoma	Large cell
Hypercoagulable state	✓	✓	✓	✓
Gynecomastia				✓

^aNeurological syndromes associated with SCLC include dementia, cerebellar degeneration, limbic encephalopathy, optic neuritis and retinopathy, paraneoplastic sensory neuropathy (anti-Hu antibodies), and Lambert-Eaton syndrome

STAGING

STAGING FOR SMALL CELL LUNG CANCER

- **LIMITED STAGE** (40%, median survival 15–20 months)—tumor confined to the ipsilateral hemithorax, mediastinum, and supraclavicular nodes, which can be included within a tolerable radiation therapy port
- **EXTENSIVE STAGE** (60%, median survival 8–13 months)—non-limited stage, including pleural effusion

TNM STAGING FOR NON-SMALL CELL LUNG CANCER

T stage

- **T1**— ≤ 3 cm surrounded by lung or visceral pleura, no bronchoscopic evidence of main bronchus invasion
 - **T1A(mi)**—minimally invasive adenocarcinoma
 - **T1A**—tumor ≤ 1 cm
 - **T1B**—tumor > 1 cm to ≤ 2 cm
 - **T1C**—tumor > 2 cm to ≤ 3 cm
- **T2**— > 3 cm to ≤ 5 cm, invasion of main bronchus but not carina, invasion of visceral pleura, **or** associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
 - **T2A**—tumor > 3 cm to ≤ 4 cm
 - **T2B**—tumor > 4 cm to ≤ 5 cm

STAGING (CONT'D)

- **T3**— > 5 cm to ≤ 7 cm, associated with separate tumor nodule(s) in the same lobe as the primary tumor **or** invasion of chest wall, parietal pleura, phrenic nerve, parietal pericardium, or superior sulcus tumors
- **T4**— > 7 cm, associated with separate tumor nodule(s) in a different ipsilateral lobe as the primary tumor **or** invasion of diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina

N stage

- **N1**—ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
- **N2**—ipsilateral mediastinal or subcarinal lymph node(s)
- **N3**—contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M stage (lungs, liver, bones, brain)

- **M1A**—separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion
- **M1B**—single extrathoracic metastasis
- **M1C**—multiple extrathoracic metastases in one or more organs

STAGE GROUPINGS

Stage	TNM @ = any	Median survival	2 year survival	5 year survival
IA1	T1aN0M0	Not reached	97%	92%
IA2	T1bN0M0	Not reached	94%	83%
IA3	T1cN0M0	Not reached	90%	77%
IB	T2aN0M0	Not reached	87%	68%
IIA	T2bN0M0	Not reached	79%	60%
IIB	T1a-T1cN1M0, T2N1M0, T3N0M0	66 m	72%	53%
IIIA	T1a-T1cN2M0, T2N2M0, T3N1M0, T4N0-1M0	29 m	55%	36%

STAGING (CONT'D)

Stage	TNM @ = any	Median survival	2 year survival	5 year survival
IIIB	T1a-T1cN3M0, T2N3M0, T3N2M0, T4N2M0	19 m	44%	26%
IIIC	T3N3M0, T4N3M0	13 m	24%	13%
IVA	T@N@M1a-M1b	12 m	23%	10%
IVB	T@N@M1c	6 m	10%	0%

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, INR, PTT, Ca, albumin, CEA
- **IMAGING**—CXR (compared to old) and CT chest and upper abdomen (adrenals)
- **BIOPSY**—bronchoscopy with lavage/wash/brushings/biopsy (if central lesion), endobronchial US (EBUS) with biopsy (if suspect nodal disease), thoracentesis (if pleural effusion), CT-guided transthoracic needle aspiration (if peripheral lesion), mediastinoscopy (if any nodes on CT and potentially resectable disease, sens 90%, spc 100%), thoracotomy

SPECIAL

- **PET/CT**—sens 88%, spc 85%. Usually used for staging in patients with potentially resectable disease
- **PULMONARY FUNCTION TEST**—if surgical candidate
- **BONE SCAN**—if bone pain, elevated ALP or Ca, \geq N2
- **CT HEAD OR MR HEAD**—if \geq N2 or symptomatic NSCLC, all SCLC
- **REPEATED SPUTUM CYTOLOGY**—sens 60–80% for central lesions, 15–30% for peripheral lesions

DIAGNOSTIC AND PROGNOSTIC ISSUES**KARNOFSKY PERFORMANCE STATUS**

PS	Function
100%	Normal, no complaints, no evidence of disease
90%	Able to carry on normal activity: minor symptoms of disease
80%	Normal activity with effort: some symptoms of disease
70%	Cares for self: unable to carry on normal activity or active work
60%	Requires occasional assistance but is able to care for needs
50%	Requires considerable assistance and frequent medical care

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

PS	Function
40%	Disabled: requires special care and assistance
30%	Severely disabled: hospitalization is indicated, death not imminent
20%	Very sick, hospitalization necessary: active treatment necessary
10%	Moribund, fatal processes progressing rapidly
0%	Dead

EASTERN CO-OPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

- **0**—normal. KPS 100%
- **1**—restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work. KPS 80–90%
- **2**—ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. KPS 60–70%
- **3**—capable of only limited self-care, confined to bed or chair >50% of waking hours. KPS 40–50%
- **4**—completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. KPS 10–30%
- **5**—dead. KPS 0%

ADVERSE PROGNOSTIC FACTORS

- **GENERAL**—poor performance status (ECOG >1), involuntary weight loss (>5%), advanced stage, SCLC
- **POOR OUTCOME AFTER SURGERY**—poor performance status, weight loss (>5%), low FEV1, low $P_{50}O_2$, recent history of smoking

PROGNOSIS OF SMALL CELL LUNG CANCER—limited stage 20–40% 2-year survival, 16–24 months median survival; extensive stage <5% 2-year survival, 6–12 months median survival. Median survival post-relapse 4 months

MANAGEMENT

NON-SMALL CELL LUNG CANCER

- **STAGE I/II—lobectomy/pneumonectomy.** Consider **stereotactic radiation** if inoperable. Consider adjuvant **chemotherapy** (e.g. cisplatin–vinorelbine×4) if high-risk features (e.g. >4 cm, stage II). Consider adjuvant radiation if incomplete resection or positive margin
- **STAGE IIIA (N1 disease)—lobectomy/pneumonectomy** followed by **adjuvant chemotherapy**
- **STAGE IIIA (N2 disease) AND IIIB—concurrent chemoradiation** (e.g. cisplatin + etoposide × 4, carboplatin + pemetrexed × 4 [if non-squamous]) followed by maintenance durvalumab
- **STAGE IV—PD-L1 testing** in all patients. Also look for driver mutations in patients with adenocarcinoma, mixed histologies, and never-smokers with squamous cell carcinoma to tailor the choice of **systemic therapy** (chemotherapy, targeted therapy, and/or immunotherapy). Consider **palliative radiation** before systemic therapy (if patients present with symptomatic brain metastases, hemoptysis, SVC syndrome, severe bone pain or obstructive pneumonia). **Palliative care referral** if supportive care needs

— ADENOCARCINOMA

- **DRIVER MUTATION PRESENT**—treatment based on mutation. **EGFR mutation** (osimertinib [preferred], erlotinib, gefitinib, afatinib); **ALK fusion oncogene** (alectinib [preferred], ceritinib, crizotinib, lorlatinib, brigatinib); **ROS1 rearrangement** (entrectinib, crizotinib, lorlatinib); **MET exon 14 skipping mutation** (capmatinib, crizotinib); **RET rearrangement** (selpercatinib, vandetanib, cabozantinib); **BRAF V600E** (dabrafenib + trametinib)
- **DRIVER MUTATION ABSENT, PD-L1 ≥50%**—single agent immunotherapy (nivolumab, pembrolizumab, atezolizumab)
- **DRIVER MUTATION ABSENT, PD-L1 <50%**—doublet chemotherapy (cisplatin/carboplatin, pemetrexed) ± immunotherapy (pembrolizumab, atezolizumab) ± bevacizumab
- **RECURRENT DISEASE**—docetaxel ± ramucirumab

— SQUAMOUS CELL CARCINOMA

MANAGEMENT (CONT'D)

- **DRIVER MUTATION PRESENT**—same treatment as above, but mutations are less common in pure squamous cell carcinoma
- **DRIVER MUTATION ABSENT, PD-L1 ≥50%**—single agent immunotherapy (nivolumab, pembrolizumab, atezolizumab)
- **DRIVER MUTATION ABSENT, PD-L1 <50%**—doublet chemotherapy (carboplatin + paclitaxel) + immunotherapy (pembrolizumab)
- **RECURRENT DISEASE**—docetaxel ± ramucirumab, carboplatin + gemcitabine

SMALL CELL LUNG CANCER

- **LIMITED STAGE, T1-2N0—lobectomy** followed by **adjuvant chemotherapy** or concurrent chemoradiation (if mediastinal lymph node involvement)
- **LIMITED STAGE, >T1-2N0—concurrent chemoradiation** (e.g. cisplatin + etoposide). Consider **prophylactic cranial irradiation** if good partial/complete response
- **EXTENSIVE STAGE—palliative chemotherapy** (e.g. carboplatin + etoposide + atezolizumab [preferred], cisplatin + irinotecan). Consider **prophylactic cranial irradiation** if partial/complete response. For recurrent disease after platinum-based therapy, consider lurbinectedin, topotecan, paclitaxel, docetaxel, vinorelbine, irinotecan, oral etoposide, gemcitabine, or temozolomide

NEUROENDOCRINE TUMORS

- **LOW GRADE (TYPICAL CARCINOID)**—lobectomy
- **INTERMEDIATE GRADE (ATYPICAL CARCINOID)**—lobectomy ± adjuvant chemotherapy cisplatin-etoposide (if stage II or III)
- **HIGH GRADE LARGE CELL NEUROENDOCRINE CARCINOMA**—treat as non-small cell lung cancer
- **HIGH GRADE NEUROENDOCRINE SMALL CELL CARCINOMA OR COMBINED HISTOLOGIES**—treat as small cell lung cancer

TREATMENT ISSUES

DRIVER MUTATIONS FOR METASTATIC NSCLC—mutations that “drive” the development and progression of lung cancer and therefore can be “targetable.” Driver mutations include EGFR (15% in USA, more often in nonsmokers; 62% in Asians), ALK (4% in USA, nonsmoker and younger patients), ROS1 (1–2% in USA), BRAF (2%), MET exon 14 and RET. KRAS mutation also occur in 25% but clinical efforts to target KRAS have been disappointing

TREATMENT ISSUES (CONT'D)

PD-L1 TESTING FOR METASTATIC NSCLC—immune checkpoint inhibitors are antibodies that target the programmed death 1 (PD-1) pathway. Approximately 20% have substantial and often durable response to monotherapy immunotherapy if PD-L1 expression >50%

SMOKING CESSATION—for smokers of <20 pack year, the risk of developing lung cancer decreases significantly after 15 years of abstinence, but still slightly higher than non-smokers

NON-RESECTABLE DISEASE CRITERIA (stage IIIb or greater)—distant metastasis, mediastinal lymph node metastasis, trachea/contralateral

TREATMENT ISSUES (CONT'D)

main bronchi involvement, SVC obstruction, malignant pleural effusion, recurrent laryngeal nerve paralysis, SCLC (unless very early)

CONTRAINDICATIONS TO CHEST RADIATION—significant pre-existing lung disease, cardiomyopathy, connective tissue disease (SLE, scleroderma), prior radiation to same body region, pregnancy

CONTRAINDICATIONS TO BEVACIZUMAB—squamous cell carcinoma, hemoptysis, uncontrolled cerebral metastases, non-healing wounds, uncontrolled hypertension/proteinuria, bleeding diatheses, recent trauma/surgery

MesotheliomaScherpereel et al. *Lancet Oncol* 2018;19(3)

NCCN Guidelines v1.2020

PATHOPHYSIOLOGY**CLASSIFICATION BY HISTOLOGY**

- **EPITHELIOID**—tubulopapillary, glandular, or solid. 50–60%, better prognosis
- **SARCOMATOID**—spindle cells
- **BIPHASIC**—mixed with both epithelioid and sarcomatoid features

ASBESTOS AND MESOTHELIOMA—accounts for approximately 80% of mesothelioma. Risk of mesothelioma is higher with amphiboles/blue asbestos than chrysotile/white asbestos. Asbestos fibers may irritate the pleura, sever or pierce the mitotic spindle of cells and disrupt mitosis, induce generation of iron-related reactive oxygen species, and phosphorylate MAP kinases and ERK 1 and 2. Tumor usually starts from parietal pleura and invades locally

RISK FACTORS

- **FAMILY HISTORY**—rare
- **ENVIRONMENTAL**—asbestos, radiation

CLINICAL FEATURES

LOCOREGIONAL—pleural (pleural effusion, pleuritic chest pain, dyspnea, SVC obstruction), peritoneal (ascites, abdominal pain, bowel obstruction), pericardial (pericardial effusion, tamponade)

METASTATIC—miliary spread, liver, lung, bone, and/or adrenal lesions

CONSTITUTIONAL—weight loss, anorexia, fatigue

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bili
- **IMAGING**—CXR, CT chest/abd, or MRI chest
- **BIOPSY**—thoracentesis (sens 33–84%, cytology is usually inadequate), video-assisted thoracoscopy (VAT) with pleural biopsy

SPECIAL

- **SOLUBLE MESOTHELIN-RELATED PROTEIN (SMRP)**—serum or pleural fluid: sens 75–84%
- **PET SCAN**—if surgical candidate

PROGNOSTIC ISSUES

PROGNOSIS BY STAGE—median survival times for stage I, II, III and IV mesothelioma are 20, 19, 16 and 11 months, respectively

ADVERSE PROGNOSTIC FACTORS—male, poor performance status, sarcomatoid subtype, leukocytosis, anemia, thrombocytosis, advanced stage, high PET ratios

MANAGEMENT

STAGE I, II (resectable disease)—**surgery** (pleurectomy/decortication, extrapleural pneumonectomy, debulking). Choice of type of surgery is controversial as neither will yield an R0 resection. Pleurectomy/decortication should be the first option for patients with operable early stage disease and is an option for patients with locally advanced disease who are not candidates for extrapleural pneumonectomy. Extrapleural pneu-

MANAGEMENT (CONT'D)

monectomy should be considered for highly selected patients (age <55, performance status ≤ 1 , stage I or II, epithelioid histology) and only after a good response to **neoadjuvant chemotherapy**, to be followed by **adjuvant radiation**. Otherwise, treat as unresectable disease **STAGE III, IV** (unresectable disease)—**palliative chemotherapy** (cisplatin + pemetrexed with

MANAGEMENT (CONT'D)

vitamin B12 and folic acid supplementation \pm bevacizumab, cisplatin + gemcitabine, vinorelbine). Immunotherapy (pembrolizumab, nivolumab \pm ipilimumab). **Pleurodesis or indwelling pleural catheters** should be considered if recurrent effusion. **Palliative care referral** if supportive care needs

Thymoma and Thymic Carcinoma

NCCN Guidelines v1.2020

PATHOPHYSIOLOGY**CLASSIFICATION BY HISTOLOGY**

- EPITHELIAL
- NEUROENDOCRINE
- GERM CELL
- LYMPHOID
- STROMAL

CLINICAL FEATURES

LOCOREGIONAL—dyspnea, cough, chest pain, hoarseness, dysphagia, superior vena cava obstruction

METASTATIC

CONSTITUTIONAL—weight loss, anorexia, fatigue
PARANEOPLASTIC—myasthenia gravis (30–50%, diplopia, ptosis, dysphagia, weakness, fatigue), pure red cell aplasia (5–15%), pure white cell aplasia, pancytopenia, hypogammaglobulinemia (recurrent infections, diarrhea), rheumatologic diseases, and endocrinopathies. Note that remission of thymoma does not necessarily correlate with improvement of paraneoplastic syndromes

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bili
- **IMAGING**—CXR, CT chest
- **BIOPSY**

DIAGNOSTIC ISSUES

BIOPSY—surgical biopsy should be avoided if resectable thymoma is strongly suspected based on clinical and radiologic features. Biopsy of a possible thymoma should avoid a transpleural approach

MANAGEMENT

STAGE I, II, III (resectable disease)—**resection** (usually including adjacent lung parenchyma and pericardium) \pm **adjuvant radiation** \pm (**neo**)**adjuvant chemotherapy** (cisplatin + doxorubicin + cyclophosphamide [preferred for thymoma], carboplatin + paclitaxel [preferred for thymic carcinoma], cisplatin + etoposide)

STAGE IV (unresectable disease)—**palliative radiation** \pm **palliative chemotherapy** (cisplatin + doxorubicin + cyclophosphamide [preferred for thymoma], carboplatin + paclitaxel [preferred for thymic carcinoma], cisplatin + etoposide). **Palliative care referral** if supportive care needs

TREATMENT ISSUES

INDICATIONS FOR RADIOTHERAPY—locally advanced or metastatic unresectable disease, residual disease post-resection, and complete resection of invasive thymoma or thymic carcinoma

Breast Cancer

NCCN Guidelines v6.2020

DIFFERENTIAL DIAGNOSIS OF BREAST MASS

BENIGN—cysts (obstructed collecting ducts), fibroadenoma (overgrowth of periductal stromal connective tissue within the lobules), mammary duct ectasia, intraductal papilloma, mastitis, fat necrosis

DIFFERENTIAL DIAGNOSIS OF BREAST MASS (CONT'D)

ATYPICAL HYPERPLASIA—3–5 \times increased risk of breast cancer

DIFFERENTIAL DIAGNOSIS OF BREAST MASS (CONT'D)

CARCINOMA IN SITU—ductal (DCIS), lobular (LCIS)

MALIGNANT—breast cancer

PATHOPHYSIOLOGY

CLASSIFICATION OF IN SITU LESIONS

- **DUCTAL CARCINOMA IN SITU (DCIS)**—non-invasive breast cancer
- **LOBULAR CARCINOMA IN SITU (LCIS)**—not a cancer, diffuse and can be bilateral (risk of contralateral invasive breast cancer may be as high as ipsilateral disease). Marker for increased risk of development of invasive cancer (absolute risk ~1%/year of development of invasive cancer)

CLASSIFICATION OF MALIGNANT LESIONS

- **DUCTAL ADENOCARCINOMA**—80%
- **LOBULAR ADENOCARCINOMA**—10%, more likely to be bilateral and multicentric. Tends to metastasize later than ductal carcinoma and spreads to unusual sites such as GI tract, peritoneum, and meninges. Most are ER +ve and 20–30% have E-cadherin mutations (associated with hereditary diffuse-type gastric cancer). Clinically, more difficult to detect by palpation and by mammography
- **TUBULAR, MEDULLARY, PAPILLARY, COLLOID, SPINDLE CELL, MUCINOUS**—10%, better prognosis
- **SARCOMA LIKE**—phyllodes, post-radiation angiosarcoma

CLASSIFICATION BY RECEPTOR STATUS—important clinically as defines natural history, prognosis, and therapeutic options

- **ESTROGEN RECEPTOR (ER) AND PROGESTERONE RECEPTOR (PR)**—70% of breast cancer is ER +ve, PR +ve or both +ve. These cancers are sensitive to anti-estrogen therapies
- **HER2 RECEPTOR (HER2)**—15–20% of breast cancer is Her2 amplified. HER2 positivity is a poor prognostic factor but predicts response to trastuzumab, pertuzumab, lapatinib, adotrastuzumab emtansine (T-DM1), trastuzumab deruxtecan, and tucatinib
- **TRIPLE NEGATIVE BREAST CANCER (ER -ve, PR -ve, HER2 -ve)**—15% of all breast cancer, most aggressive and more likely to be associated with BRCA1 mutation. Primary treatment is chemotherapy

RISK FACTORS

- **PERSONAL**—female, increased age, early age of menarche, late age of first parity, lack of breast feeding, late age of menopause, oral contraceptives (↑ risk if >4 years of use), hormone replacement, high socioeconomic status

PATHOPHYSIOLOGY (CONT'D)

- **FAMILY HISTORY (10%)**—affected relatives, BRCA1 and BRCA2 mutations (BRCA1 is associated with basal-like subtype and triple negative phenotype. BRCA2 is associated with luminal subtype), Li-Fraumeni syndrome, Cowden syndrome
- **ENVIRONMENTAL**—alcohol, low caloric intake, low physical activity, weight gain
- **PRIOR BREAST PATHOLOGY**—atypical hyperplasia, prior breast tumor (in situ or carcinoma)
- **GAIL MODEL**—used to estimate the risk of breast cancer in the Breast Cancer Detection and Demonstration Project. Includes age at menarche, age at first live birth, number of previous breast biopsies, presence of atypical hyperplasia in breast biopsy, and number of first-degree relatives with breast cancer

CLINICAL FEATURES

LOCOREGIONAL—breast lump (with or without pain), nipple discharge, eczema or retraction, skin erosion, erythema or edema, change in breast size, axillary adenopathy

METASTATIC—bone pain, seizure, headache, dyspnea, jaundice

CONSTITUTIONAL—fatigue, weight loss, anorexia

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—mammogram (15% false negative), US breast, MRI breast (for dense breasts or those with BRCA1/2 mutations)
- **BIOPSY**—needle core biopsy (FNA provides cytology only and cannot differentiate between invasive and in situ disease), excisional biopsy (only when core biopsy is non-diagnostic)

SPECIAL

- **IMAGING**—bone scan and CT chest/abd/pelvis (if clinical suspicion or clinical stage IIIA [T3N1M0] or greater)
- **TUMOR MARKERS**—CA 15-3 or CA 27.29 only if metastatic disease

STAGING

TNM STAGING (staging is complex; stage grouping includes TNM stage, ER/PR/Her2 status and grade; for details please refer to *AJCC Cancer Staging Manual*, 8th ed.)

STAGING (CONT'D)**Anatomic Staging**

- **T1**— ≤ 20 mm
 - **T1mi**— ≤ 1 mm
 - **T1a**— > 1 mm to ≤ 5 mm
 - **T1b**— > 5 mm to ≤ 10 mm
 - **T1c**— > 10 mm to ≤ 20 mm
- **T2**— > 20 mm to ≤ 50 mm
- **T3**— > 50 mm
- **T4**—fixed or invades bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall
 - **T4a**—extension to chest wall
 - **T4b**—ulceration and/or ipsilateral satellite nodules and/or edema (*peau d'orange*)
 - **T4c**—both T4a and T4b
 - **T4d**—inflammatory carcinoma

N stage

- **N1**—clinically movable ipsilateral axillary lymph nodes. Pathologically 1–3 axillary lymph node(s)
- **N2**—clinically fixed/matted ipsilateral axillary lymph nodes **or** ipsilateral internal mammary lymph nodes. Pathologically 4–9 axillary lymph node(s)
- **N3**—clinically ipsilateral internal mammary lymph nodes **and** axillary lymph nodes, ipsilateral infraclavicular lymph nodes, or ipsilateral supraclavicular lymph nodes. Pathologically ≥ 10 axillary lymph node(s)

M stage

- **M1**—distant metastasis

DIAGNOSTIC AND PROGNOSTIC ISSUES

MAMMOGRAPHIC FINDINGS OF BREAST CANCER—spiculated, crab-like, puckering lesions, architectural distortion, clustered microcalcifications

PROGNOSIS BY STAGE—5 year disease-free survival rates for stage I, II, III are 98–100%, 85–98% and 70–95%, respectively. Median survival for stage IV breast cancer is 2 years

POOR PROGNOSTIC FACTORS—young age, advanced stage (especially nodal status and tumor size), high grade, Her2 +ve, ER –ve, PR –ve, lymphatic/vascular invasion

MANAGEMENT**DCIS**

- **RESECTION**—breast-conserving surgery plus adjuvant radiation, or mastectomy
- **ADJUVANT HORMONAL THERAPY**—tamoxifen or aromatase inhibitor may be considered after breast-conserving surgery for selected individuals if ER/PR positive

MANAGEMENT (CONT'D)**LCIS**

- **RESECTION**—observation, breast-conserving surgery or bilateral mastectomy for selected individuals
- **HORMONAL THERAPY**—tamoxifen or raloxifene may be used for prevention of invasive breast cancer in selected individuals

STAGE I AND II

- **RESECTION**—breast-conserving surgery or mastectomy, plus sentinel node biopsy. Axillary lymph node dissection if clinically node positive and biopsy proven. If sentinel lymph node positive, proceed to axillary dissection
- **ADJUVANT SYSTEMIC THERAPY**—taxane \pm anthracycline. If Her2 +ve, add trastuzumab \pm pertuzumab (if stage II disease)
- **ADJUVANT RADIATION**—always give adjuvant radiation after breast-conserving surgery. Adjuvant radiation should be considered after mastectomy if large tumor, skin involvement, muscle involvement, positive nodes, positive margins, or lymphovascular invasion
- **ADJUVANT HORMONAL THERAPY**—if ER/PR positive. Treatment with aromatase inhibitor or tamoxifen for 5–10 years depending on tolerability. In premenopausal women, also consider oophorectomy or LHRH agonists if high risk disease

STAGE III

- **NEOADJUVANT SYSTEMIC THERAPY**—taxane \pm anthracycline. If Her2 +ve, add trastuzumab \pm pertuzumab (if stage II disease)
- **RESECTION**—breast-conserving surgery or mastectomy and axillary \pm sentinel node evaluation \pm lymph node dissection
- **ADJUVANT RADIATION**—almost always given for stage III disease
- **ADJUVANT HORMONAL THERAPY**—if ER/PR +ve. Treatment with aromatase inhibitor or tamoxifen for 5–10 years depending on tolerability. In premenopausal women, also consider oophorectomy or LHRH agonists if high risk disease

STAGE IV—systemic therapy is main stay and mostly based on ER/PR/Her2 status. Consider **palliative radiation** for symptomatic control of localized disease (e.g. bone metastasis, painful skin lesions). Consider adding osteoclast inhibitors if bone metastasis. Consider **palliative care referral** for patients with supportive care needs

- **ER/PR +ve AND Her2 –ve**—endocrine therapy is mainstay. BRCA and PIK3CA testing upfront
 - **FIRST LINE**—if not rapidly progressive/symptomatic and no significant visceral involvement, consider endocrine therapy

MANAGEMENT (CONT'D)

first instead of chemotherapy. **Endocrine therapies** include aromatase inhibitors or fulvestrant + CDK4/6 inhibitor (palbociclib, ribociclib, abemaciclib). In premenopausal women, the use of aromatase inhibitors and fulvestrant require either oophorectomy or LHRH agonists

- **SUBSEQUENT LINES**—exemestane and everolimus is common second line. If PIK3CA +ve, fulvestrant + alpelisib is standard of care. If BRCA carrier, consider PARP inhibitors (olaparib, talazoparib)
- **ER/PR +ve AND Her2 +ve**—anti-Her2 therapy is mainstay
 - **FIRST LINE**—docetaxel or paclitaxel + trastuzumab + pertuzumab
 - **SUBSEQUENT LINES**—trastuzumab deruxtecan, tucatinib, trastuzumab + capecitabine, ado-trastuzumab emtansine (T-DM1). Otherwise, consider trastuzumab plus single agent or combination chemotherapy (see Triple Negative Disease), or trastuzumab plus endocrine therapy
- **ER/PR -ve AND Her2 +ve**—anti-Her2 therapy is mainstay
 - **FIRST LINE**—docetaxel or paclitaxel + trastuzumab + pertuzumab
 - **SUBSEQUENT LINES**—trastuzumab deruxtecan, tucatinib, trastuzumab + capecitabine, ado-trastuzumab emtansine (T-DM1). Otherwise, consider trastuzumab plus single agent or combination chemotherapy (see Triple Negative Disease)
- **ER/PR -ve AND Her2 -ve (TRIPLE NEGATIVE)**—chemotherapy is mainstay. BRCA and PD-L1 testing upfront
 - **FIRST LINE**—taxane + immunotherapy (if PD-L1 >1%)
 - **SUBSEQUENT LINES**—anthracyclines (doxorubicin, pegylated liposomal doxorubicin), taxanes (if not tried already, paclitaxel, docetaxel, albumin-bound paclitaxel), antibody drug conjugate (sacituzumab govitecan), PARP inhibitors (olaparib, talazoparib), microtubule inhibitors (vinorelbine, eribulin, ixabepilone), platinum (carboplatin, cisplatin), anti-metabolites (gemcitabine, capecitabine), or various combinations (e.g. doxorubicin + cyclophosphamide, gemcitabine + carboplatin)

TREATMENT ISSUES**PRINCIPLES OF BREAST CANCER SURGERY**

- **COMPLETE SURGERY**—modified radical mastectomy. Indications for mastectomy include multicentric disease, diffuse malignant appearing microcalcifications on mammography, prior breast radiation, genetic mutation such as BRCA1 or BRCA2, and pregnancy. Relative indications include large tumor (>5 cm), connective tissue disease (radiation contraindicated), and patient preference
- **BREAST CONSERVING SURGERY**—excisional biopsy, lumpectomy, partial mastectomy, quadrantectomy, wide local excision. Breast conserving surgery should always be followed by whole breast radiation
- **SURGICAL MARGIN**—positive margin is defined as tumor touching ink and would require re-excision
- **AXILLARY LYMPH NODE DISSECTION (ALND)**—removal of level I and II axillary nodes. May be avoided if sentinel lymph node negative
- **SENTINEL LYMPH NODE BIOPSY (SLNB)**—indicated for clinically node negative tumors. Contraindications include locally advanced breast cancer, any palpable lymph nodes, multifocal cancers, previous disruptive breast procedures, and adverse reactions to dyes. Proceed to ALND if positive nodes or unable to identify sentinel node

PRINCIPLES OF HORMONAL THERAPY

- **OVARIAN ABLATION** (premenopausal only)—oophorectomy, radiation, or LHRH agonists (*goserelin* 3.6 mg IM every month, leuprolide). Consider combining with tamoxifen (in adjuvant or metastatic settings) or aromatase inhibitors (in metastatic setting only) for maximal effect
- **SELECTIVE ESTROGEN RECEPTOR MODULATORS** (premenopausal or postmenopausal)—*tamoxifen* 20 mg PO daily. Side effects include hot flashes, mood swings, vaginal discharge, thromboembolism, and endometrial cancer. Protective effect with bones and lipids
- **AROMATASE INHIBITORS** (for postmenopausal women or premenopausal women after ovarian ablation as suppress peripheral estrone production only)—inhibit aromatase, an enzyme in skin, adipose tissue, and breast that converts androstenedione (from the adrenals) to estrone and estradiol. **Steroidal** (*exemestane* 25 mg PO daily), **non-steroidal**

TREATMENT ISSUES (CONT'D)

(*anastrozole* 1 mg PO daily, *letrozole* 2.5 mg PO daily). Side effects include hot flashes, mood swings, vaginal dryness, myalgia/arthralgia, headache, osteoporosis, dyslipidemia, weight gain, and potentially CAD

- **ANTIESTROGEN**—*fulvestrant* 500 mg IM loading dose on days 1 and 15, then 500 mg monthly
- **OTHERS**—*megestrol acetate* 160 mg PO daily, methyltestosterone
- **ADJUVANT SETTING**—for premenopausal women, consider tamoxifen \times 5–10 years or LHRH agonist/oophorectomy + AI \times 5 years if higher risk. For postmenopausal women, consider one of the following: *anastrozole* \times 5 years, *letrozole* \times 5 years, tamoxifen \times 2–3 years followed by exemestane or *anastrozole* to complete 5 years of adjuvant hormonal therapy, tamoxifen \times 5 years followed by *letrozole* \times 5 years, or tamoxifen \times 10 years. Consider aromatase inhibitors as first hormonal agent if $>10\%$ risk of relapse in first 2 years (e.g. ≥ 4 positive nodes, low ER or grade 3 disease)
- **NEOADJUVANT SETTING**—for post-menopausal women who require neoadjuvant therapy but could not tolerate chemotherapy, neoadjuvant endocrine therapy \times 4–6 months may be an option

PRINCIPLES OF HER2-DIRECTED THERAPY

—HER2 positive disease should be treated with chemotherapy plus trastuzumab in the adjuvant/neoadjuvant settings. Do not give concomitantly with anthracyclines. In the metastatic setting, give chemotherapy and then maintenance trastuzumab until progression. Trastuzumab is classically associated with reversible heart failure and cardiac function monitoring every 3 months is required

PRINCIPLES OF ADJUVANT/NEOADJUVANT CHEMOTHERAPY

- **PATIENT SELECTION**
 - **TRIPLE NEGATIVE DISEASE**—consider (neo) adjuvant chemotherapy if tumor >5 mm
 - **HER2 +VE DISEASE**—consider (neo)adjuvant chemotherapy if tumor >5 mm
 - **ER/PR +VE, HER2 -VE DISEASE**—if lymph node negative, consider Oncotype Dx Breast Recurrence[®] testing (a 21-gene assay) to help with risk stratification: recurrence score 50 years; however, for premenopausal patients <50 , there is a small benefit. If lymph node positive disease, chemotherapy is generally recommended

TREATMENT ISSUES (CONT'D)

although there is emerging data on use of Oncotype Dx[®] for risk stratification as well

- **ADJUVANT VS. NEOADJUVANT THERAPY**—neoadjuvant therapy is administered before surgery; in contrast, adjuvant therapy starts 4–10 weeks after surgery. Neoadjuvant chemotherapy is historically used to downstage cancer (i.e. T3-4 or N2-3 disease) making non-resectable disease more amenable to resection. Now also used to evaluate sensitivity to treatment especially in HER2 amplified and triple negative breast cancers. Typically given for 5 months
- **ADJUVANT/NEOADJUVANT THERAPY REGIMENS**
 - **HER2 -VE DISEASE**—dose dense adriamycin + cyclophosphamide (AC) \times 4 followed by weekly paclitaxel \times 12 or docetaxel + cyclophosphamide (TC) \times 4 cycles if anthracyclines contraindicated
 - **HER2 +VE DISEASE**—docetaxel + carboplatin + trastuzumab + pertuzumab \times 6 (TCHP), AC followed by paclitaxel + trastuzumab \pm pertuzumab (THP), paclitaxel + trastuzumab (TH). Need trastuzumab \pm pertuzumab to complete 1 year total
- **ADJUVANT THERAPY REGIMENS FOR PATIENTS WITH RESIDUAL DISEASE POST NEOADJUVANT THERAPY**
 - **TRIPLE NEGATIVE DISEASE**—capecitabine
 - **HER2 +VE DISEASE**—T-DM1

PRINCIPLES OF PALLIATIVE CHEMOTHERAPY

—patients with rapidly growing disease, especially involvement of visceral organs such as lung or liver, may benefit more from chemotherapy compared to hormonal therapy due to a more rapid response. The choice of first line palliative chemotherapy depends on prior adjuvant chemotherapy, disease-free interval, patient's performance status, and willingness/ability to tolerate side effects. Doublet regimens are associated with higher response rate, while single agents are better tolerated and are particularly appropriate for patients who are elderly or have poor performance status. Consider doublet regimens in patients that need a rapid response to relieve tumor-related symptoms. At eventual disease progression, change chemotherapy to non-cross-resistance single agents

PRINCIPLES OF OSTEOCLAST INHIBITOR THERAPY

—for patients with bone metastases, consider bisphosphonates (*zoledronate* 4 mg IV over 15 min q4w for up to 2 years) or *denosumab* 120 mg SC q4wk. Dental clearance is necessary

TREATMENT ISSUES (CONT'D)

prior to start of these agents due to risk of osteonecrosis of the jaw

LOCAL RECURRENCE—biopsy to try to distinguish recurrence from new primary, metastatic workup. If isolated local recurrence, resection/completion mastectomy ± radiation. Hormonal and/or chemotherapy may also be considered

BRAIN METASTASES—steroids, resection plus radiation, or radiation alone if resection not pos-

TREATMENT ISSUES (CONT'D)

sible. Surgery plus radiation is associated with better overall survival than radiation alone for eligible candidates (10 vs. 6 months). Stereotactic radiation if <3 lesions and all <3 cm [<1.2 in.]. May consider re-irradiation if over 1 year from first whole brain radiation

Related Topics

Cancer Screening (p. 239)

Hereditary Cancers (p. 241)

Cancer Survivorship (p. 245)

Esophageal Cancer

NCCN Guidelines v4.2020

PATHOPHYSIOLOGY**CLASSIFICATION BY HISTOLOGY**

- **ADENOCARCINOMA**—75% in distal esophagus
- **SQUAMOUS**—evenly distributed between upper, middle, and lower thirds of esophagus
- **MELANOMA**
- **LEIOMYOSARCOMA**
- **LYMPHOMA**
- **CARCINOID**

RISK FACTORS

	Squamous	Adeno
Barrett esophagus	–	>8 ×
Reflux symptoms	–	4–8 ×
Obesity	–	2–4 ×
Smoking	4–8 ×	2–4 ×
Alcohol use	4–8 ×	–
Caustic injury to esophagus	>8 ×	–
Achalasia	4–8 ×	–
Poverty	2–4 ×	–
History of H&N cancer	>8 ×	–
History of breast cancer with radiation	4–8 ×	4–8 ×
Plummer–Vinson syndrome	>8 ×	–
Non-epidermolytic palmoplantar keratoderma	>8 ×	–
Frequent hot beverages	<2 ×	–

CLINICAL FEATURES

LOCAL—dysphagia (74%), odynophagia (17%), upper GI bleed, epigastric pain

REGIONAL—dyspnea, cough, hoarseness, pain (retrosternal, back, RUQ)

METASTATIC—Virchow node, hepatomegaly, pleural effusion

CONSTITUTIONAL—anorexia, fatigue, weight loss

Related Topics

Barrett Esophagus (p. 131)

Esophageal Dysphagia (p. 128)

Gastric Cancer (p. 217)

STAGING

TNM STAGING (staging is complex and evolving; stage grouping includes TNM stage and grade; it differs between squamous cell carcinoma and adenocarcinoma and has different criteria for clinical, pathological and post-neoadjuvant staging (for details please refer to *AJCC Cancer Staging Manual*, 8th ed.)

T stage

- **T1**—invades lamina propria, muscularis mucosa, or submucosa
- **T2**—invades muscularis propria
- **T3**—invades adventitia
- **T4**—invades into adjacent structures (pleura, pericardium, diaphragm, aorta, vertebral body, trachea, mediastinum)

STAGING (CONT'D)**N stage**

- **N1**—1–2 regional lymph nodes
- **N2**—3–6 regional lymph nodes
- **N3**—7 or more regional lymph nodes

M stage (spreads rapidly and early. Over 50% unresectable/metastatic disease at presentation)

- **M1**—distant metastasis

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CEA
- **IMAGING**—CXR, barium swallow, CT chest and abd, endoscopic US (excellent for staging), PET scan (preoperative workup)
- **BIOPSY**—gastroscopy ± laparoscopy

DIAGNOSTIC AND PROGNOSTIC ISSUES

SCREENING (for Barrett esophagus)—consider screening gastroscopy in patients with risk factors (age ≥ 50 , male, white race, chronic GERD >5 years, hiatal hernia, high BMI or intra-abdominal fat distribution, \pm tobacco use, \pm nocturnal reflux)

SURVEILLANCE (for Barrett)—endoscopic surveillance with four-quadrant biopsies q3–5 years (if no dysplasia on biopsy), q6–12 months (low-grade dysplasia), q3 months (high-grade dysplasia without eradication therapy)

PROGNOSIS BY STAGE—5 year overall survival rates for localized, locally advanced and metastatic cancer are 47%, 25%, and 5%, respectively

POOR PROGNOSTIC FACTORS—weight loss $>10\%$, dysphagia, large tumors, advanced age, lymphatic micrometastases

MANAGEMENT

NUTRITIONAL SUPPORT—dietitian consult. Consider supplemental feeding if significant weight loss, but only if benefit greater than risk. Palliative care referral for symptom management

RESECTABLE

- **SURGICAL RESECTION** (right transthoracic approach, transhiatal approach)—surgery only for T1N0 disease. Add preoperative chemoradiation (weekly carboplatin + paclitaxel, or cisplatin + 5-fluorouracil, 4140–5040 cGy) if T2–4 or N+ disease. Endoscopic resection is a reasonable alternative to surgery, particularly for older individuals, medically inoperable patients
- **DEFINITIVE CHEMORADIATION WITHOUT SURGERY**—weekly carboplatin + paclitaxel, or cisplatin or oxaliplatin + 5-fluorouracil, or 5-fluorouracil +

MANAGEMENT (CONT'D)

leucovorin + oxaliplatin + docetaxel (FLOT, this regimen for adenocarcinoma only), 4140–5040 cGy may be a reasonable alternative to surgery, particularly for patients with squamous cell carcinoma, older individuals, medically inoperable patients, and cervical esophageal carcinoma (difficult resection)

- **PERI-OPERATIVE CHEMOTHERAPY REGIMEN**—epirubicin + cisplatin + 5-fluorouracil $\times 3$ (ECF), followed by surgical resection and then ECF $\times 3$ similar to treatment for gastric cancer if GE junction involved, good performance status, and not dysphagic.
- **IMMEDIATE RESECTION FOLLOWED BY POSTOPERATIVE CHEMORADIATION**—if unsuitable for preoperative therapy

LOCALLY ADVANCED, UNRESECTABLE

(T3–4N1, 65%, median survival 12–14 months)

- **ADENOCARCINOMA**—definitive chemoradiation or peri-operative chemotherapy as above. For peri-operative chemotherapy, FLOT $\times 4$ followed by surgical resection and then FLOT $\times 4$ is an alternative regimen
- **SQUAMOUS CELL CARCINOMA**—definitive chemoradiation as above. Palliative surgical resection may be considered for selected patients (increased local control) although squamous cell carcinoma is very sensitive to chemoradiation, and thus surgery may not be needed

METASTATIC, UNRESECTABLE

- **MUTATION TESTING**—MSI, PD-L1, HER2 and NTRK gene fusion gene
- **PALLIATIVE CHEMOTHERAPY**
 - **FIRST LINE**—standard regimens include carboplatin + paclitaxel, 5-fluorouracil + leucovorin + oxaliplatin (FOLFOX), 5-fluorouracil + leucovorin + irinotecan (FOLFIRI), or 5-fluorouracil or irinotecan alone. Three drug regimens, such as ECF, docetaxel + cisplatin + 5-fluorouracil (DCF), and epirubicin + oxaliplatin + capecitabine (EOX), have greater toxicities and should be reserved for medically fit patients with good performance status. For HER2 positive disease, trastuzumab added to first line therapy.
 - **SECOND LINE**—for adenocarcinoma, taxane \pm ramucirumab, FOLFIRI, irinotecan alone. For squamous cell carcinoma, immunotherapy if PD-L1 expression levels by combined positive score of ≥ 10
 - **THIRD LINE**—for adenocarcinoma, immunotherapy if PD-L1 expression levels by combined positive score of ≥ 1

MANAGEMENT (CONT'D)

- **PALLIATIVE RADIATION**—brachytherapy, external beam radiation
- **PALLIATIVE CARE**—referral for patients with supportive care needs
- **PALLIATIVE PROCEDURES**—dilatation and endoluminal stent if obstruction, phototherapy, G-tube insertion

Gastric Cancer

NCCN Guidelines v3.2020

PATHOPHYSIOLOGY**CLASSIFICATION BY HISTOLOGY**

- **ADENOCARCINOMA** (95%)—diffuse, intestinal, or mixed type
- **LEIOMYOSARCOMA** (5%)
- **LYMPHOMA**—mucosal-associated lymphoma
- **CARCINOID**
- **GI STROMAL**

PATHOLOGIC SUBTYPES

	Diffuse type	Intestinal type
Location	Proximal	Distal
Age of onset	Younger	Older
Gender	F > M	M > F
Risk factors	Hereditary	Endemic
<i>H. pylori</i>	32%	89%
Metastasis	Peritoneal	Hepatic
Outcome	Worse	Better

LINITIS PLASTICA (15%)—diffuse disease involving the entire stomach. Very poor prognosis; slightly better with superficial/expansive type (5–10%)

LOCATION—35% proximal, 25% body, 40% distal

RISK FACTORS

- **ETHNICITY**—Asian origin (Japanese and Chinese)
- **FAMILY HISTORY**—affected relatives (L), HNPCC, FAP, Li-Fraumeni, Peutz-Jeghers syndrome, hereditary diffuse gastric cancer
- **ENVIRONMENTAL**—nitrite consumption (pickled, salted, and cured foods), alcohol (U), smoking (U), lower socioeconomic status (L)
- **DISEASES**—*Helicobacter pylori* (L), EBV, hiatal hernia (U), pernicious anemia (3–18×), chronic gastritis, gastric polyps, previous partial gastrectomy where U=upper stomach, L=lower stomach

TREATMENT ISSUES

FOLLOW-UP—no agreed upon surveillance program. Clinical assessment every 3 months during the first year, then every 6 months for a total of 5 years. Endoscopy as clinically indicated

CLINICAL FEATURES

LOCOREGIONAL—epigastric pain, nausea and vomiting, dysphagia, upper GI bleed (melena, hematemesis), anemia, abdominal mass

METASTATIC—hepatomegaly, Virchow node (left supraclavicular lymph node), Irish node (left axillary lymph node), dyspnea, Sister Mary Joseph nodule (umbilicus), Krukenberg tumor (ovaries)

CONSTITUTIONAL—anorexia, fatigue, weight loss
PARANEOPLASTIC—acanthosis nigricans, seborrheic keratosis (Leser-Trelat sign), inflammatory myositis, circinate erythema, cerebellar ataxia, thromboembolism, Cushing, carcinoid

STAGING

TNM STAGING (staging is complex and evolving; stage grouping has different criteria for clinical, pathological and post-neoadjuvant staging (for details please refer to *AJCC Cancer Staging Manual*, 8th ed.)

T stage

- **T1**—invades lamina propria, muscularis mucosa or submucosa
- **T2**—invades muscularis propria
- **T3**—penetrates subserosa without invasion of serosa (visceral peritoneum)
- **T4**—invades serosa (visceral peritoneum) or adjacent structures (esophagus, small bowel, transverse colon, spleen, liver, pancreas, adrenal gland, kidney, diaphragm, abdominal wall, retroperitoneum)

N stage (around stomach and along left gastric, common hepatic, splenic, celiac arteries)

- **N1**—1–2 regional lymph nodes
- **N2**—3–6 regional lymph nodes
- **N3**—7 or more regional lymph nodes

M stage (liver, lung, peritoneum, left supraclavicular lymph node, left axillary lymph node, umbilicus, ovary)

- **M1**—distant metastasis

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lyses, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CEA, CA 19–9
- **IMAGING**—CXR, barium swallow, endoscopic US, CT abd, US abd, PET/CT
- **BIOPSY**—gastroscopy (biopsy with *H. pylori* testing), laparotomy

DIAGNOSTIC AND PROGNOSTIC ISSUES

SCREENING—screening program in Japan may have contributed to the improved survival in that population through early detection of resectable gastric cancer. Not recommended outside countries with a high gastric cancer burden

PROGNOSIS BY STAGE—5 year overall survival rates for localized, locally advanced and metastatic cancer are 69%, 31%, and 5%, respectively

Related Topics

Dyspepsia (p. 130)
 Leser-Trelat Sign (p. 410)
 MALT (p. 197)
 Melena (p. 134)

MANAGEMENT

STAGE IA—gastrectomy (total or subtotal) with D2 dissection

STAGE IB, II, III

- **OPTION 1**—neoadjuvant epirubicin + cisplatin + infusional 5-fluorouracil (ECF) × 3 + surgery + adjuvant ECF × 3; 43% of patients able to complete treatment
- **OPTION 2**—gastrectomy (total or subtotal) with D2 dissection + adjuvant chemoradiation (5-fluorouracil)
- **INSUFFICIENT EVIDENCE**—adjuvant radiation alone, adjuvant chemotherapy alone, and neoadjuvant radiation

STAGE IV (T1–4N1–3M0)—same treatment approach as stage III if resectable disease. Otherwise, same treatment approach as metastatic disease

MANAGEMENT (CONT'D)**STAGE IV (M1)**

- **MUTATION TESTING**—MSI, PD-L1, HER2 (15–20%, intestinal > diffuse, high grade less likely) and NTRK fusion gene
- **PALLIATIVE CHEMOTHERAPY**
 - **FIRST LINE**—standard regimens include carboplatin + paclitaxel, 5-fluorouracil + leucovorin + oxaliplatin (FOLFOX), 5-fluorouracil + leucovorin + irinotecan (FOLFIRI), or 5-fluorouracil or irinotecan alone. Three drug regimens, such as ECF, docetaxel + cisplatin + 5-fluorouracil (DCF), and epirubicin + oxaliplatin + capecitabine (EOX), have greater toxicities and should be reserved for medically fit patients with good performance status. For HER2 positive disease, trastuzumab added to first line therapy
 - **SUBSEQUENT LINES**—immunotherapy if MSI-high tumor or if PD-L1 expression levels by combined positive score of ≥1
- **PALLIATIVE RADIATION**—for bony metastasis or bleeding tumors
- **PALLIATIVE SURGERY**—gastrojejunostomy, partial gastrectomy to bypass obstruction
- **PALLIATIVE CARE**—referral for patients with supportive care needs

TREATMENT ISSUES**LYMPH NODE RESECTION**

- **D1 dissection**—removal of the stomach and less and greater omentum with the associated N1 perigastric lymph nodes
- **D2 dissection**—D1 dissection, plus removal of N2 lymph nodes, including a splenectomy and distal pancreatectomy

VITAMIN B12 DEFICIENCY—may develop after a few years in patients who received subtotal or total gastrectomy

FOLLOW-UP—no agreed upon surveillance program. Every 3 months for first year, then every 6 months for a total of 5 years. Endoscopy as clinically indicated

Colorectal Cancer

NCCN Guidelines v4.2020
 NCCN Guidelines v6.2020

PATHOPHYSIOLOGY**CLASSIFICATION BY HISTOLOGY**

- **ADENOCARCINOMA**—mucinous subtype, signet-ring cells, adenosquamous, medullary

PATHOPHYSIOLOGY (CONT'D)

- **CARCINOID**—mostly involving appendix and rectum, less malignant

PATHOPHYSIOLOGY (CONT'D)

- **RARE**—squamous cell, small cell, undifferentiated
- **ADENOMATOUS POLYP**—pre-malignant

RISK FACTORS

- **PERSONAL**—age
- **FAMILY HISTORY**—affected relatives (2 ×), hereditary nonpolyposis colorectal cancer/Lynch syndrome (HNPCC: mutation in MSH-2, MLH-1, PMS-1, PMS-2, or MSH-6 genes responsible for mismatch repair, 6% of all colon cancers), familial adenomatous polyposis (FAP: 1% of all colon cancers related to mutation in APC gene, all affected will have colon cancer by age 40), Peutz-Jeghers syndrome, juvenile polyposis, Gardner syndrome, Turcot syndrome, flat adenoma syndrome
- **ENVIRONMENTAL**—decreased fiber intake
- **DISEASES**—prior colon cancer, polyps, ovarian, breast, endometrial cancer, Crohn disease, ulcerative colitis (1%/year after 10 years), diabetes, obesity

LOCATION—50% rectosigmoid, 18% descending colon, 11% transverse colon, 20% in the ascending colon and cecum

DISTINGUISHING FEATURES BETWEEN COLON AND RECTAL CANCER

	Colon cancer	Rectal cancer
Frequency	2/3	1/3
Location	>12 cm [>4.7 in.] from anal verge or above	<12 cm [<4.7 in.] from anal verge or below
	peritoneal reflection	peritoneal reflection
Metastasis	Liver	Liver and lung
Adjuvant treatments	Chemo	RT and chemo

MOLECULAR SEQUENCE FOR DEVELOPMENT OF COLON CANCER

—the Vogelstein model of carcinogenesis developed based on analysis of FAP lesions. Normal epithelium → loss of 5q (e.g. APC, β-catenin) over decades → adenoma development → loss of 18q (e.g. k-ras) over 2–5 years → late adenoma → loss of 17p (e.g. p53) over 2–5 years → early cancer → loss of 8p → late cancer

MICROSATELLITE INSTABILITY (MSI)—may either be inherited as in HNPCC or spontaneous (15% of sporadic colon cancers). Compared to

PATHOPHYSIOLOGY (CONT'D)

MSI-low tumors, MSI-high (i.e. mutated) tumors are associated with female sex, right sided tumors, poorly differentiated tumors, lower response to 5-fluorouracil-based adjuvant chemotherapy, higher response to checkpoint inhibitors and better prognosis

RIGHT-SIDED COLON CANCER—compared to left-sided tumors, right-sided tumors are associated with MSI-high status, BRAF V600E mutants, lower response to EGFR-based therapy (panitumumab, cetuximab), and worse prognosis

RAS-RAF PATHWAY—about 40% of colon cancer has mutation in KRAS, which plays a key role in signal transduction downstream of EGFR. Tumors with mutant K-ras or defects along the pathway (N-ras, B-raf V600E mutation) are unlikely to respond to EGFR-based therapy (panitumumab, cetuximab) unless given with a BRAF inhibitor

HER2 MUTANT—anti-HER2 therapy is only indicated in HER2 amplified tumors that are also RAS and BRAF wild type

CLINICAL FEATURES

LOCOREGIONAL—bowel habit change, hemochezia, paradoxical diarrhea, tenesmus, abdominal pain, iron deficiency anemia

METASTATIC—RUQ pain, dyspnea

CONSTITUTIONAL—weight loss, anorexia, fatigue

OTHER—*Streptococcus bovis* bacteremia and *Clostridium septicum* sepsis; colorectal cancer in 16–32% of patients with *S. bovis* bacteremia

STAGING

TNM STAGING (staging is complex and evolving; stage grouping has different criteria for clinical, pathological and post-neoadjuvant staging; for details please refer to *AJCC Cancer Staging Manual*, 8th ed.)

T stage

- **T1**—invades submucosa
- **T2**—invades muscularis propria
- **T3**—penetrates subserosa or non-peritonealized pericolic tissues
- **T4**—perforation of visceral peritoneum or directly invades into adjacent structure (bowel, bladder, uterus, pelvic wall)

N stage (mesenteric)

- **N1**—1–3 regional lymph nodes
- **N2**—≥4 regional lymph nodes

M stage (liver, lung, bone, brain)

- **M1**—distant metastasis

STAGING (CONT'D)**STAGE GROUPING**

Stage	TNM @ = any
I	T1-2N0M0
IIA	T3N0M0
IIB	T4aN0M0
IIC	T4bN0M0
IIIA	T1-2N1M0, T1N2aM0
IIIB	T3-4aN1M0, T2-3N2aM0, T1-2N2bM0
IIIC	T4aN2aM0, T3-4aN2bM0, T4bN1-2M0
IV	T@N@M1

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CEA, CA19–9
- **IMAGING**—barium enema, CT abd, CXR, MRI, and endorectal US in rectal cancer
- **BIOPSY**—colonoscopy with biopsy, laparoscopy, laparotomy

PROGNOSTIC ISSUES

PROGNOSIS BY STAGE—5 year overall survival rates for localized, locally advanced and metastatic disease are 90%, 71%, and 14% for colon cancer and 89%, 71% and 15% for rectal cancer, respectively

MANAGEMENT OF COLON CANCER

STAGE I—surgical resection only

STAGE II—surgical resection. Consider **adjuvant chemotherapy** (capecitabine, 5-fluorouracil-leucovorin, consider FOLFOX if high risk or MSI-high tumors) if adverse prognostic features (T4, perforation, obstruction, poorly differentiated, signet ring cell and mucinous histology, lymphovascular invasion, inadequate lymph node sampling <12)

STAGE III—surgical resection + adjuvant chemotherapy (FOLFOX is the first choice. Other possibilities include capecitabine, 5-fluorouracil-leucovorin, infusional 5-fluorouracil if patient is not fit or has contraindications to oxaliplatin)

STAGE IV

- **MUTATION TESTING**—MSI, KRAS, NRAS, BRAF, HER2
- **RESECTION OF OLIGOMETASTASES**—if metastasis limited to liver and potentially resectable, consider liver resection plus perioperative chemotherapy. Radiofrequency ablation could be considered if patient unfit for surgery

MANAGEMENT OF COLON CANCER (CONT'D)

- **PALLIATIVE CHEMOTHERAPY**—standard regimens include 5-fluorouracil + leucovorin + oxaliplatin (FOLFOX) ± bevacizumab, 5-fluorouracil + leucovorin + irinotecan (FOLFIRI) ± bevacizumab, or 5-fluorouracil + leucovorin, capecitabine, regorafenib, trifluridine + tipiracil (TAS-102). Raltitrexed if 5-fluorouracil intolerant. Cetuximab + irinotecan or single-agent panitumumab in third line if KRAS wild type. Pembrolizumab or nivolumab if MSI-high. Trastuzumab + pertuzumab if Her2 +ve and KRAS wild type
- **PALLIATIVE CARE**—referral for patients with supportive care needs

Related Topics

Cancer Screening (p. 239)
Hematochezia (p. 137)
Hereditary Cancers (p. 241)
Cancer Survivorship (p. 245)

MANAGEMENT OF RECTAL CANCER

HIGHLY RESECTABLE (stage I)—**transanal excision** only if T1, 0.3 cm [>0.12 in.], mobile, within 8 cm [3.1 in.] of anal verge, no lymphovascular or perineural invasion, well or moderately differentiated tumor, and no evidence of lymphadenopathy on pretreatment imaging. Otherwise, **total mesorectal excision** via low anterior resection or abdominoperineal resection

RESECTABLE (stage II and some stage III with no high risk features (i.e. not fixed, not low <5 cm [2 in.], not bulky)—**neoadjuvant radiation** (short course, 1 week) + **total mesorectal excision + adjuvant chemotherapy** based on pathologic stage (FOLFOX $\times 12$ if pathologic node positive; capecitabine $\times 8$ if pathologic node negative. The type and the number of cycles of adjuvant chemotherapy are, however, not well established. Local guideline may vary. Neoadjuvant chemoradiation is also an appropriate option for these patients

POSSIBLY RESECTABLE (locally advanced disease, particularly if tethered to rectum or low-lying tumor <5 cm [<2 in.] from anus)—**neoadjuvant chemoradiation** (long course, 5 weeks, 5040 cGy plus infusional 5-fluorouracil or capecitabine) \pm neoadjuvant chemotherapy + **total mesorectal excision + adjuvant chemotherapy** for 4 months.

MANAGEMENT OF RECTAL CANCER (CONT'D)

Capecitabine or FOLFOX may be considered depending on the extent of downstaging with neoadjuvant chemoradiation and the pathologic stage

METASTATIC (stage IV)—see Management for Stage IV Colon Cancer

TREATMENT ISSUES

MODULATORS OF 5-FLUOROURACIL ACTIVITY—leucovorin (LV) promotes formation of a stable ternary complex with thymidylate synthetase, permitting prolonged inhibition of the enzyme by 5-fluorouracil

Carcinoid Tumors

NCCN v2.2020

PATHOPHYSIOLOGY**CLASSIFICATION OF NEUROENDOCRINE TUMORS**

- **HIGH GRADE**—poorly differentiated neuroendocrine carcinomas, small cell-like tumors
- **LOW GRADE**—carcinoid tumors, pancreatic islet tumors (VIPoma, glucagonoma, gastrinoma, insulinoma, somatostatinoma), paragangliomas, pheochromocytomas, medullary thyroid carcinomas

CLASSIFICATION BY LOCATION

- **FOREGUT CARCINOID**—lungs, bronchi, stomach
- **MIDGUT CARCINOID**—small intestine, appendix, proximal large bowel
- **HINDGUT CARCINOID**—distal colon, rectum, genitourinary tract

SPECIFIC DETAILS BY LOCATION

- **LUNGS AND BRONCHI**—derived from epithelial endocrine cells
 - **WELL-DIFFERENTIATED NEUROENDOCRINE TUMOR** (typical carcinoid, 67%)—more indolent. May secrete corticotrophin but rarely secretes serotonin; 90% 5-year survival
 - **WELL-DIFFERENTIATED NEUROENDOCRINE CARCINOMA** (atypical carcinoid, 33%)—may be aggressive with high chance of metastases; 40–60% 5-year survival
- **STOMACH**—derived from enterochromaffin-like cells
 - **TYPE 1: CHRONIC ATROPHIC GASTRITIS-TYPE-A-ASSOCIATED CARCINOID TUMOR** (75%)—indolent, usually multiple, not associated with carcinoid syndrome
 - **TYPE 2: CARCINOID TUMOR ASSOCIATED WITH ZOLLINGER-ELLISON SYNDROME OR MEN 1** (5–10%)—indolent, may be multiple, not associated with carcinoid syndrome
 - **TYPE 3: SPORADIC CARCINOID TUMOR** (15–25%)—may be aggressive with high

PATHOPHYSIOLOGY (CONT'D)

chance of metastases. Contain a variety of endocrine cells. May be associated with atypical carcinoid syndrome

- **SMALL BOWEL**—derived from intraepithelial endocrine cells. Often multiple, usually in ileum. Associated with carcinoid syndrome in 5–7% of patients with liver metastasis (first-pass metabolism)
- **APPENDIX**—carcinoid tumors are the most common neoplasms in the appendix. Derived from subepithelial endocrine cells. Usually indolent
- **COLON**—derived from epithelial endocrine cells. Usually right sided, often presents at late stage
- **RECTUM**—derived from epithelial endocrine cells. Carcinoid syndrome rare

Related Topics

Wheezing (p. 1)
Chronic Diarrhea (p. 139)

FUNCTIONALITY—carcinoid tumors arise from neuroendocrine cells. Contain membrane-bound neurosecretory granules such as serotonin, histamine, dopamine, substance P, neurotensin, prostaglandins, kallikrein, ACTH, calcitonin, gastrin. Release of these vasoactive agents leads to episodic symptoms. However, about 50% of tumors are non-secretory and thus non-functional

SEROTONIN SYNTHESIS—5-hydroxytryptophan (with aromatic acid decarboxylase) → serotonin (with monoamine oxidase) → 5-hydroxyindoleacetic acid (5-HIAA) → excreted in urine

METASTASIS—liver and sometimes bones (osteoblastic)

CLINICAL FEATURES

GENERAL—the majority of patients are asymptomatic (carcinoid syndrome only seen in 10% of small bowel carcinoids in the presence of liver metastases, <1% appendix, none in the rectum); 75–80% of patients with the carcinoid syndrome have small bowel carcinoids

LOCAL—obstruction (airway, bowel), pain (abdominal), bleeding

NEUROENDOCRINE SYNDROMES (30–40% of tumors active)—serotonin mainly (episodic purplish flushing, diarrhea, wheezing, hypotension and eventually right-sided valvular heart disease), fibrosing mesenteritis, Cushing, acromegaly (rare). Attacks may be spontaneous or precipitated by stress, exercise, eating or alcohol use, palpation of the liver and anesthesia. Gastric and bronchial carcinoids are associated with atypical carcinoid syndromes (histamine). Somatostatinoma is associated with the triad of diabetes mellitus (insulin release impaired), cholelithiasis (reduced gallbladder contractility), and diarrhea/steatorrhea (pancreatic insufficiency)

NIACIN DEFICIENCY—pellagra as tryptophan directed to production of serotonin

METASTASIS—jaundice, liver failure, bone pain
CARCINOID HEART DISEASE—occurs in 1/2 of patients with carcinoid syndrome. Factors (e.g. serotonin) secreted by liver metastases into hepatic vein → plaque like, fibrous endocardial thickening involving the right side of the heart → tricuspid regurgitation most common. Tricuspid stenosis, pulmonary regurgitation, and pulmonary stenosis may also occur. Pulmonary carcinoids may produce left-sided valvular disease

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, serum chromogranin A, 24 h urine 5-HIAA (sens 73%, spc 100%)
- **IMAGING**—CT chest/abd/pelvis, somatostatin scintigraphy (sens 89%), MIBG scan (useful if somatostatin scan negative). Echocardiogram
- **BIOPSY**—ensure pathology includes Ki67 immunohistochemistry

SPECIAL

- **PANCREATIC NEUROENDOCRINE TUMOR WORKUP**—pancreatic polypeptide, α -hCG, chromogranin A, gastrin, somatostatin, serum VIP, glucagon, insulin and C-peptide levels
- **SERUM SEROTONIN**—when urinary 5-HIAA equivocal
- **EPINEPHRINE OR PENTAGASTRINE PROVOCATION TESTS**—if flushing and normal markers

MANAGEMENT**SYMPTOM CONTROL (AVOID PRECIPITATING FACTORS)**

- **DIARRHEA**—*octreotide* 100–600 μ g SC div 2–4 doses, *octreotide depot* 10–30 mg IM every 28 days, *lanreotide*, *loperamide* 4 mg \times 1 dose, then 2 mg q4h PRN, maximum 16 mg/day, *atropine-diphenoxylate* 1–2 tabs q6–8 h, *cyproheptadine*, *methysergide*, *ondansetron* 8 mg PO TID. Gastric carcinoid can respond to a histamine blocker
- **HYPOTENSION**—pure α -adrenergic medications such as methoxamine and angiotensin. Corticosteroids may be useful for prophylaxis. Strictly avoid β -adrenergic agonists such as epinephrine and dopamine as they may aggravate hypotension
- **FLUSHING**—*octreotide*, *prochlorperazine* 10 mg PO QID (foregut), *phenoxybenzamine* 10–20 mg PO BID, *prednisone* 20–40 mg PO daily (foregut)
- **BRONCHOSPASM**—*salbutamol* 2 puffs INH q4h PRN, *ipratropium*, *theophylline*
- **CARCINOID HEART DISEASE**—medical management of heart failure, valvular replacement may be considered but patients are usually high-risk surgical candidates

LOCALIZED DISEASE—resection**ADVANCED/METASTATIC DISEASE**

- **PALLIATIVE RESECTION**—for debulking, prevention of mesenteric fibrosis by mid-gut carcinoids, and treatment of obstruction and extraintestinal primary tumors such as bronchial and ovarian carcinoids that rarely cause carcinoid syndrome without liver metastasis. Consider resection, radiofrequency ablation and cryoablation, hepatic artery embolization for liver metastasis
- **TARGETED AGENTS**—everolimus, sunitinib
- **CHEMOTHERAPY**—limited activity, consider temozolomide + capecitabine, streptozocin + 5-fluorouracil or doxorubicin. Consider cisplatin + etoposide for patients with poorly differentiated tumors
- **TARGET RADIOTHERAPY WITH RADIOLABELED SOMATOSTATIN ANALOGUES**—177 Lu-dotatate
- **PALLIATIVE CARE**—referral for patients with supportive care needs

TREATMENT ISSUES

SOMATOSTATIN ANALOGUES—*octreotide* is a long-acting somatostatin analogue that binds to somatostatin receptor 2 and to a certain extent receptors 3 and 5 and inhibits secretion of various

TREATMENT ISSUES (CONT'D)

hormones. Lanreotide shares the same mechanism of action as octreotide

- **INDICATIONS**—symptomatic with hormone-induced syndromes. Can be used in asymptomatic patients to delay progression for midgut tumors, and perioperatively to prevent carcinoid crisis. Controversial indications include post-surgery, post-embolization or radiofrequency ablation, and post-adjuvant treatment with no evidence of disease
- **DOSING**—give *octreotide* 50 µg as test dose (may cause gastric atony and skin toxicity), then 100–150 µg SC BID–TID. May double dose

TREATMENT ISSUES (CONT'D)

every 3–4 days until symptom free. Once on a stable dose, may switch to long-acting formulation (200–600 µg/day → 20 mg/month or 750–1500 µg/day → 30 mg/month). Continue life long

- **ADVERSE EFFECTS**—nausea, gastric atony, abdominal cramps, diarrhea/constipation, gallstones, impaired glucose tolerance, hypothyroidism, dyspnea, arrhythmia, HTN, fatigue, headache, dizziness, fever, flu-like symptoms
- FOLLOW-UP**—clinical assessment along with chromogranin A and 24 h urine 5-HIAA every 3–6 months, routine imaging every 6–12 months

Gastrointestinal Stromal Tumor**PATHOPHYSIOLOGY**

HISTOLOGY—spindle cell or epithelioid tumor that may be derived from interstitial cells of Cajal (pacemaker cells involved in peristalsis)

LOCATIONS—stomach (50%), small intestine (25%), colon (10%), esophagus, rectum, mesentery, and retroperitoneum

MOLECULAR BIOLOGY—characteristic *c-kit*/CD117 (90%) and/or PDGFRα mutation, CD34+ (66%)

NATURAL HISTORY—clinical behavior of GIST is variable and the risk of recurrence and metastases depends on various adverse prognostic factors. Metastases most commonly involve liver, rarely regional lymph nodes and almost never lungs

CLINICAL FEATURES

LOCOREGIONAL—GI bleed, abdominal mass, abdominal pain

METASTATIC—RUQ pain, jaundice

CONSTITUTIONAL—weight loss, anorexia, fatigue, hypoglycemia from secretion of IGFII (rare)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—CT abd/pelvis ± MRI, US abd, chest imaging, PET/CT in selected patients
- **BIOPSY**—endoscopy, laparotomy. Consider KIT and PDGRA mutational testing for KIT-negative tumors

PROGNOSTIC ISSUES

ADVERSE PROGNOSTIC FACTORS—size, mitotic rate, tumor site (small intestine worse), incomplete resection (<35% vs. 50–65% 5-year survival)

PREDICTIVE FACTORS—exon 11 KIT mutation is predictive of response to imatinib compared to exon 9 KIT mutation or wild type

MANAGEMENT

RESECTABLE DISEASE—**surgery** does not routinely cure GIST. Complete resection is possible in approximately 85% of patients with primary tumors. Segmental resection without regional lymphadenectomy. **Adjuvant imatinib** 400 mg PO daily is recommended for 36 months for patients with high-risk GIST

UNRESECTABLE, RECURRENT, OR METASTATIC DISEASE—**imatinib** 400 mg/day (until disease progression) is recommended, except for exon 9 mutation in which **imatinib** 800 mg/day is appropriate. For patients with non-metastatic but unresectable disease, consider neoadjuvant imatinib followed by resection if possible. For patients with potentially resectable metastatic GIST, surgery should be offered to those with stable disease, responding to tyrosine kinase inhibitor therapy, or with focal progression only. Hepatic chemoembolization could be considered in isolated unresectable liver metastases. If progression on imatinib, **increase dose** to 800 mg/day. With further disease progression, consider second line sunitinib, third line regorafenib and fourth line ripretinib. **Palliative care** referral for patients with supportive care needs

Cancer of the Exocrine Pancreas

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **ADENOCARCINOMA** (85–90%)—male predominance, 60% arising from head of pancreas, metastasizes widely
- **DUCTAL CARCINOMAS**
- **ADENOSQUAMOUS CARCINOMA**—rare variant of ductal adenocarcinoma, history of prior chemotherapy or radiotherapy, relatively poor prognosis
- **COLLOID CARCINOMA** (1–2%)—composed of pools of mucus that contains clusters of malignant duct cells
- **ACINAR CELL CARCINOMA** (1%)—lipase release, equal distribution throughout pancreas
- **MUCINOUS CYSTIC NEOPLASMS** (1%)—cystic, significant malignant potential, strong female predominance, 70–90% in pancreatic body/tail
- **SEROUS CYSTOADENOMAS**—cystic, benign
- **SEROUS CYSTADENOCARCINOMA**—cystic, malignant behavior
- **SOLID AND PSEUDOPAPILLARY CYSTIC TUMORS**—young female (childbearing) predominance, local invasion into adjacent structures common but metastases rare, frequent intracystic hemorrhage
- **INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM**—male predominance, benign lesion with high potential for malignant change
- **PANCREATOBLASTOMA**—rare (0.5%); first and second decades of life, prognosis better than for infiltrating ductal carcinoma
- **MISCELLANEOUS CANCERS**—liposarcomas, leiomyosarcomas, fibrosarcomas, and lymphomas
- **OTHER LESS COMMON VARIANTS**—pleomorphic, sarcomatoid, and giant cell carcinomas

RISK FACTORS

- **PERSONAL**—Ashkenazi Jewish origin, low socioeconomic status, habitation of industrialized societies, obesity, and low physical activity
- **FAMILY HISTORY**—HNPCC, FAP, BRCA1/2 gene, hereditary pancreatitis, ataxia telangiectasia, Peutz-Jeghers syndrome, familial atypical multiple mole melanoma syndrome (FAMMM), Li-Fraumeni syndrome
- **ENVIRONMENTAL**—smoking
- **DISEASES**—chronic pancreatitis, diabetes (may be a manifestation of early disease rather than a true risk factor), pernicious anemia, partial gastrectomy

CLINICAL FEATURES

LOCREGIONAL—abdominal pain (80%), jaundice (50%), pruritus, altered bowel habits (steatorrhea, pale stools), glucose intolerance

METASTATIC—RUQ pain, dyspnea

CONSTITUTIONAL—weight loss, anorexia, fatigue

OTHERS—Trousseau syndrome, polymyositis, dermatomyositis, panniculitic arthritis—eosinophilia syndrome, depression

STAGING

TNM STAGING

T stage

- **T1**—≤ 2 cm, limited to pancreas
- **T2**—> 2 cm, limited to pancreas
- **T3**—extends beyond pancreas, but not involving celiac axis or superior mesenteric artery
- **T4**—invades celiac axis or superior mesenteric artery

N stage (portal, peripancreatic, periaortic, celiac axis lymph nodes)

- **N1**—metastasis in regional lymph node(s)

M stage (liver, lungs, bone, pleura, adrenal)

- **M1**—distant metastasis

STAGE GROUPINGS

Stage TNM @ = any

IA	T1N0M0
IB	T2N0M0
IIA	T3N0M0
IIB	T1-3N1M0
III	T4N@M0
IV	T@N@M1

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CA 19–9, CEA, BRCA genetic testing for all pancreatic cancer patients
- **IMAGING**—CXR, CT abd (allows for establishment of resectability criteria, >90% accurate in the staging), US abd, endoscopic US (EUS), MRCP
- **BIOPSY**—percutaneous needle biopsy (only if unresectable disease), endoscopic US-guided biopsy, ERCP (also useful for treatment of biliary obstruction), laparoscopy, laparotomy

DIAGNOSTIC & PROGNOSTIC ISSUES

CT FINDINGS FOR PANCREATIC CANCER—mass (identified in 96% of cases), dilatation of the bile and pancreatic ducts (double-duct sign) suggests a pancreatic head lesion, dilatation of the pancreatic duct proximal to the tumor, atrophy of the pancreas distal to a tumor

PROGNOSIS BY STAGE—5 year overall survival rates for localized, locally advanced and metastatic pancreatic cancer are 37%, 12%, and 3%, respectively

MANAGEMENT

RESECTABLE (T1-3N0-1, 10–20%)—**Whipple procedure** plus either **adjuvant chemotherapy** (gemcitabine or 5-fluorouracil) or **adjuvant chemoradiation** (5-fluorouracil) ± gemcitabine in selected patients)

NON-RESECTABLE (locally advanced and metastatic disease, 80–90%)

- **BORDERLINE RESECTABLE**—if good performance status, consider 5-fluorouracil + leucovorin + irinotecan + oxaliplatin (FOLFIRINOX) ± subsequent chemoradiation or surgery. If borderline performance status, consider gemcitabine + nab-paclitaxel ± subsequent chemoradiation or surgery. For known BRCA1/2 or PALB2 mutation, can also consider gemcitabine with cisplatin
- **PALLIATIVE CHEMOTHERAPY**—if good performance status, consider FOLFIRINOX. If borderline performance status, consider gemcitabine + nab-paclitaxel or gemcitabine ± erlotinib. Other potential options include gemcitabine +

MANAGEMENT (CONT'D)

capecitabine, gemcitabine + cisplatin, FOLFOX, XELOX, single agent gemcitabine, single agent capecitabine, or infusional 5-fluorouracil. Olaparib for genetic BRCA1/2 mutations

- **CHEMORADIATION** (5-fluorouracil)—in selected patients with limited advanced unresectable cancer
- **PALLIATIVE CARE**—referral for patients with supportive care needs. For pain control, consider opioids, percutaneous celiac ganglion ablation; for anorexia-cachexia, consider dietitian referral, nutrition supplements, and steroids; for biliary obstruction, consider ERCP stent placement or percutaneous transhepatic cholangiography with drainage

TREATMENT ISSUES

RESECTABLE DISEASE CRITERIA—no liver, peritoneal, or other metastases; no involvement of celiac axis, superior mesenteric artery, and hepatic artery; and no encasement of portal vein and superior mesenteric vein (*adherence* of the tumor to a segment of these veins *may* allow resection with venous reconstruction). If in doubt, patients should be evaluated by a hepatobiliary surgeon

Related Topics

Cachexia (p. 442)
Cancer Pain (p. 434)
Jaundice (p. 155)

Hepatocellular Carcinoma**DIFFERENTIAL DIAGNOSIS OF FOCAL LIVER LESION (BY ULTRASOUND)****SOLID LESION**

- **HYPOECHOIC**—**malignant** (hepatocellular carcinoma, metastasis), **benign** (focal nodular hyperplasia, hepatic adenoma, hamartoma)
- **HYPERECHOIC**—hemangioma, calcification, focal fat

CYSTIC LESION

- **SIMPLE**—benign
- **COMPLEX**—bleeding, infections, *Echinococcus*

PATHOPHYSIOLOGY

RISK FACTORS—any causes of cirrhosis, particularly HBV, HCV, alcohol, and hemochromatosis. Note that HBV may cause hepatocellular carci-

PATHOPHYSIOLOGY (CONT'D)

noma without cirrhosis as the virus can integrate into host genome. Environmental toxins include aflatoxin, the bluegreen algal toxin microcystin, and betelnut chewing

CLINICAL FEATURES

LOCOREGIONAL—upper abdominal pain, early satiety, obstructive jaundice, intra-abdominal bleeding due to tumor rupture, decompensation of liver disease (ascites, encephalopathy, jaundice, and variceal bleeding)

METASTATIC—bone pain, dyspnea

CONSTITUTIONAL—weight loss, fever due to central tumor necrosis

CLINICAL FEATURES (CONT'D)

PARANEOPLASTIC SYNDROME—hypoglycemia, erythrocytosis, hypercalcemia, watery diarrhea, cutaneous features

STAGING FOR HEPATOCELLULAR CARCINOMA OR INTRAHEPATIC BILE DUCT CANCER**TNM STAGING****T stage**

- **T1**—solitary tumor without vascular invasion
- **T2**—solitary tumor with vascular invasion or multiple tumors ≤ 5 cm
- **T3**—multiple tumors > 5 cm or tumor that involves major branch of portal or hepatic vein
- **T4**—invades adjacent structures other than gallbladder or with perforation of the visceral peritoneum

N stage (along portal vein, hepatic artery, inferior vena cava, hepatoduodenal ligament)

- **N1**—metastasis in regional lymph node(s)

M stage (lungs, liver, bones, brain)

- **M1**—distant metastasis

STAGE GROUPINGS

Stage **TNM @ = any**

I	T1N0M0
II	T2N0M0
IIIA	T3N0M0
IIIB	T4N0M0
IVA	T@N1M0
IVB	T@N@M1

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, albumin, AFP
- **IMAGING**—CXR, CT abd (biphasic or triphasic), US abd, MRI abd, liver/spleen scan (if suspect FNH)

SPECIAL

- **BIOPSY**—liver biopsy only if non-specific imaging and meeting AASLD clinical criteria (> 1 cm, atypical vascular pattern on multiple imaging modalities including multiphase CT or MR) or if biopsy would have an impact on management options; if imaging definitive for HCC, biopsy not required and increases risk of seeding needle track

DIAGNOSTIC ISSUES

CT SCAN—characteristic features for hemangioma, FNH (central scar)

DIAGNOSTIC ISSUES (CONT'D)

LIVER SPLEEN SCAN—useful for distinguishing FNH and hepatoma

GALLIUM SCAN—useful for identifying hepatoma and abscesses (increased blood flow)

APPROACH TO HEPATOMA—start with US abd, followed by CT/nuclear scans to rule out other causes

- **LOW CLINICAL SUSPICION**—consider percutaneous biopsy
- **HIGH CLINICAL SUSPICION** (known cirrhosis)—patient should be referred to hepatobiliary surgeon for resection. Biopsy is not required

PROGNOSIS BY STAGE—5 year overall survival rates for localized, locally advanced and metastatic liver cancer are 33%, 11%, and 2%, respectively

MANAGEMENT

EARLY STAGE (1 lesion or 3 lesions ≤ 3 cm, Child-Pugh A-B and ECOG 0)—if only 1 lesion < 2 cm or CIS, bilirubin not significantly elevated and no portal hypertension, proceed to **resection**. If unresectable disease, consider **liver transplant** if no comorbidity plus either 1 lesion ≤ 5 cm or up to 3 lesions ≤ 3 cm (Milan Criteria). Consider **locoregional therapies** such as radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE) \pm drug eluting beads, and/or transarterial radioembolization (TARE) with yttrium-90 microspheres as either bridge therapy while waiting for transplant, downstaging therapy so tumor is small enough for transplant or if patient is not transplant candidate

INTERMEDIATE STAGE (multinodular disease, Child-Pugh A-B and ECOG 0; median survival 20 months)—**chemoembolization**

ADVANCED STAGE (portal invasion, N1, M1, Child-Pugh A–B or ECOG 1–2; median survival 11 months)—for patients with Child-Pugh A disease, consider **sorafenib** or **lenvatinib**. **Immunotherapy** and **bevacizumab** recently approved for first line. **Chemoembolization** may also represent an option for some patients. Median survival 11 months. **Palliative care** referral for patients with supportive care needs

TERMINAL STAGE (Child-Pugh C or ECOG > 2 ; median survival < 3 months)—supportive care only

TREATMENT ISSUES

CRITERIA FOR RESECTABLE DISEASE—well-compensated cirrhosis, single lobe involvement, no vascular invasion, N0, M0

TREATMENT ISSUES (CONT'D)

ABLATION—include thermal (radiofrequency), chemical (percutaneous ethanol or acetic acid), cyro and microwave ablation. Criteria for ablation include 1 lesion ≤ 5 cm or 3 lesions ≤ 3 cm, accessible location to percutaneous/laparoscopic/open approaches. Tumors ≤ 3 cm may be curable with ablation alone

ARTERIAL DIRECTED THERAPIES—include TACE, TACE with drug-eluting beads, TARE, and transarterial bland embolization (TAE). Useful for larger volume disease or tumors in inaccessible location. Relative contraindications include bilirubin >3 mg/dL, portal vein thrombosis, and Child-Pugh C. Adverse effects include decompensated liver failure, cholecystitis, and non-target embolization. No proven survival benefit but can shrink tumor

FOLLOW-UP OF RESECTABLE DISEASE—AFP and CT abd every 3–6 months for 2 years, then every 6–12 months

SPECIFIC ENTITIES

HEMANGIOMA—prevalence 5%. May gradually increase in size due to vascular expansion. Usually asymptomatic and no treatment required

FOCAL NODULAR HYPERPLASIA (FNH)—prevalence 0.5%. Hyperplasia of liver cells in response to hyperperfusion from an anomalous artery. Rarely exceeds 10 cm. Usually asymptomatic

HEPATIC ADENOMA—mainly in young woman on oral contraceptive pills. May cause abdominal pain. Potential for malignant transformation. Treat initially by withdrawal of oral contraceptives and follow lesions by US. If fails to regress, consider resection

Related Topics

Hepatitis B (p. 147)

Hepatitis C (p. 148)

Hepatic Failure (p. 145)

Chronic Liver Disease (p. 149)

Renal Cancer

NCCN Guidelines v1.2021

DIFFERENTIAL DIAGNOSIS OF SOLID RENAL MASS**MALIGNANCY**

- **RENAL CELL CARCINOMA (RCC)** (80–85%)
 - **CLEAR CELL** (75–85%)—proximal tubule
 - **PAPILLARY/CHROMOPHILIC** (12–14%)—proximal tubule
 - **CHROMOPHOBIC** (4–6%)—intercalated cell of cortical collecting duct
 - **ONCOCYTIC** (2–4%)—intercalated cell of cortical collecting duct
 - **COLLECTING DUCT** (1%)—medullary collecting duct
- **UROTHELIAL CARCINOMA** (15–20%)—usually arises from the renal pelvis
- **LYMPHOMA**
- **SARCOMA**
- **RENINOMA**—usually arises from the juxtaglomerular cells. Mostly benign. May secrete renin
- **HEMANGIOPERICYTOMAS**—usually secrete renin. May be malignant
- **WILM TUMOR**—nephroblastomas. Mostly in children

ANGIOMYOLIPOMA—distinctive fat density on CT; association with tuberous sclerosis; benign

DIFFERENTIAL DIAGNOSIS OF SOLID RENAL MASS (CONT'D)

ONCOCYTOMA—a homogeneous, well-circumscribed solid mass with a central scar; typically benign (low metastatic potential)

XANTHOGRANULOMATOUS PYELONEPHRITIS—variant of chronic pyelonephritis

PATHOPHYSIOLOGY**RISK FACTORS**

- **PERSONAL**—age, obesity
- **ENVIRONMENTAL**—smoking (2 \times), phenacetin
- **FAMILY HISTORY**—affected relatives
- **HEREDITARY SYNDROMES**—von Hippel-Lindau syndrome, hereditary papillary renal cell carcinoma, Birt-Hogg-Dubé syndrome, tuberous sclerosis complex, hereditary leiomyomatosis & RCC, autosomal dominant polycystic kidney disease

CLINICAL FEATURES

LOCOREGIONAL—classic triad of flank pain, hematuria, and abdominal mass. Other symptoms include varicocele (left $>$ right due to obstruction of testicular vein), ascites, and leg swelling (if infe-

CLINICAL FEATURES (CONT'D)

rior vena cava involvement). Two-thirds of renal tumors are found incidentally

METASTATIC—dyspnea, bone pain, jaundice

CONSTITUTIONAL—fever, weight loss, anorexia, fatigue

PARANEOPLASTIC SYNDROMES—hypertension (40%, due to renin secretion), hypercalcemia (5%), polycythemia (5%, due to EPO secretion), anemia, thrombocytosis, AA amyloidosis, hepatic dysfunction (Stauffer syndrome, without liver metastases)

STAGING**TNM STAGING****T stage**

- **T1**— ≤ 7 cm, limited to the kidney (T1a = ≤ 4 cm, T1b = >4 to ≤ 7 cm)
- **T2**— >7 cm, limited to the kidney
- **T3**—extends into major veins or perinephric tissues, but not into the ipsilateral adrenal gland and not beyond Gerota fascia
- **T4**—invades beyond Gerota fascia

N stage

- **N1**—metastasis in regional lymph node(s)

M stage (lungs, liver, bones, brain)

- **M1**—distant metastasis

STAGE GROUPINGS

Stage	TNM @ = any	5-year survival
I	T1N0M0	$>90\%$
II	T2N0M0	75–95%
III	T1–2N1M0, T3N@M0	60–70%
IV	T4N@M0, T@N@M1	See risk model below

INVESTIGATIONS**BASIC**

- **LABS**—CBC with differential (neutrophil count), lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, urinalysis (hematuria, proteinuria)
- **URINE CYTOLOGY**—if urothelial carcinoma suspected (e.g. central mass)
- **IMAGING**—CXR, US abd, CT or MRI abd/pelvis with contrast (most useful), CT chest (if suspicious), bone scan (if suspicious), MRI brain (if suspicious)
- **NEPHRECTOMY/BIOPSY**—biopsy is usually not required prior to surgery for solitary renal mass because of its low specificity and potential for seeding. Nephrectomy is both diagnostic and therapeutic. May consider

INVESTIGATIONS (CONT'D)

biopsy if non-RCC etiology is suspected (e.g. lymphoma, metastasis) or patient is not a surgical candidate

DIAGNOSTIC AND PROGNOSTIC ISSUES

PROGNOSIS BY STAGE—5 year overall survival rates for localized, locally advanced and metastatic renal cell carcinoma are 93%, 70%, and 12%, respectively

ADVERSE PROGNOSTIC FACTORS—stage III–IV, histologic grade 3–4, ECOG performance status ≥ 1

INTERNATIONAL METASTATIC RENAL CELL CARCINOMA DATABASE CONSORTIUM (IMDC) CRITERIA—interval from diagnosis to treatment upper normal limit, hemoglobin upper normal limit, calcium $>$ upper normal limit. Risk model is used to guide treatment in metastatic RCC

Factors	Risk group	Median survival	2-year survival
0	Favorable	-	75%
1–2	Intermediate	27 months	53%
3–6	Poor	9 months	7%

Heng et al. *J Clin Oncol* 2009;27(34)

MANAGEMENT

STAGE I (T1a)—nephrectomy; ablative techniques (e.g. cryotherapy, radiofrequency ablation); active surveillance

STAGE I (T1b)—nephrectomy; active surveillance in select patients

STAGE II—nephrectomy followed by surveillance

STAGE III—nephrectomy followed by surveillance; may consider adjuvant sunitinib

STAGE IV—treatment is palliative in most cases

- **SURGERY**—cytoreductive nephrectomy in select patients (e.g. ECOG performance status 0–1, no brain metastasis). Metastasectomy in select patients with oligometastatic disease
- **SYSTEMIC THERAPY**—first line therapy may include vascular endothelial growth factor inhibitors (e.g. sunitinib, pazopanib, axitinib, cabozantinib) and/or immune checkpoint inhibitors (e.g. ipilimumab, nivolumab, pembrolizumab). Selection of agents and combinations is guided by risk group (see IMDC criteria above). Chemotherapy is typically ineffective in clear cell RCC

MANAGEMENT (CONT'D)

- **RADIATION**—control of bleeding, pain or bone metastases
- **PALLIATIVE CARE**—referral for patients with supportive care needs

SPECIFIC ENTITIES

VON HIPPEL-LINDAU DISEASE—a familial cancer syndrome due to mutation of the VHL gene. Disease spectrum includes renal cell carcinomas (clear cell type, 40%) and cysts, pancreatic carcinomas and cysts, pheochromocytomas,

SPECIFIC ENTITIES (CONT'D)

hemangioblastomas of the cerebellum and spinal cord, and retinal hemangiomas. HIF1 α is hydroxylated in normoxic conditions, which is then ubiquitinated by VHL protein complex and destroyed. Accumulation of HIF1 α happens with hypoxic conditions or mutated VHL protein, which then heterodimerizes with HIF1 β and activates transcription of various genes such as VEGF. Development of targeted therapy for renal cell carcinoma is facilitated by our understanding of the VHL-HIF1 α -VEGF pathway

Bladder Cancer

NCCN Guidelines v6.2020

PATHOPHYSIOLOGY**CLASSIFICATION BY HISTOLOGY**

- **UROTHELIAL CARCINOMA** (90%)
- **SQUAMOUS** (8%)
- **ADENOCARCINOMA** (2%)
- **RHABDOMYOSARCOMA**
- **LYMPHOMA**
- **CARCINOID**

NATURAL HISTORY OF SUPERFICIAL TUMORS—low-grade superficial tumors have high recurrence rate (80%) and low risk of becoming invasive (10%). High-grade superficial tumors are frequently associated with carcinoma in situ, which is usually multifocal and has a high chance of becoming invasive (80% within 10 years)

RISK FACTORS

- **PERSONAL**—age
- **ENVIRONMENTAL**—smoking (4 \times), occupation (dye, rubber, textiles, leather, and petroleum industries with exposure to aniline, arylamines such as benzidine and 2-naphthylamine and amides), drugs (cyclophosphamide), pelvic radiation
- **FAMILY HISTORY**—affected relatives
- **DISEASES** (usually squamous cell carcinoma)—schistosomiasis, chronic bladder infection, Balkan endemic nephropathy

CLINICAL FEATURES

LOCREGIONAL—painless intermittent hematuria (80%), bladder irritability (25%, hesitancy, urgency, frequency, and dysuria), abdominal mass, suprapubic or flank pain, lymphedema

METASTATIC—dyspnea, bone pain, jaundice

CONSTITUTIONAL—weight loss, anorexia, fatigue

PARANEOPLASTIC—hypercalcemia, systemic fibrinolysis, neuromuscular syndromes

STAGING**TNM STAGING****T stage**

- **TA**—non-invasive papillary carcinoma
- **TIS**—carcinoma in situ (CIS): flat tumor
- **T1**—invades lamina propria
- **T2**—invades muscularis propria
- **T3**—invades perivesical tissue
- **T4**—extravesical tumor invades surrounding tissue (prostate, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall)

N stage

- **N1**—single regional lymph node in the true pelvis (perivesical, obturator, internal & external iliac, or sacral)
- **N2**—multiple regional lymph node in the true pelvis
- **N3**—metastasis to the common iliac lymph node

M stage (bone, liver, lungs)

- **M1A**—lymph nodes beyond the common iliac lymph nodes
- **M1B**—non-lymph node distant metastases

STAGE GROUPINGS**Stage** **TNM @ = any**

Oa	TaNOM0
Ois	TisNOM0
I	T1NOM0
II	T2a-bNOM0
III	T3a-bNOM0, T4aNOM0, T1-T4aN1-3M0
IV	T4bN@M0, T@N@M1a-b

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin

INVESTIGATIONS (CONT'D)

- **IMAGING**—CT (CT urography) or MRI abd/pelvis, include upper urinary tract; chest imaging (if muscle invasive), bone scan (if suspicious)
- **URINE CYTOLOGY**—low sensitivity
- **CYSTOSCOPY WITH BIOPSY**
- **TRANS-URETHRAL RESECTION OF BLADDER TUMOR (TURBT)**—must have muscle in specimen for adequate staging

PROGNOSTIC ISSUES

PROGNOSIS BY STAGE—5 year overall survival rates for in situ, localized, locally advanced and metastatic bladder cancer are 96%, 70%, 36%, and 5%, respectively

ADVERSE PROGNOSTIC FACTORS—for non-muscle invasive disease: CIS, high grade, T1, multifocal, >3 cm

MANAGEMENT**SUPERFICIAL/NON-MUSCLE INVASIVE**

- **STAGE 0a, 0is, I**—repeat TURBT, intravesical therapy (e.g. Bacillus Calmette–Guerin [BCG]).

Cystectomy may be considered for T1 disease

MUSCLE INVASIVE

- **STAGE II, III**—**neoadjuvant cisplatin-based chemotherapy** (preferred over adjuvant chemotherapy) followed by **cystectomy**, concurrent chemoradiation (if not surgical candidate), radiation (if frail)
- **STAGE IV**—**systemic therapy** (chemotherapy; immune checkpoint inhibitors, e.g. pembrolizumab, atezolizumab), concurrent chemoradiation (if M0 disease). **Palliative care** referral for patients with supportive care needs

Prostate Cancer

NCCN Guidelines v2.2020

PATHOPHYSIOLOGY**CLASSIFICATION BY HISTOLOGY**

- **ADENOCARCINOMA** (>95%)
- **PROSTATE INTRAEPITHELIAL NEOPLASM (PIN)**
- **UROTHELIAL CARCINOMA**
- **SMALL CELL CARCINOMA**
- **SQUAMOUS CELL CARCINOMA**
- **SARCOMA**

GLEASON SCORE—assigned by a pathologist based on the aggressiveness of the predominant population (1–5) plus second most common population (1–5) with a total of between 2 and 10

RISK FACTORS

- **PERSONAL**—age (most important), race (Black > Caucasian > Asian)
- **FAMILY HISTORY/GENETIC FACTORS**—affected relatives (2–5 ×), breast cancer, *BRCA2*
- **ENVIRONMENTAL**—total and saturated fat intake

CLINICAL FEATURES

LOCOREGIONAL—mostly asymptomatic with diagnosis made by rise in PSA or incidentally through TURP for BPH. Potential symptoms include urinary obstruction, urinary frequency, nocturia, hesitancy, slow stream, urge incontinence

METASTATIC—bony pain, cord compression. Hypercalcemia and fractures are not very com-

CLINICAL FEATURES (CONT'D)

mon as the metastatic lesions tend to be osteoblastic instead of lytic

CONSTITUTIONAL—weight loss, anorexia, fatigue

PARANEOPLASTIC—systemic fibrinolysis, neuromuscular syndromes

STAGING**TNM STAGING****T stage**

- **T1**—clinically inapparent tumor that is not palpable
- **T2**—confined within prostate that is palpable
 - **T2a**—invades less than or equal to half of one lobe
 - **T2b**—invades more than half of one lobe
 - **T2c**—invades both lobes
- **T3**—extends through the prostate capsule
 - **T3a**—extracapsular extension
 - **T3b**—invades seminal vesicle(s)
- **T4**—fixed or invades bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

N stage (obturator, hypogastric → iliac)

- **N1**—metastasis in regional lymph node(s)

M stage (non-regional lymph nodes, bone, liver. Biologically heterogeneous with variable course)

- **M1**—distant metastasis

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, PSA, testosterone
- **IMAGING**—CXR, CT or MRI abd/pelvis (if high-risk disease), bone scan (if high-risk disease)
- **BIOPSY**—US-guided transrectal biopsy (6–12 core needles)

Related Topics

Cancer Screening (p. 239)
Tumor Markers (p. 237)
Cancer Survivorship (p. 245)

DIAGNOSTIC AND PROGNOSTIC ISSUES

PROSTATE-SPECIFIC ANTIGEN—a serine protease that liquifies semen physiologically. Elevated in prostate cancer, prostatitis, BPH, endoscopy, prostate surgery, prostate biopsy (remains elevated for 6–8 weeks), and with increasing age (normal PSA by age: age 40–50 < 2.5 ng/mL, age 50–60 < 3.5 ng/mL, age 60–70 < 4.5 ng/mL, age 70–80 < 6.5 ng/mL). May be used for screening, diagnosis, prognostication, selection of treatment modality and following treatment response

- **FREE PSA**—proportion of PSA unbound to antichymotrypsin or α_2 macroglobulin. A decreased ratio of free to total PSA is associated with higher chance of prostate cancer
- **PSA DENSITY**—PSA/prostate volume and may be associated with increased PPV and NPV
- **PSA DOUBLING TIME**—predictive of prostate cancer-specific mortality in biochemical relapse
- **SCREENING**—PSA > 4 ng/mL is considered abnormal, spc 32%. With the addition of DRE, spc 48%. A PSA increase of 20%/year also should warrant a biopsy. So far, PSA screening has not been proven to reduce mortality from prostate cancer. Discuss potential risks/benefits with men > 50 years, high risk (family history, ethnicity)
- **BIOCHEMICAL RELAPSE**—for patients with previous prostatectomy, PSA relapse is indicated by a PSA ≥ 0.2 ng/mL that is confirmed on a second PSA ≥ 0.2 ng/mL. For patients with previous external beam radiation or brachytherapy, PSA relapse is indicated by PSA ≥ 2 ng/mL from nadir PSA

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

PROGNOSIS BY STAGE—5 year overall survival rates for localized, locally advanced and metastatic cancer are ~100%, ~100%, and 31%, respectively

ADVERSE PROGNOSTIC FACTORS—pre-treatment PSA, Gleason score, T stage

RISK CATEGORIES FOR LOCALIZED DISEASE

Risk category	PSA(ng/ mL)	Gleason score	Stage
Low (highly curable)	<10	≤ 6	$\leq T2a$
Intermediate (curable) ^a	10–20	7	T2b-c
High (rarely curable)	>20	8–10	$\geq T3a$

^aIf more than one risk factors present, consider shifting to high risk group

MANAGEMENT**LOCALIZED DISEASE (T1-3N0M0)**

- **LOW RISK**—if <10-year life expectancy, consider observation for symptoms. If ≥ 10 -year life expectancy, options include **active surveillance** (preferred), **external-beam radiation (EBRT)** or **brachytherapy**, or **radical prostatectomy (RP)**. Active surveillance involves PSA testing every ≥ 6 months, prostate biopsy every ≥ 12 months, MRI prostate every ≥ 12 months and consider treatment with disease progression (i.e. meet criteria for intermediate or higher risk). Send for germline testing if family history positive
- **INTERMEDIATE RISK**—if <10-year life expectancy, options include observation for symptoms and EBRT or brachytherapy. If ≥ 10 -year life expectancy, options include **active surveillance**, **EBRT** or **brachytherapy \pm androgen deprivation therapy (ADT)**, or **radical prostatectomy**. ADT involves LHRH agonist (e.g. leuprolide). Send for germline testing if family history positive
- **HIGH RISK**—if ≤ 5 -year life expectancy and asymptomatic, options include observation for symptoms, ADT, or EBRT. If >5-year life expectancy or symptomatic, options include **EBRT \pm brachytherapy + ADT**, or **radical prostatectomy**. Send for germline testing

ADVANCED DISEASE (T4, N1–3, M1)

- **CASTRATION-SENSITIVE (CSPC)**—options include ADT \pm chemotherapy (docetaxel) or androgen

MANAGEMENT (CONT'D)

receptor-targeted therapy (abiraterone, enzalutamide, apalutamide). Patients require life-long **castration** surgically or medically with LHRH agonist (e.g. leuprolide, goserelin) plus antiandrogen (e.g. bicalutamide, flutamide) for ≥ 7 days when starting LHRH agonist to prevent initial testosterone flare response. Early initiation of ADT is recommended in symptomatic disease. Early ADT may improve disease-specific survival compared to delayed ADT, ie, starting treatment when patients become symptomatic

- **CASTRATION-RESISTANT (CRPC)**

- **FIRST-LINE**—options include chemotherapy (docetaxel if not previously used) or AR-

MANAGEMENT (CONT'D)

targeted therapy (abiraterone or enzalutamide depending on agent used for CSPC)

- **SECOND-LINE**—options include chemotherapy (docetaxel if not previously used, cabazitaxel), AR-targeted therapy (abiraterone, enzalutamide), PARP inhibitors (olaparib, if mutation in homologous recombination repair gene), or immune checkpoint inhibitor (pembrolizumab, if microsatellite instability-high or mismatch repair-deficient)

- **BONE METASTASES**—bisphosphonates (zoledronic acid), radium-223, palliative radiation

- **PALLIATIVE CARE**—referral for patients with supportive care needs

TREATMENT ISSUES**COMPARISON OF TREATMENTS FOR LOCALIZED DISEASE**

	Prostatectomy^b	Brachytherapy	External beam radiation^c
5 year disease free survival	>85%	96%	80%
Indications	Preferred for patients with low-risk disease, life expectancy >20 years, or significant urinary symptoms	Eligibility criteria include PSA ≤ 15 ng/mL, Gleason score ≤ 7 , stage $\leq T2c$, prostate volume ≤ 60 mL, and life expectancy >5 years	Preferred for patients with high-risk disease or older
Contraindications	Age >70, high-risk disease	Significant urinary symptoms (as prostate swells significantly shortly after procedure), prior TURP	Pelvic kidney, inflammatory bowel disease, connective tissue disease (SLE, scleroderma), or prior radiation to same region
Impotence ^a	50–90%	50%	50%
Urinary incontinence ^a	10–20%	1–2%	1–2%
Urinary irritation ^a	15–60%	12–30%	2–30%
GI irritation ^a	2–17%	10%	30%

^aSide effects at 5 years are listed

^bSide effects tend to decrease over time with prostatectomy

^cSymptoms tend to increase over time with radiation

TREATMENT ISSUES (CONT'D)**LHRH AGONISTS**

- **INDICATIONS**—high intermediate or high-risk localized disease (in combination with EBRT), salvage setting, or advanced disease setting. Requires the use of an antiandrogen (flutamide) for first ≥ 7 days to counter testosterone flare response
- **ADVERSE EFFECTS**—fatigue, hot flushes, mood changes, weight gain, decreased libido, impo-

TREATMENT ISSUES (CONT'D)

tence, gynecomastia, and over the long-term decreased muscle mass, anemia, and osteoporosis. All patients initiated on LHRH agonists should have baseline bone density scan and be started on calcium and vitamin D supplements. Bisphosphonates should be given if osteoporosis confirmed by DEXA

Testicular Cancer

NCCN Guidelines v3.2020

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **TESTICULAR INTRAEPITHELIAL NEOPLASIA (TIN)**—70% chance of progression to testicular cancer in 7 years
- **GERM CELL TUMOR (95%)**—can differentiate into any immature or mature tissue type, usually mixed
 - **SEMINOMA (40%)**—neoplastic counterpart of spermatocyte. Age thirties to forties, pure, α FP negative and sometimes slightly β hCG positive. Few metastasize. Very chemo- and radiosensitive
 - **NON-SEMINOMA (60%)**—age twenties to thirties, pure or mixed, more metastasize. Chemosensitive. Include the following subtypes
 - **EMBRYONAL CELL CARCINOMA**—neoplastic counterpart of inner cell mass of embryo. May be β hCG+, α FP+
 - **YOLK SAC TUMOR**—neoplastic counterpart of yolk sac. Usually α FP+
 - **CHORIOCARCINOMA**—neoplastic counterpart of chorionic villus. Usually β hCG+
 - **IMMATURE TERATOMA**—neoplastic counterpart of fetal tissue. Marker negative
 - **MATURE TERATOMA**—neoplastic counterpart of mature adult tissue. Marker negative. Completely resistant to chemotherapy. May transform into malignant mesodermal, endodermal, or ectodermal elements
- **SEX CORD STROMAL TUMORS**
 - **SERTOLI CELL TUMOR**
 - **LEYDIG CELL TUMOR**
 - **GRANULOSA CELL TUMOR**
 - **MIXED CELL TYPE (SERTOLI-LEYDIG CELL)**
- **MIXED GERM CELL AND STROMAL TUMORS**
 - **GONADOBLASTOMA**
- **LYMPHOMA**
- **RHABDOMYOSARCOMA**
- **CARCINOID**

ISOCHROMOSOME 12P—characteristic of germ cell tumors. Poorly differentiated neoplasms of unknown primary with this cytogenetic feature are highly sensitive to cisplatin-based chemotherapy

PATHOPHYSIOLOGY (CONT'D)

RISK FACTORS

- **FAMILY HISTORY**—affected relatives
- **DISEASES**—prior testicular cancer, cryptorchidism (10–40 \times), testicular feminization syndromes, Klinefelter syndrome

CLINICAL FEATURES

LOCOREGIONAL—testicular mass \pm pain, acute epididymitis (25% of embryonal cell tumor and mixed teratoma), back pain (10%), gynecomastia (β hCG), infertility (3%)

METASTATIC—dyspnea, cough, headaches, stroke

CONSTITUTIONAL—weight loss, anorexia, fatigue

STAGING

T stage

- **T1**—limited to testis without vascular/lymphatic invasion
- **T2**—limited to testis with vascular/lymphatic invasion **or** tumor invading hilar soft tissue or epididymis, or penetrating visceral mesothelial layer covering tunica albuginea \pm vascular/lymphatic invasion
- **T3**—invades the spermatic cord \pm vascular/lymphatic invasion
- **T4**—invades the scrotum \pm vascular/lymphatic invasion

N stage (pelvic \rightarrow paraaortic lymph node)

- **N1**—1 or more lymph nodes, all \leq 2 cm
- **N2**—1 or more lymph nodes between >2 – \leq 5 cm
- **N3**—any lymph node \geq 5 cm

M stage (lungs, liver, bones, brain)

- **M1A**—lung metastasis
- **M1B**—sites other than non-regional lymph nodes or lung (e.g. bone)

SERUM TUMOR MARKER DESIGNATION

Post-orchietomy serum tumor markers are used

	α FP (ng/mL)	β hCG (IU/L)	LDH
S1	<1000	<5000	<1.5 \times
S2	1000–10,000	5000–50,000	1.5–10 \times
S3	>10,000	>50,000	>10 \times

STAGING (CONT'D)**STAGE GROUPINGS**

Stage	TNM @ = any
IA	T1N0M0S0
IB	T2–4N0M0S0
IS	T@N0M0S1–3
IIA	T@N1M0S0–1
IIB	T@N2M0S0–1
IIC	T@N3M0S0–1
IIIA	T@N@M1aS0–1
IIIB	T@N@M0–1aS2
IIIC	T@N@M0–1aS3, T@N@M1bS@

RISK STRATIFICATION FOR ADVANCED DISEASE

Risk group	Non-seminoma	Seminoma
Good (90% 5-year survival)	Testicular or retroperitoneal tumor, S1, and absence of non-pulmonary visceral metastases	Any location, any marker, and absence of non-pulmonary visceral metastases
Intermediate (70–80% 5-year survival)	Testicular or retroperitoneal tumor, S2, and absence of non-pulmonary visceral metastases	Any location, any marker, and any non-pulmonary visceral metastases
Poor (50% 5-year survival)	Testicular, retroperitoneal, or mediastinal primary tumor, S3, or non-pulmonary visceral metastases	Not applicable

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, α FP, β hCG, LDH, TSH, T3, T4, total testosterone, LH, FSH
- **IMAGING**—testicular US, CXR, CT abd/pelvis, CT chest (if CXR or CT abd/pelvis abnormal), CT head (if advanced disease with intermediate or

INVESTIGATIONS (CONT'D)

poor prognosis), bone scan (if suspect metastasis)

- **RADICAL INGUINAL ORCHIECTOMY**

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIFFERENTIAL DIAGNOSIS OF TESTICULAR MASS—epididymitis, hydroceles, varicoceles, spermatoceles, inguinal hernias, orchitis (gummatous, tuberculous), hematoma, testicular torsion

TUMOR MARKERS—essential for diagnosis, staging, risk stratification and monitoring treatment response

- **LDH**—less specific, indicates tumor bulk
- **β hCG**—elevated in trophoblastic tumor, choriocarcinoma. Half-life 1–3 days
- **α FP**—elevated in yolk sac tumor. Half-life 5–7 days

Tumor	β hCG	α FP
Non-seminoma	↑ in up to 85%	↑ in up to 80%
Seminoma	↑ in 15–25%	Normal

PROGNOSIS BY STAGE—5 year overall survival rates for localized, locally advanced and metastatic cancer are 99%, 96%, and 73%, respectively

PROGNOSTIC FACTORS—lymphovascular invasion is the most important indicator for relapse in stage IA-IB non-seminoma

MANAGEMENT

All testicular cancer patients should undergo orchiectomy. All patients should be discussed with an interdisciplinary team experienced in its management

SEMINOMA

- **STAGE I—surveillance** (preferred), adjuvant **chemotherapy** (carboplatin) or **radiation**. All three options are acceptable with comparable long-term survival rates (>90%)
- **STAGE IIA, IIB**—adjuvant **radiation** or **chemotherapy** (bleomycin/etoposide/cisplatin, BEP)
- **STAGE IIC, III**—adjuvant **chemotherapy**. Choice of regimen based on risk group

NON-SEMINOMA

- **STAGE IA, IB**—**surveillance** (preferred), **adjuvant chemotherapy** with bleomycin, etoposide + cisplatin (BEP) or **nerve-sparing**

MANAGEMENT (CONT'D)

retroperitoneal lymph node dissection (RPLND). All three options are acceptable with comparable long-term survival rates (>90%)

- **STAGE IS—chemotherapy** (BEP, EP)
- **STAGE IIA, IIB—chemotherapy** (BEP) or **RPLND**
- **STAGE IIC, III—chemotherapy.** Choice of regimen based on risk group

TREATMENT ISSUES**POST-CHEMOTHERAPY RESIDUAL MASSES**

—resect all residual masses in non-seminoma if surgically feasible because of possible teratoma (chemoresistant) and/or viable disease

GROWING TERATOMA SYNDROME—defined as enlargement of a residual mass post-chemotherapy, despite complete normalization of tumor marker suggesting eradication of malignant population. Surgical resection is indicated for a growing teratoma as it does not respond to che-

TREATMENT ISSUES (CONT'D)

motherapy or radiation and may transform into malignant tumors such as adenocarcinoma or rhabdomyosarcoma

RADICAL ORCHIECTOMY—should always be done prior to any further treatment, except for life-threatening metastatic disease in which chemotherapy should be given first

ORGAN-PRESERVING SURGERY—should be done at experienced centers only. Consider if synchronous bilateral testis tumors, metachronous contralateral (second) testis tumor, or tumor in a solitary testis and sufficient endocrine function

FERTILITY ISSUES—consider cryopreservation before orchiectomy and testicular sperm extraction if bilateral orchiectomy. Testosterone replacement should be given if bilateral orchiectomy. Patients planning to father children should have hormone and semen analysis for 1- to 3-year post-treatment

Brain Tumors

See BRAIN TUMORS (p. 319)

Cancer of Unknown Origin

NCCN Guidelines v3.2020

PATHOPHYSIOLOGY**CLASSIFICATION BY HISTOLOGY**

- **ADENOCARCINOMA**—well to moderately differentiated (60%)
- **ADENOCARCINOMA/CARCINOMA**—poorly differentiated (30%)
- **SQUAMOUS CELL CARCINOMA** (5%)
- **UNDIFFERENTIATED NEOPLASMS** (5%)

NATURAL HISTORY—early, unpredictable, and aggressive metastasis. Primary too small to cause symptoms

Related Topic

Tumor Markers (p. 237)

IMMUNOHISTOCHEMICAL MARKERS

- **CARCINOMA**—cytokeratin negative, common leukocyte antigen, S100, vimentin negative. Breast cancer may be ER/PR positive

PATHOPHYSIOLOGY (CONT'D)

- **LYMPHOMA**—common leukocyte antigen
- **SARCOMA**—vimentin positive (mesenchymal), desmin positive (rhabdomyosarcoma), factor VII antigen (angiosarcoma)
- **MELANOMA**—S100, HMB 45, MART, vimentin, NSE positive
- **NEUROENDOCRINE TUMORS**—neuron-specific enolase, synaptophysin, chromogranin

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, LDH, INR, PTT, β -hCG, AFP, PSA, Ca 125, CEA, CA 19-9
- **IMAGING**—CT chest/abd/pelvis
- **SPECIAL**—EGD/colonoscopy (if clinically indicated), tissue biopsy

MANAGEMENT

TREAT UNDERLYING CAUSE—see table below for tailored treatment of cancer of unknown primary based on most likely tumor type

MANAGEMENT (CONT'D)

PALLIATIVE CARE—referral for patients with supportive care needs

Presentation	Likely primary	Key history and physical	Investigations	Empiric treatment(s)
Poorly differentiated midline disease in young men	Germ cell tumor (testicular, retroperitoneal)	Gynecomastia suggests seminoma. Perform testicular examination	β -hCG, AFP. Look for isochromosome 12 which suggests tumor responsive to platinum-based therapy	Treat as germ cell tumor (BEP). Potentially curable
Squamous cell carcinoma with cervical lymphadenopathy	Head and neck cancer (hypopharynx, oropharynx, nasopharynx), skin, esophagus, lung	Smoker, alcohol use	Quadoscopy, CT chest, PET scan. Bronchoscopy and upper GI endoscopy may be considered. FNA first, then core biopsy if negative	Neck dissection and radiation. Potentially curable
Axillary lymphadenopathy in women	Breast cancer	Breast exam	Mammogram, US breast, MRI breast	Mastectomy with axillary dissection or whole breast irradiation, adjuvant chemotherapy. If lytic metastasis in postmenopausal women, consider hormonal treatment
Squamous cell carcinoma with inguinal lymphadenopathy	Cervical/anal cancer	Pelvic exam, colposcopy	Anoscopy, sigmoidoscopy, CT abd/pelvis	Lymph node dissection, chemoradiation
Peritoneal carcinomatosis	Ovarian cancer variant, primary peritoneal cancer, metastasis from colorectal or stomach cancer	Pelvic exam	Colonoscopy, gastroscopy, CT abd/pelvis, CEA, CA-125 (ratio 1/20)	Chemotherapy
Liver metastasis	GI (colorectal [usually otherwise well]), pancreatic, esophageal, gastric, hepatic (Asians or cirrhosis), lung, breast	General	CEA, CA 19-9, CA 15-3, AFP, colonoscopy	Chemotherapy, consider surgery if resectable

MANAGEMENT (CONT'D)

Presentation	Likely primary	Key history and physical	Investigations	Empiric treatment(s)
Lung nodule(s)	Metastasis (lower lobes, multiple), lung cancer (upper lobe, single)	Smoking history	CT chest	Chemotherapy, consider surgery if resectable, stereotactic body radiation (SBRT)
Malignant pleural effusion	Lung, mesothelioma, breast	Smoking, asbestos exposure	Thoracentesis	Chemotherapy
Blastic bone metastasis	Prostate (most common), lung, breast	DRE	PSA, plain X-rays of bones, bone scan	Systemic therapy if suspect prostate cancer, surgery if impending fracture, radiation if pain

Tumor Markers**PATHOPHYSIOLOGY**

DEFINITION—substances that can be measured quantitatively in the serum in order to detect a cancer and its organ of origin. May act as surrogate of tumor bulk

TYPES OF TUMOR MARKERS

- **TUMOR-SPECIFIC PROTEINS**—fusion gene product in CML (bcr-abl), monoclonal band in multiple myeloma
- **ONCOFETAL ANTIGENS** (non-specific)—expressed during embryological development and in cancer cells. Examples include CEA in all GI and some other tumors, AFP in hepatocellular carcinoma and germ cell tumor, and CA 125 in ovarian cancer
- **OVER-EXPRESSED PROTEINS** (non-specific)—present in normal differentiated cells but lesser amount. Examples include PSA in prostate cancer and CA 15-3 in breast cancer

UTILITY OF TUMOR MARKERS—screening, diagnosis, prognosis, monitor response to treatment, monitor recurrence (after adjuvant therapy)

PROSTATE SPECIFIC ANTIGEN (PSA)

NORMAL RANGE—< 4 ng/mL (age-dependent range: 40–49 years old <2.5 ng/mL, 50–59 years old <3.5 ng/mL, 60–69 years old <4.5 ng/mL, 70–79 years old <6.5 ng/mL)

ELEVATED—prostate cancer, BPH, prostatitis, perineal trauma (including catheterization), endoscopy, prostate biopsy, recent DRE, or ejaculation

PROSTATE SPECIFIC ANTIGEN (PSA) (CONT'D)**UTILITY IN PROSTATE CANCER**

- **SCREENING**—varying guidelines for using PSA for screening; always discuss risks and benefits (including false positives and negatives) with patients. If proceeding, start at age 50 for men with life expectancy >10 years. Perform PSA annually if PSA >1 ng/mL, and every 4 years if PSA <1 ng/mL. Combine with annual DRE
- **DIAGNOSIS, PROGNOSIS, RESPONSE, FOLLOW-UP FOR RELAPSE**—extremely useful. See PROSTATE CANCER for more details (p. 230)

CARCINOEMBRYONIC ANTIGEN (CEA)

NORMAL RANGE—<4 µg/L (<5 µg/L for smokers)

ELEVATED—colorectal cancer (sens <25% in early cancer and 75% in advanced cancer), gastric cancer (sens 50%), pancreatic cancer (sens 50%), breast cancer (sens 40–73%), lung cancer (sens 77%), ovarian cancer, IBD (4–10 µg/L), cirrhosis, hepatitis, pancreatitis, peptic ulcer disease, smoking (sens 19%), chronic lung disease, hypothyroidism, normal (sens 3%)

UTILITY IN COLORECTAL CANCER

- **PROGNOSIS**—CEA >5 µg/L may correlate with poorer prognosis
- **ADJUVANT SETTING**—elevated postoperative CEA implies the presence of persistent disease and requires further evaluation. For stage II and III disease post-resection, CEA levels should be

CARCINOEMBRYONIC ANTIGEN (CEA) (CONT'D)

performed every 3 months for at least 3 years if the patient is a potential candidate for surgery or chemotherapy for metastatic disease (even if previously CEA negative)

- **METASTATIC SETTING**—CEA is the marker of choice for monitoring the response of metastatic disease to systemic therapy

CA 19-9

NORMAL RANGE—< 37 kU/L

ELEVATED—pancreatic cancer (sens 70–90%, spc 80–90%), cholangiocarcinoma, colorectal cancer (sens 20–40%), gastric cancer (sens 20–40%), ovarian cancer, pancreatitis, liver failure

UTILITY IN PANCREATIC CANCER

- **DIAGNOSIS**—level >120 kU/L is suggestive of malignancy. Level >1000 kU/L predicts metastatic disease (PPV of 97%)
- **RESECTABLE DISEASE**—elevated CA19-9 postoperatively may predict for recurrent disease
- **LOCALLY ADVANCED OR METASTATIC DISEASE**—elevations in serial CA 19-9 suggest progressive disease but confirmation with other studies needed

CA 15-3

NORMAL RANGE—< 28 kU/L

ELEVATED—breast cancer (sens for stage I, 5–30%; stage II, 15–50%; stage III, 60–70%; stage IV, 65–90%), ovarian cancer (46%), lung cancer (26%), liver cancer (30%)

UTILITY IN BREAST CANCER

- **DIAGNOSIS**—may be used sometimes to determine the presence of metastatic disease. 86 kU/L + history of breast cancer strongly suggests metastasis
- **METASTATIC SETTING**—may be used to suggest treatment failure, particularly if disease is not readily measurable

CA 125

NORMAL RANGE—< 35 kU/L

ELEVATED—epithelial ovarian cancer (sens 50% in stage I, 85% in all), breast cancer, colorectal

CA 125 (CONT'D)

cancer, pancreatic cancer, lung cancer, endometrial cancer, benign ovarian tumors (sens 26%), ascites, peritonitis, pelvic inflammatory disease, cirrhosis, menstruation, endometriosis, salpingitis, fibroids, right-sided heart failure, first trimester pregnancy

UTILITY IN EPITHELIAL OVARIAN CANCER

- **SCREENING**—may have a role in early detection of ovarian cancer in women with hereditary ovarian cancer syndrome in combination with transvaginal US
- **DIAGNOSIS**—in postmenopausal women with asymptomatic palpable pelvic masses, CA 125 > 65 kU/L has PPV of 90% for ovarian cancer
- **PROGNOSIS**—rate of decrease in CA 125 after cytoreductive surgery and during cytotoxic chemotherapy has prognostic value
- **RESPONSE**—useful for following disease response during cytotoxic chemotherapy
- **ADJUVANT SETTING**—every 3 months for 2 years. However, limited treatment for relapsed disease limits clinical value of detection

TUMOR MARKERS IN EVERYDAY PRACTICE

Tumor type	Tumor marker
Prostate	PSA
Colorectal	CEA
Pancreas	CA 19-9, CEA
Liver	α FP
Breast	CA 15-3, CEA, CA 125, CA 27.29
Ovary	CA 125, CA 15-3, CA 19-9, CEA
Lung	CEA, CA 19-9, CA 125, LDH
Germ cell tumor	α FP, β hCG, LDH
GTN	β hCG
Carcinoid tumor	Chromogranin, 5-HIAA
Non-Hodgkin	LDH
Hodgkin	ALP
Myeloma	M-protein, β 2 microglobulin

UTILITY OF SPECIFIC TUMOR MARKERS

Tumor marker	Tumor type	Screen	Diagnosis	Prognosis	Response	Follow-up (recurrence)
PSA	Prostate	?	✓	✓	✓	✓
CEA	Colorectal	x	x	✓	M?	✓
CA 19-9	Pancreas	x	x?	x	✓?	✓?
CA 15-3	Breast	x	x	x	M?	x

CARCINOEMBRYONIC ANTIGEN (CEA) (CONT'D)

Tumor marker	Tumor type	Screen	Diagnosis	Prognosis	Response	Follow-up (recurrence)
CA 125	Ovary	x?	x?	✓	M?	✓?
αFP	Germ cell	x	✓	✓	✓	✓
	Liver	x?	✓	✓	✓	x
βhCG	Germ cell	x	✓	✓	✓	✓
	GTN	x	✓	✓	✓	✓
LDH	Germ cell	x	✓	✓	✓	✓
	Lymphoma	x	x	✓	✓?	x

✓ useful, ? debatable or not routinely conducted, x not useful, M metastatic setting only

Cancer Screening

Canadian Task Force on Preventive Health Care (CTFPHC) Guidelines
 US Preventive Service Task Force (USPSTF) Recommendations

PRINCIPLES OF SCREENING

GOAL—screening itself does not diagnose disease, but triggers investigations that lead to diagnosis. Early diagnosis in asymptomatic patients would allow early intervention that could lead to improved outcome. Up to 35% of cancer deaths may be prevented by early detection

CRITERIA FOR SCREENING

- **DISEASE**—major cause of death, high prevalence, natural history from latency to overt disease well characterized, treatment available and beneficial
- **TEST**—acceptable to population (easy to administer, minimal discomfort), cost-effective, high specificity (key) and sensitivity. Prefer high sensitivity if serious and highly treatable or infectious disease, or subsequent diagnosis cheap and easy. May sacrifice sensitivity for specificity if high cost of subsequent testing
- **PATIENTS**—life expectancy >10 years, lack of significant comorbidities (screening may alter their clinical outcome)

CHALLENGES WITH SCREENING TRIALS

- **PATIENT POPULATION**—healthy individuals instead of patients (less motivated)
- **STUDY DESIGN**—longer duration of follow-up, larger sample size, more expensive
- **SURROGATE ENDPOINTS**—cancer incidence, dysplasia, polyps instead of survival

BIASES ASSOCIATED WITH SCREENING TRIALS

- **VOLUNTEER BIAS**—volunteers tend to have better health and lower mortality rate

PRINCIPLES OF SCREENING (CONT'D)

- **LEAD TIME BIAS**—screening may allow disease to be detected earlier (asymptomatic) than when it would have been detected due to symptoms. Thus, people with disease detected by screening may appear to have longer overall survival. To correct for this, should compare not the length of survival from diagnosis to death, but rather the age-specific death rates. Alternatively, estimate the lead time and take it into account
- **LENGTH BIAS**—disease detected by screening may have a more indolent course, and thus more favorable prognosis. May control for this by comparing the experience of screened and symptom-detected cases at subsequent screening examinations

SCREENING FOR SPECIFIC CANCERS

- **BREAST**—self-breast examination, clinical breast examination, mammography
 - **CERVICAL**—Pap smear, HPV DNA
 - **LUNG**—annual low dose CT chest for patients aged 55–90 with at least a 30 pack year history who are either current smokers or quit within the last 15 years (reduces lung cancer mortality by 20%)
 - **COLORECTAL**—fecal occult blood test (FOBT), fecal immunochemical test (FIT) sigmoidoscopy, double-contrast barium enema, colonoscopy, CT colonography
 - **PROSTATE**—DRE, PSA
 - **OVARIAN**—US, CA125
 - **GASTRIC**—gastroscopy (Asia)
- underlined = good evidence to support screening

PROSTATE CANCER SCREENING

DIGITAL RECTAL EXAMINATION (DRE)—no survival benefit demonstrated

PROSTATE-SPECIFIC ANTIGEN (PSA)—see Tumor Markers (p. 237). Evidence for survival benefit conflicting

OVERALL—the CTFPHC 2014 guideline does not recommend PSA screening regardless of age. The USPSTF 2018 statement recommends against PSA screening for men over 70 years and recommends a personalized discussion for men aged 55–69 (consider PSA testing \pm digital rectal exam [DRE] if life expectancy >10 years and who desire screening after extensive counseling on the risks and benefits). If PSA 3 ng/mL \pm suspicious DRE, consider biopsy

Related Topics

Tumor Markers (p. 237)

Hereditary Cancer Syndromes (p. 241)

COLORECTAL CANCER SCREENING

FLEXIBLE SIGMOIDOSCOPY—case–control studies demonstrated 60–80% reduction in mortality. Potential survival benefit. Negative test in 75–93% of cases (30–65% negative even with advanced polyp) \rightarrow repeat in 5 years; positive in 7–25% \rightarrow proceed to colonoscopy

COLONOSCOPY—case–control studies demonstrated 50% reduction in mortality. Potential survival benefit. Negative test (i.e. no adenomatous polyps) in 50–80% of cases (2–12% negative even with advanced polyp) \rightarrow repeat in 10 years; positive (i.e. ≥ 1 polyp) in 20–50% \rightarrow repeat colonoscopy depending on findings

DOUBLE-CONTRAST BARIUM ENEMA—insufficient evidence to support benefit

CT COLONOGRAPHY—for polyps >10 mm, sens 85–93%, and spc 97%; for polyps 6–9 mm, sens 70–86%, and spc 86–93%. After detection of polyp, patient would need to undergo optical colonoscopy (ideally on standby) for resection. Risk of radiation exposure

FECAL OCCULT BLOOD TEST (FOBT)—detects peroxidase in blood. Rehydrated stool samples have been shown to reduce colorectal cancer mortality by 33% after 13 years if done annually and 21% after 18 years if done biennially; non-rehydrated stool samples have been shown to reduce colorectal cancer mortality by 18% after 18

COLORECTAL CANCER SCREENING (CONT'D)

years if done biennially. Negative test in 90–98% of cases (15–50% negative even with cancer) \rightarrow repeat in 1–2 years; positive in 2–10% \rightarrow proceed to colonoscopy

FECAL IMMUNOCHEMICAL TEST (FIT)—detects hemoglobin. More specific and less sensitive than FOBT

STOOL DNA TEST (sDNA)—need to provide entire stool sample. To be used in conjunction with colonoscopy

OVERALL APPROACH

- **AVERAGE RISK**—the CTFPHC 2016 guideline recommends screening with FOBT or FIT every 2 years, or flexible sigmoidoscopy every 10 years, but not colonoscopy, for adults aged 50–74. The USPSTF 2016 statement recommends screening for adults aged 50–75 and individualized decision for adults aged 76–85; screening strategies may include yearly FOBT, yearly FIT, multitargeted stool DNA test every 1–3 years, colonoscopy every 10 years, CT colonography every 5 years, flexible sigmoidoscopy every 5 years, or flexible sigmoidoscopy every 10 years plus FIT yearly
- **POLYPS ON COLONOSCOPY**—1–2 tubular adenomas \rightarrow colonoscopy in 5 years; >2 adenomas \rightarrow colonoscopy in 3 years; incomplete exam, numerous polyps, advanced adenoma, large sessile adenoma \rightarrow repeat colonoscopy based on clinical judgment
- **POSITIVE FAMILY HISTORY**—one first-degree relative with cancer or adenomatous polyp at age <60 or two or more first-degree relatives with cancer or adenomatous polyp at any age \rightarrow colonoscopy every 5 years beginning at 40 or 10 years earlier than youngest index case (whichever first)
- **HNPCC, FAP, OR ATTENUATED ADENOMATOUS POLYPOSIS COLI (AAPC)**—genetic counseling and special screening. For HNPCC, colonoscopy every 1–2 years starting at 20–25 or 10 years earlier than youngest index case in family (whichever first); for FAP, colonoscopy annually beginning at 10–12 years of age **and** upper endoscopy with both end- and side-viewing instruments to screen for duodenal/ampullary adenomas at 25–30 years. For AAPC, colonoscopy annually beginning at 16–18 years of age
- **IBD (ulcerative colitis or Crohn disease)**—staging colonoscopy 8–10 years after diagnosis; screening interval should decrease with increasing duration of disease (variable). Annual colonoscopy for any patient with PSC (starting at diagnosis)

BREAST CANCER SCREENING

BREAST SELF-EXAMINATION (BSE)—no survival benefit demonstrated on its own and not recommended in general

CLINICAL BREAST EXAMINATION (CBE)—usually combined with mammography in studies
MAMMOGRAPHY—sensitivity 16–40%. Meta-analysis showed 20–30% relative risk reduction (RRR) in breast cancer mortality for women 50–69, 17% reduction for women 40–49, and inconclusive for women aged 70–74

BREAST MRI—sensitivity 77–100% for breast cancer but not very specific and less sensitive than mammography in detecting DCIS. Studies only in high-risk women. No survival benefit demonstrated

BREAST US—may represent an alternative in women with dense breasts and increased risk of breast cancer who cannot tolerate MRI. No survival benefit demonstrated

OVERALL—the CTFPHC 2018 guideline recommends screening mammogram every 2–3 years for women aged 50–74 but not routinely for women aged 40–49. The USPSTF 2016 statement recommends screening mammogram every 2 years for women aged 50–74 and considers it optional for women aged 40–49 (individualized discussion). Breast MRI should be considered for patients at high risk of developing breast cancer (e.g. BRCA carriers, Li-Fraumeni, previous chest irradiation)

OVARIAN CANCER SCREENING

CA125—elevated in 80% of women with advanced ovarian cancer, <50% of stage I ovarian cancer, and 1–2% of normal population. Low specificity

TRANSVAGINAL US—sensitivity 85% with PPV of 27% for women over age 50 at average risk and those over age 25 with family history of ovarian cancer

OVERALL—routine screening for average risk, asymptomatic individuals is not recommended by

OVARIAN CANCER SCREENING (CONT'D)

the USPSTF 2018 statement. For those at high risk (family history, BRCA mutation), the decision should be individualized and may consist of transvaginal US and CA 125 every 6 months starting at age 35 or 5–10 years earlier than the youngest age at diagnosis in the family

CERVICAL CANCER SCREENING

PAP SMEAR—50–60% reduction in mortality if done every 1–3 years in women aged 18 and greater. Sensitivity and specificity for CIN2 and CIN3 are 55 and 97%, respectively

BETHESDA SYSTEM OF REPORTING CERVICAL CYTOLOGIC DIAGNOSIS

- **SQUAMOUS CELL**—atypical squamous cells of undetermined significance (ASC-US); atypical squamous cells cannot exclude HSIL (ASC-H)
- **LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION (LSIL)**—encompassing human papillomavirus, mild dysplasia, cervical intraepithelial neoplasia (CIN) 1
- **HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL)**—encompassing moderate and severe dysplasia, carcinoma in situ, CIN2 and CIN3
- **SQUAMOUS CELL CARCINOMA**
- **GLANDULAR CELL**—atypical glandular cells (AGC); atypical glandular cells, favor neoplastic; endocervical adenocarcinoma in situ (AIS); adenocarcinoma

HPV DNA TESTING—for high-risk serotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68). Sensitivity and specificity for CIN2 and CIN3 are 95 and 94%, respectively

OVERALL—the CTFPHC 2013 guideline recommends routine screening with Pap smear every 3 years for women aged 25–69. The USPSTF 2018 statement recommends routine screening with Pap smear every 3 years for women aged 21–29; for women aged 30–65, screening may involve Pap smear every 3 years, high risk HPV DNA every 5 years or both Pap smear and HPV DNA every 5 years

Hereditary Cancer Syndromes**HALLMARKS OF HEREDITARY CANCER****YOUNGER AGE**

≥2 PRIMARY CANCERS

≥2 GENERATIONS

HALLMARKS OF HEREDITARY CANCER (CONT'D)**≥2 FIRST- OR SECOND-DEGREE RELATIVES**

(same side of family)

BRCA SYNDROMES		
	BRCA1	BRCA2
Genetics	Autosomal dominant with variable penetrance, 17q21	Autosomal dominant with variable penetrance, 13q13
Pathophysiology	Tumor suppressor, granin protein family with zinc finger motif, packaging and export of peptide hormones	Tumor suppressor
Cancer types	Breast (triple negative; 19% by age 40, 50% by age 50, 85% by age 70), ovarian (14–45% lifetime risk), prostate (8–16%), colon (6%)	Breast (ER +ve, 50–85%), ovarian (<20%), male breast (6%), prostate (8–16%)
Clinical features	Young age of breast cancer, bilateral breast cancer, ER–(70%), lobular	Young age of breast cancer, bilateral breast cancer, male breast cancer, lobular
Genetic testing	2 common mutations	1 common mutation
Surveillance	Breast—starting at young age, clinical breast exam, mammogram, and MRI q6months Ovarian—screening decision individualized (consider transvaginal US ± CA-125)	
Prophylaxis	PROPHYLACTIC MASTECTOMY —breast cancer risk reduction of 90% PROPHYLACTIC OOPHORECTOMY —when childbearing is complete. Breast cancer risk reduction of 75% and ovarian cancer risk reduction of 95% HORMONAL —neither tamoxifen nor raloxifene is routinely recommended, especially in BRCA1 families, where the majority of cancers are ER negative	

LI-FRAUMENI SYNDROME

GENETICS—autosomal dominant

PATHOPHYSIOLOGY—tumor suppressor, p53 mutation

CANCER TYPES—soft-tissue sarcoma, osteosarcoma, leukemia, breast, melanoma, colon, pancreas, adrenal cortex, brain

VON HIPPEL-LINDAU SYNDROME

PATHOPHYSIOLOGY—VHL mutation

CANCER TYPES—hemangioblastomas of the brain, spinal cord, retina, renal cysts, and clear cell renal cell carcinoma (40%), pheochromocytomas, endolymphatic sac tumors of the middle ear, serous cystadenomas and neuroendocrine tumors of the pancreas, papillary cystadenomas of the epididymis and broad ligament

HEREDITARY MALIGNANT MELANOMA

CANCER TYPES—melanoma, pancreatic

HEREDITARY DIFFUSE GASTRIC CANCER (HDGC)

PATHOPHYSIOLOGY—E-cadherin gene CDH1 mutation

CANCER TYPES—diffuse signet ring cell type gastric, colon, breast (lobular), prostate, ovary

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC, LYNCH SYNDROME)

GENETICS—autosomal dominant

PATHOPHYSIOLOGY—DNA mismatch repair genes (hMLH1, hMSH2, hPMS1, hPMS2, hMSH6). MSH2 and MLH1 account for most of the mutations

CANCER TYPES—colorectal (70–80% lifetime risk), endometrial (most common extracolonic cancer in women), small bowel, gastric, ovarian, hepatobiliary, pancreatic, kidney, ureter, brain (Turcot syndrome), skin (sebaceous adenomas ± keratoacanthomas in the Muir–Torre variant syndrome)

FEATURES—for colon cancer, predominant involvement of right colon, poorly differentiated, increased frequency of mucinous and signet cell tumors, lymphocytic infiltration, MSI high (90%), and better prognosis. Clinical diagnosis can be made by the Amsterdam criteria ★321★: ≥3 relatives with colorectal cancer (two of whom must be first-degree relatives), ≥2 generations involved, and ≥1 family member diagnosed before age 50. FAP should be excluded

SURVEILLANCE—for individuals who have a mismatch repair gene mutation or are strongly suspected of having Lynch syndrome, consider

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER (HNPCC, LYNCH SYNDROME) (CONT'D)

colonoscopy every 1–2 years starting at age 20–25 years or 10 years earlier than the youngest age of colon cancer diagnosis in the family (start at age 30 for MSH6 mutations) and annually after age 40. Annual screening for endometrial and ovarian cancer (pelvic examination, endometrial aspirate, transvaginal US) beginning at age 30–35 years or 5–10 years earlier than the earliest age of first diagnosis of these cancers in the family. Median age of diagnosis is 48. Annual urinalysis and cytologic examination beginning at age 25–35. Annual skin surveillance. Periodic upper endoscopy should be considered

PROPHYLAXIS—total or subtotal colectomy with ileorectal anastomosis for HNPCC patients with colorectal cancer or advanced adenoma (and post-surgical rectal surveillance). Discussion of prophylactic hysterectomy and salpingo-oophorectomy at around age 35 or at the end of childbearing

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

GENETICS—autosomal dominant, 5q21–q22

PATHOPHYSIOLOGY—adenomatous polyposis coli (APC) gene, a tumor suppressor gene that

FAMILIAL ADENOMATOUS POLYPOSIS (FAP) (CONT'D)

normally prevents accumulation of β -catenin by facilitating its phosphorylation and resultant degradation. One-third of patients have no family history (new germline APC mutations or due to MYH gene mutations)

CANCER TYPES—colorectal (risk approaches 100% by age 45), duodenal, ampullary, gastric, follicular or papillary thyroid, hepatoblastoma, medulloblastoma (Turcot syndrome)

FEATURES—colon polyps (more than 100), duodenal adenomatous polyps, extraintestinal manifestations (Gardner syndrome) such as desmoid tumors, sebaceous or epidermoid cysts, lipomas, osteomas, supernumerary teeth, gastric polyps, and juvenile nasopharyngeal angiofibromas

SURVEILLANCE (all at-risk family members)—sigmoidoscopy or colonoscopy annually starting age 10–12. Upper endoscopy with end- and side-viewing endoscopes. Annual thyroid palpation

PROPHYLAXIS—total proctocolectomy at time of diagnosis in patients with multiple large (>1 cm) adenomas or adenomas with villous histology and/or high-grade dysplasia

Oncologic Emergencies**MALIGNANT SPINAL CORD COMPRESSION**

PATHOPHYSIOLOGY—tumor invasion of epidural space (usually above L1 level) → surrounds thecal sac → obstruction of epidural venous plexus → vasogenic edema in white and subsequently gray matter → spinal cord infarction; 60% T-spine, 30% L-spine, 10% C-spine. Median survival post-spinal cord compression is 6 months

CAUSES—prostate cancer, breast cancer, lung cancer, renal cell carcinoma, non-Hodgkin lymphoma, multiple myeloma, cancer of unknown primary, colorectal cancer, sarcoma

CLINICAL FEATURES—**back pain** (particularly may worsen with recumbency, nocturnal), **radicular pain** (band like in abdomen, legs), **weakness** (hip flexion, arm extension), **reflexes** (hyperreflexic, Babinski upgoing), **sensory loss** (usually 1–5 levels down from actual lesion, *no* sacral paresthesia), **Lhermitte sign**, **retention/incontinence** (urinary, bowel), **gait ataxia**

MALIGNANT SPINAL CORD COMPRESSION (CONT'D)

DIAGNOSIS—important to have a high index of suspicion as the diagnosis tends to be delayed until patients have incontinence or difficulty walking. Clinical examination followed by spine imaging (X-ray, CT, MRI). MRI and myelogram are best. Image whole spine regardless of clinical findings

TREATMENTS—consult Medical Oncology, Neurosurgery and Radiation Oncology. **corticosteroid** (*dexamethasone* 10 mg IV/PO \times 1 dose, then 16 mg/day in divided doses (e.g. 4 mg IV/PO every 6 hours). Surgery if spine instability is present. **Treat underlying cause urgently** (radiation \pm radical resection, chemotherapy for chemosensitive tumors). Functional recovery (ambulatory vs paralysis) depends on timing of diagnosis and treatment

MALIGNANT CAUDA EQUINA SYNDROME

PATHOPHYSIOLOGY—compression of lumbosacral nerves roots (lower motor neurons, mostly below L1 level)

MALIGNANT CAUDA EQUINA SYNDROME (CONT'D)

CLINICAL FEATURES—lower limb weakness, depressed tendon reflexes in legs and sacral paresthesia

DIAGNOSIS—similar to malignant spinal cord compression

TREATMENTS—similar to malignant spinal cord compression

SUPERIOR VENA CAVA SYNDROME

PATHOPHYSIOLOGY—invasion or external compression of the SVC by contiguous pathologic processes involving the right lung, lymph nodes, and other mediastinal structures, or by thrombosis within the SVC. Venous collaterals establish alternative pathways, but despite well-developed collateral drainage patterns, central venous pressures remain high, producing characteristic signs and symptoms of SVC syndrome

CAUSES—**neoplasm** (NSCLC 50%, SCLC, lymphoma, metastatic cancer, germ cell tumor, thymoma, mesothelioma), **inflammatory** (fungal infections, TB, sarcoidosis, sclerosing cholangitis), **thrombosis** (indwelling catheters, pacemaker leads)

CLINICAL FEATURES—dyspnea; facial swelling and head fullness (especially with bending forward); Pemberton sign (elevation of arms causes facial congestion/cyanosis); arm edema; cough; stridor; cyanosis, plethora; venous distension on face, neck, and chest wall

DIAGNOSIS—CXR, CT chest, bilateral venography. For patients presenting with SVC syndrome and suspected cancer, tissue diagnosis is required (supraclavicular lymph node, sputum cytology, mediastinoscopy, thoracentesis, bronchoscopy)

TREATMENTS—elevate patient's head. **Treat underlying cause** (radiation, chemotherapy for chemosensitive diseases). **Dexamethasone** 4 mg PO q6h (for lymphoma and thymoma). Consider **endovascular stenting** if urgent (central airway obstruction as manifested by stridor or depressed CNS function as manifested by altered mental status, coma) or refractory disease

Related Topics

Febrile Neutropenia (p. 250)

Spinal Cord Compression (p. 243)

HYPERCALCEMIA OF MALIGNANCY

PATHOPHYSIOLOGY—local osteolytic hypercalcemia 20% (cytokines), humoral hypercalcemia of malignancy 80% (PTHrP), 1,25(OH)₂ vitamin

HYPERCALCEMIA OF MALIGNANCY (CONT'D)

D-secreting lymphomas, and ectopic hyperparathyroidism (PTH) are all known mechanisms. Median survival of 1 month with hypercalcemia in the advanced cancer setting

CLINICAL FEATURES—bony pain, abdominal pain, constipation, polyuria, renal failure, renal stones, confusion

DIAGNOSIS—Ca, PO₄, albumin, PTH, PTH-related protein, 1,25(OH)₂ vitD, bone scan

SYMPTOM CONTROL—NS 200–500 mL/h IV to maintain urine output 100–150 mL/h, stop when euvolemic, monitor fluid status. If malignancy and Ca >3.2 mmol/L [>12.8 mg/dL], **bisphosphonates** (*pamidronate* 60–90 mg in 500 mL NS IV over 2 h, *zoledronate* 4 mg in 50 mL NS IV over 15 min), **denosumab** 120 mg SC (if refractory to bisphosphonate), **calcitonin** 200 U SC/IM BID

TREAT UNDERLYING CAUSE

See HYPERCALCEMIA for more details (p. 388)

TUMOR LYSIS SYNDROME

PATHOPHYSIOLOGY—treatment-induced lysis of tumor cells, leading to release of cell contents → hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, high LDH → calcium phosphate deposition in renal parenchyma and uric acid nephropathy → oliguria. Usually occurs within 3 days before or 7 days after chemotherapy

RISK FACTORS—underlying renal insufficiency, hyperuricemia, hypovolemia, increased tumor proliferation, high chemosensitivity tumor (aggressive lymphomas, ALL, AML, solid tumors)

DIAGNOSIS—a clinical diagnosis with a combination (but not necessarily all) of the following criteria: high uric acid (>475 μmol/L [>4 mg/dL] or ↑ 25% from baseline), high K (>6 mmol/L or ↑ 25% from baseline), high PO₄ (>1.45 mmol/L [>4.5 mg/dL] or ↑ 25% from baseline), low Ca (<1.75 mmol/L [<7 mg/dL] or ↓ 25% from baseline), acute renal failure, arrhythmia, and seizure

TREATMENTS—most important is primary prophylaxis with fluids (NS 150–250 mL/h), *allopurinol* 300 mg PO TID, consider *rasburicase* 3 mg IV flat dose if uric acid >7.5 mg/dL (promotes uric acid degradation). Febuxostat, a xanthine oxidase selective inhibitor, may be considered if allopurinol and rasburicase are not available or tolerable. Monitor urine output, K, Ca, PO₄, Cr, uric acid, and LDH q6h. If tumor lysis syndrome is established, treat uric acid nephropathy with aggressive hydration, furosemide diuresis, rasburicase, and dialysis as a last resort

Febrile Neutropenia

See FEBRILE NEUTROPENIA (p. 250)

Cancer Survivorship

2013 ASCO Guideline Breast Cancer Followup and Management

2015 ASCO Guideline Prostate Cancer Survivorship
Denlinger et al. *J Natl Compr Canc Netw* 2014;12(1)

PRINCIPLES

DEFINITION—the National Cancer Institute defines cancer survivorship as care that “focuses on the health and well-being of a person with cancer from the time of diagnosis until the end of life. This includes the physical, mental, emotional, social, and financial effects of cancer that begin at diagnosis and continue through treatment and beyond. The survivorship experience also includes issues related to follow-up care (including regular health and wellness checkups), late effects of treatment, cancer recurrence, second cancers, and quality of life. Family members, friends, and caregivers are also considered part of the survivorship experience.” This section focuses on survivorship care after the patient has completed definitive treatments and has no evidence of active disease

MONITORING FOR RECURRENCE—new lumps, bleeding, new symptoms that are persistent or worsening, unexplained weight loss, symptoms similar to initial presentation

HIGHER RISK OF SECOND MALIGNANCIES—genetics or acquired risk factors (e.g. smoking, alcohol, obesity). For example, lung cancer patients are at higher risk of head and neck cancer because smoking is a common risk factor. Furthermore, some cancer treatments may contribute to carcinogenesis (e.g. alkylating agents and acute leukemias, topoisomerase II inhibitors and acute leukemias, radiation therapy and solid cancers)

TREATMENT COMPLICATIONS

- **CHEMOTHERAPY**—fatigue, cognitive impairment (“chemobrain”), chemotherapy induced peripheral neuropathy
- **RADIATION**—fibrosis (e.g. dry mouth and dental issues post head and neck irradiation)
- **HORMONAL THERAPY**—bone and cardiovascular health

HEALTH PROMOTION

- **DIET**—healthy balanced diet to maintain healthy body weight
- **EXERCISE**—at least 150–300 min of moderate-intensity activity or 75 minutes of vigorous-intensity activity over the course of a week

PRINCIPLES (CONT'D)

- **SMOKING CESSATION**—counseling and resources
- **PSYCHOSOCIAL ISSUES**—anxiety, depression, post-traumatic stress disorder; changes in bodily function, body image, financial distress, relationship concerns

CARE COORDINATION—communication between oncology specialists and primary care to clarify roles and responsibilities

BREAST CANCER SURVIVORSHIP

MONITORING—history and physical 1–4 times per year for 5 years, then annually. Mammogram annually. Risk of breast cancer recurrence and second primary breast cancer remains elevated 15 years post-treatment

GENETICS SCREENING—periodic review of family history; referral to genetic counselor if indicated; consider hereditary cancer syndromes, e.g. BRCA1/2-related breast/ovarian cancer syndrome

SECOND PRIMARY—elevated risk of breast, esophageal, lung, endometrial, sarcoma, myelodysplastic syndromes and acute myeloid leukemia

TREATMENT COMPLICATIONS

- **SURGERY**—lymphedema, post-mastectomy pain syndrome, breast reconstruction
- **CHEMOTHERAPY**—chemotherapy-induced peripheral neuropathy (taxanes), cardiotoxicity (anthracyclines, trastuzumab), premature ovarian failure
- **HORMONAL THERAPY**—tamoxifen is associated with endometrial cancer and requires pelvic examination; bone health with aromatase inhibitors; vasomotor and sexual symptoms with endocrine therapy

COLORECTAL CANCER SURVIVORSHIP

MONITORING—for patients with stage II and III disease who would be candidates for salvage treatment if recurrence, surveillance includes medical visit with history, physical examination and CEA every 3–6 months × 2 years, then every 6 months for the next 3 years. CT chest/abd (+ CT

COLORECTAL CANCER SURVIVORSHIP (CONT'D)

pelvis for rectal cancer) yearly×5 years. Colonoscopy at 1 year and 3 years after initial diagnostic colonoscopy, then every 5 years. Proctosigmoidoscopy every 6 months for 5 years if rectal cancer but radiation not given

GENETICS SCREENING—periodic review of family history; referral to genetic counselor if indicated; consider hereditary cancer syndromes, e.g. hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome

SECOND PRIMARY—patients who completed pelvic radiation have greater risk of secondary malignancies

TREATMENT COMPLICATIONS

- **SURGERY**—ostomy care, chronic diarrhea, bowel/urinary/sexual dysfunction (rectal)
- **CHEMOTHERAPY**—chemotherapy-induced peripheral neuropathy (oxaliplatin), cardiovascular toxicities (capecitabine)
- **RADIATION**—radiation proctitis, pelvic fractures (pelvic radiation)

Related Topics

Breast cancer (p. 210)

Colorectal cancer (p. 218)

Prostate cancer (p. 230)

PROSTATE CANCER SURVIVORSHIP

MONITORING—PSA every 6–12 months for first 5 years (more frequently if high risk features), then PSA annually. Annual DRE

GENETICS SCREENING—periodic review of family history; referral to genetic counselor if indicated; consider hereditary cancer syndromes, e.g. BRCA1/2-related breast/ovarian cancer syndrome

SECOND PRIMARY—patients who completed pelvic radiation have greater risk of colorectal cancer and bladder cancer. Colorectal cancer screening should be instituted

TREATMENT COMPLICATIONS

- **ANDROGEN DEPRIVATION THERAPY**—assess vasomotor symptoms; monitor bone mineral density with DEXA scan and anemia. Consider bisphosphonate or denosumab if high risk of osteoporosis
- **SURGERY, BRACHYTHERAPY, RADIATION**—patients may be at increased risk of sexual, bowel and bladder dysfunction

INFECTIOUS DISEASES

Stephanie W. Smith and Keely Hammond



Fever of Unknown Origin

DEFINITIONS

FEVER OF UNKNOWN ORIGIN (FUO)

- **FUO**— $\geq 38.3^{\circ}\text{C}$ [$\geq 101^{\circ}\text{F}$], duration ≥ 3 weeks, diagnosis uncertain after 3 days in hospital or 3 outpatient visits
- **NOSOCOMIAL FUO**—hospitalized patients, $\geq 38.3^{\circ}\text{C}$ [$\geq 101^{\circ}\text{F}$], diagnosis uncertain after 3 days and infection not present or incubating on admission
- **IMMUNE-DEFICIENT (NEUTROPENIC) FUO**— $\geq 38.3^{\circ}\text{C}$ [$\geq 101^{\circ}\text{F}$], >3 days, neutrophil count $\leq 500/\text{mm}^3$. See p. 250 for details
- **HIV-RELATED FUO**—HIV patients, $\geq 38.3^{\circ}\text{C}$ [$\geq 101^{\circ}\text{F}$], duration ≥ 3 weeks for outpatients or ≥ 3 days for inpatients

FEVER NYD—persistent fever that has not yet met the definition for FUO

DIFFERENTIAL DIAGNOSIS

Etiology of FUO grouped into one of 5 categories; infections account for 15–55%

INFECTIONS—**TB** (pulmonary, extrapulmonary, miliary), nontuberculous **mycobacterial** infections, occult **abscesses** (liver, splenic, perinephric, psoas, diverticular, pelvis), **osteomyelitis**, **endocarditis**, **prosthetic associated infections**. Consider **occult pathogens** (Q fever, leptospirosis, psittacosis, tularemia, melioidosis, syphilis, gonococcemia, chronic meningococcemia, Whipple disease, yersiniosis, brucellosis)

NEOPLASTIC—**hematologic** (lymphoma, leukemia, multiple myeloma, myelodysplastic syndrome), **solid tumors** (renal cell, hepatoma)

INFLAMMATORY—**vasculitis** (giant cell arteritis, Still disease, polyarteritis nodosa, Takayasu arteritis, granulomatosis with polyangiitis, mixed cryoglobulinemia), **lupus**, **rheumatoid arthritis**, **alcoholic hepatitis**, **polymyalgia rheumatica**

DIFFERENTIAL DIAGNOSIS (CONT'D)

DRUGS—**antimicrobials** (sulfonamides, penicillins, nitrofurantoin, antimalarials), **antihistamines**, **antiepileptics** (barbiturate, phenytoin), **NSAIDs/ASA**, **antihypertensives** (hydralazine, methyl dopa), **antiarrhythmics** (quinidine, procainamide), **antithyroid**, **iodides**, **quinine**, **illicit** (cocaine)

OTHER—**central fever**, **endocrine** (hypothalamic dysfunction, hyperthyroidism, pheochromocytoma, adrenal insufficiency), **hereditary periodic fever syndromes** (familial Mediterranean fever, periodic fever with aphthous stomatitis, pharyngitis, and adenitis [PFAPA] syndrome, TNFR-1-associated periodic syndrome, hyper-IgD syndrome, Muckle–Wells syndrome, familial cold autoinflammatory syndrome), hemophagocytic lymphohistiocytosis (HLH) hematoma, **factitious fever**

CLINICAL FEATURES

HISTORY—pattern and duration of fever, associated symptoms (cough, dyspnea, hemoptysis, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, hematuria, neck stiffness, headache), rash (palpable purpura, exanthem), exposure (food, water, plants, animals, insects, infected human secretions), weight loss, night sweats, travel history, sexual history, HIV risk factors, immunizations, past medical history (rheumatologic disorders, malignancy, alcohol), medications

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), temporal artery, abdominal examination (hepatosplenomegaly), prostate examination, skin lesions (morphology, distribution), tick bite marks, joint examination

INVESTIGATIONS**BASIC**

- **LABS**—CBC (differential helpful for evidence of left shift), lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, CK, serum protein electrophoresis, urinalysis, ESR, CRP, ANA, ENA, RF, immunoglobulins, C3, C4, ANCA, cryoglobulin
- **MICROBIOLOGY**—blood C&S (including *Mycobacteria*), sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, serology (HBV, HCV, HIV, monospot, CMV IgM, endemic fungi)
- **IMAGING**—CXR, echocardiogram (if suspect endocarditis), CT chest/abd/pelvis as guided by symptoms, FDG-PET (may be useful for identifying sites of inflammation and malignancy in FUO)

SPECIAL

- **ECG**
- **BIOPSY**—affected tissue (e.g. bone marrow biopsy, lymph node) sent for pathology and for culture

DIAGNOSIS AND PROGNOSTIC ISSUES

DIAGNOSIS—the most important diagnostic strategy is a careful history and physical examination with frequent reassessment and laboratory testing as indicated by history and physical examination

PROGNOSIS—up to 30–50% will not have a diagnosis despite detailed workup; 5-year mortality in those without a diagnosis is 3%. 75% will resolve with or without a diagnosis

MANAGEMENT

EMPIRIC ANTIBIOTICS—ONLY if suspect infectious etiology and therapy cannot be delayed due to severity of patient's disease (see EMPIRIC ANTIBIOTICS p. 275). In general, therapeutic trials of antimicrobials or steroids are discouraged

Hayakawa et al. *Am J Med Sci* 2012;344(4)

Wright et al. *Open Forum Infect Dis* 2020;7(5)

TREAT UNDERLYING CAUSE**Fever and Rash****DIFFERENTIAL DIAGNOSIS****INFECTIONS**

- **GRAM-POSITIVE COCCI**—scarlet fever, toxic shock syndrome, staphylococcal scalded skin syndrome, acute rheumatic fever (erythema marginatum, subcutaneous nodules)
- **GRAM-NEGATIVE COCCI**—meningococemia (purpura), disseminated gonococcal infection
- **GRAM-NEGATIVE BACILLI**—*Salmonella typhi*, *Pseudomonas* (ecythema gangrenosum), *Vibrio vulnificus*
- **FUNGAL**—disseminated *Candida*, endemic fungi (*Blastomyces*, *Coccidioides*, *Histoplasma*)
- **SPIROCHETES**—*Borrelia burgdorferi* (Lyme erythema migrans), *Treponema pallidum* (chancere, secondary syphilis)
- **RICKETTSIAL**—Rocky Mountain spotted fever, ehrlichiosis, typhus
- **VIRAL EXANTHEM**—acute HIV, mononucleosis, rubella, measles, roseola, erythema infectiosum, chickenpox, shingles, coxsackie virus, echovirus, coronavirus

RHEUMATOLOGIC

- **SEROPOSITIVE**—systemic lupus erythematosus, dermatomyositis

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **SERONEGATIVE**—inflammatory bowel disease, reactive arthritis
- **VASCULITIS**—granulomatosis with polyangiitis, polyarteritis nodosa
- **BEHÇET DISEASE**
- **MALIGNANCY**—lymphoma, leukemia, metastatic, paraneoplastic
- **MEDICATIONS**—penicillins, cephalosporins, sulfas, barbiturates, phenytoin, procainamide, quinidine
- **OTHERS**—sarcoidosis, erythema nodosum; Sweet syndrome (acute febrile neutrophilic dermatosis)

CLINICAL FEATURES**SETTINGS**

- **AGE**—viral exanthems, scarlet fever, and acute rheumatic fever are more likely in children. Mononucleosis is more common in young adults
- **SEASON**—tick-borne diseases are more common in spring and summer. Coxsackie virus and echovirus are more common in summer and fall. Meningococcus and parvovirus are more common in winter and spring

CLINICAL FEATURES (CONT'D)

- **GEOGRAPHIC LOCATION**—Lyme disease in Pacific northwest, the Midwest, and the northeast USA and some southern Canadian locations. RMSF in south-central and Atlantic states. Ehrlichiosis in midwestern, south-central, and southeastern states. Tularemia in western, southeastern, and south-central states and Canada. Relapsing fever (*Borrelia hermsii*) in mountainous areas of the western USA. Endemic fungal infections include *Blastomyces dermatitidis* (southeastern states, Manitoba, and Ontario), *Coccidioides immitis* (southwestern states), and *Histoplasma capsulatum* (Mississippi, Ohio River valleys, and Quebec)

HISTORY—pattern and duration of fever, associated symptoms (cough, dyspnea, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, neck stiffness, headache), rash (prodrome, location, progression, treatment), exposure (food, water, plants, animals, infected human secretions), weight loss, night sweats, travel history, sexual history, immunizations, past medical history (rheumatologic disorders, malignancy), medications

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenomegaly), skin lesions (morphology, distribution), tick bite eschar, joint examination

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, ESR/CRP, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, monospot test, CMV IgM, EBV, HIV, and other serologies (e.g. rickettsial serology)

SPECIAL

- **LUMBAR PUNCTURE**—if suspect meningococcus
- **SKIN BIOPSY**—dermatology consult
- **INFLAMMATORY WORKUP**—CRP, ANA, ENA

MANAGEMENT

ISOLATION PRECAUTIONS—point-of-care risk assessment key to ensure appropriate PPE is worn (e.g. for purpura with bacterial sepsis, institute droplet and contact isolation precautions). See p. 289 for more details

TREAT UNDERLYING CAUSE**SPECIFIC ENTITIES****TOXIC SHOCK SYNDROME**

- **PATHOPHYSIOLOGY**—exotoxin by specific strains of *Staphylococcus aureus* or group A *Streptococcus* (toxic shock syndrome toxin-1 TSST-1) acting as superantigens, activating T cells, leading to cleavage at the granular layer of the dermis
- **CLINICAL FEATURES**—young person with fever, malaise, generalized macular, erythematous rash including mucous membranes, palms and soles, evolves into petechiae, vesicles, and bullae. Ulcerations may be seen on mucous membranes. Exclude retained foreign bodies (especially tampons, contraceptive sponges). Hypotension and organ failure may occur
- **TREATMENTS**—fluid resuscitation as needed. Empiric treatment includes *vancomycin* (15 to 20 mg/kg/day IV q8–12h) plus β -lactam plus *clindamycin* (900 mg IV q8h) plus either a *carbapenem* (*imipenem* 500mg IV q6h) or combination drug containing beta-lactamase inhibitor and penicillin (*piperacillin-tazobactam* 4.5g IV q6h). For treatment of MSSA, *oxacillin* or *nafcillin* (2g IV q4h) plus *clindamycin* if susceptible (900mg IV q8h). If unresponsive to fluids or vasopressors, consider *IVIG* (400 mg/kg \times 1 dose, limited evidence). Surgical debridement as appropriate

RICKETTSIAL INFECTIONS (WITHIN NORTH AMERICA)

- **THEMES**—all transmitted by ticks, except Q fever (*Coxiella burnetii*). All associated with a rash, myalgias, and headache, except Q fever and ehrlichiosis. All involve some degree of vasculitis and DIC as part of pathogenesis. All treated with doxycycline
- **ROCKY MOUNTAIN SPOTTED FEVER**—*Rickettsia rickettsii* transmitted by ticks. Most common in mid-Atlantic states. Macular/maculopapular rash begins on extremities and moves centrally, involves palms/soles. Treat with doxycycline
- **MURINE TYPHUS**—flea vector. Rash begins centrally and moves peripherally. Treat with doxycycline or chloramphenicol
- **EHRlichia**—*Ehrlichia chaffeensis* (human monocytic ehrlichiosis) transmitted by lone star tick. Peaks in May to July. Infects lymphocytes, monocytes, and neutrophils intracellularly. Fever, headache, myalgia, leukopenia, thrombocytopenia, and elevated transaminases; maculopapular or petechial rash in 1/3. Human granulocytic anaplasmosis is caused by a related *Ehrlichia* and produces similar ill-

SPECIFIC ENTITIES (CONT'D)

ness without rash. Transmitted by *Ixodes* tick and co-infection with Lyme disease possible. Treat with doxycycline

- **Q FEVER**—*C. burnetii* spread by respiratory transmission from infected animal body fluids (e.g. cattle, sheep, goats, cats). No rash. Fever, pneumonitis, hepatitis, endocarditis, CNS symptoms. Treat with doxycycline

LYME DISEASE

- **PATHOPHYSIOLOGY**—*B. burgdorferi* transmitted by *Ixodes* tick bite after attachment for >24 h; think about concomitant tick borne diseases
- **CLINICAL FEATURES**—most common tick-borne disease in USA, particularly coastal Atlantic States and California during spring and summer
 - **STAGE 1 (EARLY)**—first 3–30 days, **erythema migrans**, fever, meningismus, lymphadenopathy
 - **STAGE 2 (DISSEMINATED)**—weeks to months, hematogenous spread with **neurological symptoms** (facial nerve palsy, lymphocytic meningitis, encephalitis, chorea, myelitis, radiculitis, peripheral neuropathy) and **carditis** (AV block, dilated cardiomyopathy); may have multiple skin lesions of erythema migrans
 - **STAGE 3 (LATE)**—months to years, mono- or oligoarthritis, acrodermatitis chronica atrophicans (in Europe), progressive encephalitis, dementia (not amenable to antibiotic therapy). May develop post-Lyme syndrome with musculoskeletal pain, neurocognitive symptoms, dysesthesias and fatigue (not amenable to antibiotic therapy)
- **DIAGNOSIS**—serology (anti-*B. burgdorferi* ELISA). If positive, confirm with Western blot

SPECIFIC ENTITIES (CONT'D)

- **PREVENTION**—protective clothing and tick repellants. After tick bite (>36 h in hyperendemic area), consider *doxycycline* 200 mg × 1 dose within 72 h of the tick bite
- **TREATMENTS**—**stage 1** (*doxycycline* 100 mg PO BID × 10–21 days, or *cefuroxime* 500 mg PO BID × 10–21 days). **Lyme carditis** (*ceftriaxone* 2 g IV × 14–21 days if third degree AV block; otherwise, same as stage I with oral antibiotics). **Neurologic Lyme** (*ceftriaxone* 2 g IV × 14–21 days). **Lyme arthritis** (*doxycycline* 100 mg BID × 28 days)
- **JARISCH—HERXHEIMER REACTION**—up to 15% of patients may experience transient worsening of symptoms during first 24 h of treatment. This results from the host immune response to antigen release from dying organisms (typically Lyme and syphilis) causing fever, chills, myalgias, and exacerbation of rash

BABESIOSIS

- **PATHOPHYSIOLOGY**—*Babesia microti* (USA) or *Babesia divergens* (Europe) transmitted by *Ixodes* ticks (which also transmit Lyme disease and *Ehrlichia*) → fever, chills, sweats, malaise, myalgias, arthralgias, headache 5–33 days after, particularly in immunosuppressed individuals
- **CLINICAL FEATURES**—malaria-like but does not cause rash. Endemic in southern New England, New York, Wisconsin, and Minnesota
- **DIAGNOSIS**—blood smear ('Maltese cross' formations, not seen in malaria), PCR, serology
- **TREATMENTS**—atovaquone plus azithromycin

Related Topic

Exanthematous Lesions (p. 402)

Febrile Neutropenia**DEFINITION**

FEBRILE NEUTROPENIA—single temp ≥ 38.3 °C [101 °F] or ≥ 38 °C [100.4 °F] for >1 h, absolute neutrophil count (ANC) $<0.5 \times 10^9/L$ or $<1.0 \times 10^9/L$ with expected nadir $<0.5 \times 10^9/L$. ANC includes neutrophils + bands

CCC**BACTERIAL**

- **GRAM-POSITIVE**—*S. aureus*, coagulase-negative staphylococci, *Streptococcus pneumoniae*, corynebacterium

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **GRAM-NEGATIVE**—*Enterobacter*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas*, *Clostridioides difficile* (formerly *Clostridium*), anaerobes
- VIRAL**—HSV, VZV, CMV, EBV, HHV6, enterovirus, RSV, influenza and other respiratory viruses
- FUNGAL**—*Candida*, *Aspergillus*, endemic fungi, *Mucormycetes* (formerly *Zygomycetes*)
- REACTIVATION OF LATENT INFECTION**—*Histoplasma*, *Coccidioides*, *Toxoplasma*, tuberculosis

PATHOPHYSIOLOGY

PATHOGENESIS—chemotherapy-induced injury to mucosal barriers, immune defects due to drugs or underlying disease and invasive devices. With attenuated immune response, patients may be relatively asymptomatic until they decompensate due to overwhelming infection. Fever is sometimes the only warning sign and **should always be taken seriously in patients at risk of developing neutropenia**

NEUTROPENIA-ASSOCIATED FEBRILE EPISODES—most commonly idiopathic; bacterial source identified in approximately 30% of episodes, usually from patient's own endogenous flora. Fungal infections replace bacterial infections in prominence after 7 days. Fever usually abates with return of neutrophils. If fever persists or returns after neutropenia resolves, consider **hepatosplenic candidiasis**

CLINICAL FEATURES

HISTORY—patients usually asymptomatic other than fever. Determine severity and duration of fever, associated signs and symptoms (cough, dyspnea, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, neck stiffness, headache, rash), recent chemotherapy (nadir of neutrophil counts usually 10–14 days post-treatment), weight loss, night sweats, travel history, sexual history, immunizations, past medical history (malignancy, rheumatologic disorders), medications (chemotherapy, GCSF)

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenomegaly), skin lesions (morphology, distribution). Important sites to examine include venous access devices, sinuses, and perianal region for abscess. **Avoid DRE, rectal thermometers, enemas/suppositories** (translocation of gut microbes)

INVESTIGATIONS**BASIC**

- **LABS**—CBC (with differential to determine ANC), lytes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—blood C&S×2 (culture peripheral blood in addition to central line ports), sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, *C. difficile* toxin (if diarrhea)
- **IMAGING**—CXR

INVESTIGATIONS (CONT'D)**SPECIAL**

- **SINUS RADIOGRAPH**
- **SERUM GALACTOMANNAN**—for invasive aspergillosis

MANAGEMENT

LOW RISK (ANC $>0.1 \times 10^9/L$, peak temperature $<39^\circ C$ [$102.2^\circ F$], no significant symptoms or signs, no significant comorbidities, normal/near normal renal and hepatic function, neutropenia ≤ 7 days, no dehydration, no hypotension, age <60 years)—*ciprofloxacin* 500 mg PO BID + *amoxicillin-clavulanate* 500 mg PO q8h. Outpatient management with close follow-up

HIGH RISK (anticipated prolonged >7 days duration and profound neutropenia [ANC $\leq 0.1 \times 10^9/mL$] and/or significant medical comorbid conditions such as hypotension, pneumonia, new-onset abdominal pain, or neurologic changes)—admit for IV antibiotics

- **FIRST LINE**—*imipenem* 500 mg IV q6h, *meropenem* 2 g IV q8h, *ceftazidime* 2 g IV q8h, *cefepime* 2 g IV q8h, *piperacillin/tazobactam* 4.5 g IV q8h, *clindamycin* 600 mg IV q8h plus *tobramycin* 7 mg/kg IV q24h (in case of confirmed betalactam allergy), or *piperacillin/tazobactam* 4.5 g IV q8h plus *gentamicin* 2–2.5 mg/kg IV q8h
- **SECOND LINE**—add *vancomycin* 20 mg/kg IV q12h if suspected line infection, known colonization MRSA, Gram-positive blood culture, or hypotension
- **THIRD LINE**—add antifungal if febrile after 4–7 days and hemodynamically unstable (*fluconazole* 400 mg IV daily, *itraconazole* 200 mg IV daily, *amphotericin B* 0.5–1 mg/kg IV daily over 4 h, *casposungin* 70 mg on first day followed by 50 mg IV daily)
- **NOTE**—unexplained persistent fever in a patient whose condition is otherwise stable rarely requires an empirical change to the initial antibiotic regimen. If an infection is identified, antibiotics should be adjusted accordingly

CATHETER REMOVAL—necessary for most patients with bacteremia/candidemia with organisms other than coagulase-negative *Staphylococci*

TREATMENT ISSUES**MODIFICATION OF THERAPY DURING FIRST WEEK OF TREATMENT**

- **IF PATIENT BECOMES AFEBRILE IN 3–5 DAYS**
 - **KNOWN ORGANISM**—switch to specific antibiotics based on sensitivity

TREATMENT ISSUES (CONT'D)

- UNKNOWN ETIOLOGY AND LOW RISK—switch to ciprofloxacin plus amoxicillin–clavulanate after afebrile for 48 h
- UNKNOWN ETIOLOGY AND HIGH RISK—continue same antibiotics
- IF PERSISTENT FEVER DURING FIRST 3–5 DAYS
 - CLINICALLY STABLE BY DAY 3—continue antibiotics, stop vancomycin if cultures negative
 - PROGRESSIVE DISEASE BY DAY 3—change antibiotics
 - FEBRILE AFTER DAY 5—add antifungal

DURATION OF ANTIBIOTIC TREATMENT

- IF AFEBRILE BY DAY 3
 - STOP ANTIBIOTICS—if (1) ANC $\geq 0.5 \times 10^9/L$ for 2 consecutive days, afebrile for ≥ 48 h, cultures negative, and no obvious signs of infection, or if (2) ANC $< 0.5 \times 10^9/L$ by day 7, but afebrile for 5–7 days, patient initially at low risk, and no subsequent complications
 - CONTINUE ANTIBIOTICS—if above criteria not met
- IF PERSISTENT FEVER ON DAY 3
 - STOP ANTIBIOTICS—if ANC $\geq 0.5 \times 10^9/L$ for 4–5 consecutive days
 - CONTINUE ANTIBIOTICS—if ANC $< 0.5 \times 10^9/L$, reassess and continue antibiotics for 2 weeks. Consider stopping therapy if no disease site is found and condition is stable

PRE-MEDICATIONS FOR AMPHOTERICIN B

—*mepheridine* 50 mg IV, *acetaminophen* 2 tabs PO, *hydrocortisone* 25 mg IV 30 min before dose, and repeat $\times 1$ 1–2 h after administration

GCSF SUPPORT

- PRIMARY PROPHYLAXIS—GCSF is recommended for the prevention of febrile neutropenia if:
 - HIGH-RISK PATIENTS—based on age (>65), medical history (poor performance status, previous febrile neutropenia, extensive prior treatment, poor nutrition, open wounds, active infections), disease characteristics (bone marrow involvement), and myelotoxicity of the chemotherapy regimen (e.g. chemoradiation)
 - CHEMOTHERAPY REGIMENS—20% or higher risk of febrile neutropenia or dose dense regimens
- SECONDARY PROPHYLAXIS—GCSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (in which primary prophylaxis was not received), in which a reduced dose may compromise disease-free survival, overall survival, or treatment outcome

TREATMENT ISSUES (CONT'D)

- TREATMENT OF PATIENTS WITH FEBRILE NEUTROPENIA—GCSF should be given to those with high risk of developing complications, including expected prolonged (>10 days) and profound ($< 0.1 \times 10^9/L$) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multi-organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of the development of fever
- SPECIAL SITUATIONS
 - STEM CELL TRANSPLANT—to mobilize peripheral blood progenitor cell often in conjunction with chemotherapy. Also administered after autologous, but not allogeneic stem cell transplantation
 - DLBCL—prophylactic GCSF should be given for patients with diffuse aggressive lymphoma age 65 and older treated with curative chemotherapy (CHOP or more aggressive regimens)
 - AML—may be given shortly after completion of the initial induction chemotherapy to modestly decrease the duration of neutropenia
 - ALL—recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post-remission course, thus shortening the duration of neutropenia by approximately 1 week
 - MDS—may be used to increase the ANC in neutropenic patients. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infections
 - POST-RADIATION—GCSF should be given to patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs

**2010 IDSA Update Guideline Antimicrobial Agents Neutropenic Patients with Cancer
2018 ASCO/IDSA Guideline Fever/Neutropenia Malignancy**

SPECIFIC ENTITIES**NECROTIZING ENTEROCOLITIS (TYPHLITIS)**

- PATHOPHYSIOLOGY—mucosal injury in patients with profound neutropenia \rightarrow impaired host defense \rightarrow necrosis of bowel wall, involving cecum extending into ascending colon and terminal ileum
- CLINICAL FEATURES—abdominal pain (especially RLQ) in neutropenic patients
- DIAGNOSIS—CT abd. Avoid barium enema and colonoscopy

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—bowel rest, NG suction, IV fluids, nutritional support, broad spectrum antibiotics, GCSE. Surgical indications include peritonitis, perforation, persistent GI bleeding, or clinical deterioration

SPECIFIC ENTITIES (CONT'D)**Related Topics**

- Neutropenia (p. 165)
- Stem Cell Transplant (p. 202)

Fever with Travel History**DIFFERENTIAL DIAGNOSIS****FEVER WITH CNS INVOLVEMENT**

- **BACTERIAL**—meningococcal, typhoid fever, rickettsial, leptospirosis
- **MYCOBACTERIAL**—tuberculosis
- **VIRAL**—Japanese encephalitis, West Nile encephalitis, tick-borne encephalitis, poliomyelitis, rabies
- **FUNGAL**—cryptococcal meningitis
- **PARASITIC**—malaria, angiostrongyliasis, trypanosomiasis

FEVER WITH RESPIRATORY INVOLVEMENT

- **BACTERIAL**—*S. pneumoniae*, *Mycoplasma*, *Legionella*, Q fever, scrub typhus, melioidosis
- **MYCOBACTERIAL**—tuberculosis
- **VIRAL**—influenza, parainfluenza, metapneumovirus, respiratory syncytial virus, adenovirus, dengue, coronavirus
- **FUNGAL**—histoplasmosis, coccidioidomycosis, other endemic fungi
- **PARASITIC**—malaria, Loeffler syndrome (migration of larval helminths such as ascariis, strongyloides, and hookworm)

FEVER WITH RASH—see FEVER AND RASH (p. 248)

HEMORRHAGIC FEVER

- **BACTERIAL**—rickettsial, meningococemia, leptospirosis
- **VIRAL**—dengue, yellow fever, Ebola fever, Lassa fever, Marburg
- **PARASITIC**—malaria

FEVER WITH SEXUAL OR BLOOD EXPOSURES—syphilis, CMV, EBV, HIV, HBV

FEVER WITH EOSINOPHILIA—parasitic (acute hookworm, ascariis, strongyloides, acute schistosomiasis, visceral larva migrans, lymphatic filariasis, acute trichinosis)

FEVER WITH THROMBOCYTOPENIA—malaria, typhoid fever, dengue shock syndrome, ehrlichiosis, Rocky Mountain spotted fever

ACUTE TRAVELER'S DIARRHEA ± FEVER

- **BACTERIAL**—Enterotoxigenic or enteroaggregative *E. coli*, *Campylobacter jejuni*,

DIFFERENTIAL DIAGNOSIS (CONT'D)

- Salmonella*, *Shigella*, *Vibrio*, *Aeromonas*, *Plesiomonas*, *C. difficile*
- **VIRAL**—Caliciviruses (Norwalk, Norwalk-like), rotaviruses, Ebola fever, enteroviruses, hepatitis A
- **PARASITIC**—*Giardia lamblia*, *Cryptosporidium parvum*, *Entamoeba histolytica*, *Cyclospora cayetanensis*, *Isospora belli*, *Entamoeba polecki*, *Balantidium coli*, *Trichinella spiralis*

CHRONIC TRAVELER'S DIARRHEA ± FEVER

- **BACTERIAL**—Enteroaggregative or enteropathogenic *E. coli*, *C. jejuni*, *Shigella*, *Salmonella*, *Yersinia enterocolitica*, *Aeromonas*, *Plesiomonas*, *C. difficile*, *Tropheryma whippelii*
- **MYCOBACTERIAL**—tuberculosis, *Mycobacterium avium* complex
- **FUNGAL**—*Paracoccidioides brasiliensis*, *H. capsulatum*
- **PARASITIC**—*G. lamblia*, *E. histolytica*, *C. parvum*, *C. cayetanensis*, *Trichuris trichiura*, *Strongyloides stercoralis*, *Schistosomiasis*, *Capillaria philippinensis*, *Fasciolopsis buski*, *Metagonimus yokogawai*, *Echinostoma*
- **NON-INFECTIOUS**—tropical sprue, irritable bowel syndrome, inflammatory bowel disease, cancer, laxative use, endocrinopathy, dysmotility, idiopathic

OTHER UNDIFFERENTIATED FEVER

- **PARASITIC**—malaria
- **VIRAL**—typhoid, viral mosquito borne viruses (e.g. dengue, Zika and chikungunya)

CLINICAL FEATURES

HISTORY—pattern and duration of fever, associated symptoms (cough, dyspnea, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, neck stiffness, headache), weight loss, night sweats, travel history (specific itinerary, activities and exposures including food and fresh/saltwater history, incubation period), sexual history,

CLINICAL FEATURES (CONT'D)

immunization status, antimalarial chemoprophylaxis (medications, degree of adherence), past medical history (rheumatologic disorders, malignancy), medications

PHYSICAL—vitals (tachycardia, tachypnea, hypotension, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenomegaly), skin lesions (morphology, distribution), tick bite marks, joint examination

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, *C. diff* toxin A/B, malaria thick and thin smear (repeat $\times 1$ within 12–24 h if initially negative result), serologies (HIV, dengue, rickettsiae, schistosomiasis, strongyloidiasis, leptospira, HAV, HBV, HCV, hepatitis E)
- **IMAGING**—CXR, US abd guided by symptoms

SPECIAL

- **LUMBAR PUNCTURE**

PRE-TRAVEL CONSIDERATIONS

VACCINATIONS—standard regardless of travel (influenza, pneumococcal if age >65 , hepatitis B, MMR, DPT), developing countries (hepatitis A), specific countries (meningococcal, Japanese encephalitis, yellow fever), high-risk activity (rabies), outbreaks (cholera)

MALARIA PROPHYLAXIS—see below

DIARRHEA PROPHYLAXIS—chemoprophylaxis not routinely recommended unless underlying medical condition at high risk for diarrhea-related complications (e.g. IBD, immunocompromised, severe cardiac/renal/vascular disease); chemoprophylaxis options (antibiotic rifaximin vs. non-antibiotic bismuth, Lactobacillus), vaccination (cholera vaccination). Prophylaxis with ciprofloxacin not recommended

Thwaites et al. NEJM 2017;376(6)

SPECIFIC ENTITIES

PRIORITY—focus on those illnesses that are potentially fatal or may be public health threats

TOP TRAVEL-RELATED INFECTIONS—malaria, typhoid fever, dengue fever, diarrheal disease, respiratory infections, Lyme disease, Q fever, brucellosis

SPECIFIC ENTITIES (CONT'D)

MALARIA—the most important cause of fever in travelers returning from the tropics and subtropics. *Plasmodium falciparum* can be rapidly fatal and must be ruled out in all febrile travelers returning from malaria-endemic regions. It has the shortest incubation period and $>90\%$ of affected travelers will become ill within 30 days of return

- **PATHOPHYSIOLOGY**—anopheles mosquito bite transmits sporozoites \rightarrow travel to liver and invade hepatocytes \rightarrow divide and form schizonts, which contain merozoites (asymptomatic) \rightarrow rupture after 6–16 days and release merozoites into the bloodstream \rightarrow infect erythrocytes and mature from ring forms to trophozoites to mature schizonts (asexual form) over 48h (*Plasmodium vivax*, *Plasmodium ovale*, *P. falciparum*) or 72h (*Plasmodium malariae*) \rightarrow merozoites released from erythrocytes (fever, anemia, lactic acidosis, cytokine release) and infect new red cells \rightarrow few merozoites differentiate into male or female gametocytes (sexual forms) can circulate in blood until ingested by mosquito. *P. vivax* and *P. ovale* may stay dormant in the liver as hypnozoites and may cause late relapse by reactivating after many months. *P. falciparum* and *P. malariae* have no liver stage and do not cause relapse. *P. falciparum* specifically can induce obstruction of microvascular blood flow, and may lead to organ dysfunction (e.g. cerebral malaria, renal failure, ARDS, hypoglycemia, anemia, DIC, and gastroenteritis)
- **CLINICAL FEATURES**—*P. falciparum* acquired mostly from sub-Saharan Africa, *P. vivax* mostly from Asia or Latin America. Symptoms include spiking fevers, chills, headache, back pain, cough, GI problems. Splenomegaly and thrombocytopenia without leukocytosis may be present. Cerebral malaria (*P. falciparum*) presents as altered level of consciousness or seizures and is fatal if untreated
- **DIAGNOSIS**—thick and thin smear (need to repeat over 48 h to rule out malaria)
- **PROPHYLAXIS**—relative risk of contracting malaria varies by geographic region: Caribbean $<$ North Africa $<$ South America $<$ Southeast Asia $<$ Central America $<$ South Asia $<$ Oceania $<$ sub-Saharan Africa. Travelers should be advised to wear long sleeves/pants between dusk and dawn, use mosquito repellents containing 30–50% DEET, and consider permethrin-treated mosquito nets. Chloroquine may be used for travel to destina-

SPECIFIC ENTITIES (CONT'D)

tions with chloroquine-sensitive *P. falciparum* (most of Central America and parts of the Middle East). For destinations where chloroquine-resistant *P. falciparum* is present, chemoprophylaxis with atovaquone-proguanil, mefloquine, or doxycycline should be used. Give atovaquone-proguanil or doxycycline for travel to destinations with *P. falciparum* resistance to chloroquine, mefloquine, and sulfonamides (e.g. regions of Thailand, Cambodia, China, Laos, and Vietnam). Atovaquone-proguanil associated with fewest side effects. Mefloquine has ease of weekly dosing. Doxycycline is the cheapest, but requires prolonged course and causes sun sensitization. CDC risk assessment and prophylaxis recommendations are available online at <http://www.cdc.gov/>

- **TREATMENTS**—intravenous artesunate has emerged as the treatment of choice for complicated malaria. Other options include quinine-doxycycline, atovaquone-proguanil, and mefloquine. Chloroquine-primaquine for non-falciparum

TYPHOID FEVER

- **PATHOPHYSIOLOGY**—acquired after exposure to food or water contaminated by *S. typhi*
- **CLINICAL FEATURES**—fever, chills, headache, myalgia, abdominal pain and constipation (uncommonly diarrhea), relative bradycardia, splenomegaly, and rose spots (faint salmon-colored macules on the abdomen and trunk). Septic symptoms from intestinal perforation may occur in second week
- **DIAGNOSIS**—blood, stool, urine, or bone marrow (highest sensitivity) culture; CBC may show leukopenia
- **TREATMENTS**—fluoroquinolones, ceftriaxone, azithromycin

DENGUE FEVER

- **PATHOPHYSIOLOGY**—flavivirus transmitted by mosquito → flu-like illness 4–7 days later → lymphadenopathy, maculopapular/petechial rash → dengue shock syndrome and dengue hemorrhagic fever if previously exposed to other serotypes
- **CLINICAL FEATURES**—acquired mostly from tropical and subtropical areas. Fever, headache, retro-orbital pain, severe myalgia/arthralgia ('break-bone fever'). Leukopenia and thrombocytopenia
- **DIAGNOSIS**—serology
- **TREATMENTS**—supportive

SPECIFIC ENTITIES (CONT'D)**EBOLA FEVER**

- **EPIDEMIOLOGY**—flavivirus possibly transmitted by fruit bats → person-to-person transmission occurs from direct contact with blood or bodily fluids (saliva, blood, vomit, stool or semen) of infected symptomatic patients. Incubation period 2–21 days
- **CLINICAL FEATURES**—early symptoms include fever, headache, myalgia/arthralgia, vomiting, diarrhea, abdominal pain, conjunctival injection, and rash. Late symptoms include bleeding, shock, delirium and death
- **DIAGNOSIS**—high index of suspicion if patient has recently been in endemic area during an Ebola outbreak. Serology (sens 91%) and RT-PCR (sens ~100%, spc 97%)
- **TREATMENTS**—rapid isolation. Supportive measures are the mainstay. An experimental therapy, ZMapp®, consists of 3 monoclonal antibodies against Ebola viral antigens. Vaccine now available to those traveling to high risk areas.

CHIKUNGUNYA FEVER

- **PATHOPHYSIOLOGY**—mosquito-borne viral infection acquired in Africa and Asia. Large outbreaks in Indian Ocean islands and India
- **CLINICAL FEATURES**—fever (usually within 2–4 days of exposure) with severe joint pains involving small joints of hands, wrists, and ankles; may be prolonged. Leukopenia, thrombocytopenia, and elevated transaminases may be seen
- **DIAGNOSIS**—serology (acute and convalescent)
- **TREATMENTS**—symptomatic with NSAIDs

ZIKA FEVER

- **PATHOPHYSIOLOGY**—mosquito borne flavivirus with outbreaks in Africa, Asia, and South America. Sexual transmission described (barrier protection or abstinence recommended if pregnant partner)
- **CLINICAL FEATURES**—fever, headache, myalgia, arthralgia (small joints hands and feet), conjunctivitis, maculopapular rash
- **DIAGNOSIS**—serology, urine, blood, semen PCR. Testing indicated for all pregnant women who have travelled to highly endemic regions due to increased risk of congenital anomalies
- **TREATMENTS**—supportive

RICKETTSIAL INFECTIONS (OUTSIDE OF NORTH AMERICA)

- **PATHOPHYSIOLOGY**—African tick typhus (*Rickettsia africae*), Mediterranean tick typhus

SPECIFIC ENTITIES (CONT'D)

(*Rickettsia conorii*), and scrub typhus (*Orientia tsutsugamushi*) are all tick-transmitted

- **CLINICAL FEATURES**—tick bite ± inoculation eschar with a triad of fever, headache, and myalgia. Rash may be present. Lymphadenopathy, leukopenia, and thrombocytopenia
- **DIAGNOSIS**—serology
- **TREATMENTS**—doxycycline

RICKETTSIAL INFECTIONS (WITHIN NORTH AMERICA)—see FEVER AND RASH (p. 248)**LEPTOSPIROSIS**

- **PATHOPHYSIOLOGY**—*Leptospira interrogans*, zoonosis more common in tropical areas
- **CLINICAL FEATURES**—history of exposure to freshwater. Fever, headache, myalgia, rash, conjunctival suffusion. May be associated with aseptic meningitis, uveitis, elevated transaminases, jaundice, proteinuria, and microscopic hematuria; fulminant syndrome with jaundice, renal failure, and hemorrhage (Weil disease)
- **DIAGNOSIS**—serology; culture of blood, urine, and CSF
- **TREATMENTS**—doxycycline or amoxicillin for mild disease; penicillin/ampicillin or ceftriaxone/cefotaxime IV for severe disease

BRUCELLOSIS (undulant fever, Mediterranean fever)

- **PATHOPHYSIOLOGY**—Gram-negative facultative intracellular coccobacilli
- **CLINICAL FEATURES**—transmitted by drinking or eating infected animal products (milk), inhalation, or direct animal contact through skin wounds. Other than fever, may involve any organ system, particularly joints (sacroiliitis), GU (epididymo-orchitis), CNS (meningitis), eyes (uveitis), cardiac (endocarditis), pulmonary (pneumonitis, pleural effusion, empyema), and can cause abscesses (hepatic,

SPECIFIC ENTITIES (CONT'D)

splenic, thyroid, epidural). May develop into chronic hepatosplenic disease

- **DIAGNOSIS**—blood cultures, serology
- **TREATMENTS**—doxycycline plus streptomycin or rifampin

SCHISTOSOMIASIS

- **PATHOPHYSIOLOGY**—trematode worms *Schistosoma haematobium*, *Schistosoma mansoni*, *Schistosoma intercalatum* in sub-Saharan Africa, *S. mansoni* in part of South America, *Schistosoma japonicum* in Asia, *Schistosoma mekongi* in Cambodia. Freshwater exposure → cercariae penetrate skin → larvae migrate to lung through venous circulation → migrate to heart → migrate to liver, where they mature and pair off → migrate to mesenteric venules of bowel (*S. mansoni*, *S. mekongi*, *S. japonicum*, and *S. intercalatum*) bladder (*Schistosoma haematobium*), where females lay eggs → excreted into feces or urine → mature to cercariae
- **CLINICAL FEATURES**—generally seen in patients from endemic areas instead of travelers. Initial penetration of skin may cause pruritus. Acute schistosomiasis (Katayama fever) includes fever, headache, myalgias, RUQ pain, bloody diarrhea, and dyspnea. Chronic schistosomiasis with granuloma formation is due to host's immune response to schistosome eggs, leading to hepatic (cirrhosis), intestinal (diarrhea) or genitourinary tract symptoms (hematuria, dysuria, calcification, fibrosis), and rarely CNS (seizures, focal deficit, transverse myelitis) involvement
- **DIAGNOSIS**—serology, schistosome eggs in feces or urine, biopsy of rectum or bladder
- **TREATMENTS**—praziquantel 20 mg/kg PO q8h × 2 doses (3 doses for *S. japonicum* and *mekongi*); adjunctive corticosteroids for sp. Katayama fever

Pneumonia

See PNEUMONIA (p. 9)

Endocarditis

See ENDOCARDITIS (p. 65)

Meningitis

DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS

★DIMS★

DRUGS—neuroleptic malignant syndrome, serotonin syndrome, sympathomimetics, alcohol withdrawal

INFECTIOUS

- **MENINGITIS**—bacterial (*S. pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Listeria monocytogenes*, *Klebsiella*, *E. coli*, *Serratia*, *Pseudomonas*), viral (enterovirus, VZV, influenza, mumps, HIV), TB, fungal (*Cryptococcus*)
- **ENCEPHALITIS**—HSV, West Nile, St. Louis, equine, La Crosse
- **ABSCESS**—bacterial

METABOLIC—thyroid storm

STRUCTURAL

- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral
- **CEREBRAL INFARCT**
- **TUMOR**
- **PITUITARY APOPLEXY**
- **VASCULAR**—TTP/HUS, lupus, vasculitis, granulomatous angiitis

PATHOPHYSIOLOGY

ASSOCIATIONS WITH SPECIFIC ORGANISMS

- **AGE 0–4 WEEKS**—*Streptococcus agalactiae*, *E. coli*, *L. monocytogenes*, *K. pneumoniae*
- **AGE 1–23 MONTHS**—*S. agalactiae*, *E. coli*, *S. pneumoniae*, *H. influenzae*, *N. meningitidis*
- **AGE 2–50 YEARS**—*S. pneumoniae*, *N. meningitidis*
- **AGE >50 YEARS**—*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, aerobic Gram-negative bacilli*
- **IMMUNOCOMPROMISED**—*Listeria*, aerobic Gram-negative bacilli*
- **NEUROSURGERY/HEAD TRAUMA**—*S. aureus*, *Staphylococcus epidermidis*, aerobic Gram-negative bacilli*
- **CSF SHUNT**—*S. aureus*, *S. epidermidis*, aerobic Gram-negative bacilli*, diphtheroids
- **BASILAR SKULL FRACTURE**—*S. pneumoniae*, *H. influenzae*, group A Streptococci

*aerobic Gram-negative bacilli include *Klebsiella*, *E. coli*, *Serratia*, and *Pseudomonas*

RISK FACTORS FOR *S. PNEUMONIAE*—pneumonia, otitis media, mastoiditis, sinusitis, endocarditis, head trauma with CSF leak, alcoholism, splenectomy

PATHOPHYSIOLOGY (CONT'D)

RISK FACTORS FOR *L. MONOCYTOGENES*—extremes of age, alcoholism, malignancy, immunosuppression, diabetes, hepatic failure, renal failure, iron overload, collagen vascular disease, HIV

COMPLICATIONS—neurologic complications include herniation, stroke, vasculitis, acute cerebral hemorrhage, and aneurysm formation of cerebral vessels, with symptoms such as seizures, hearing loss, and neuropsychological impairment. Systemic complications include septic shock, pneumonia, and ARDS

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS ADULT PATIENT HAVE ACUTE MENINGITIS?

	Sens (%)	Spc (%)
History		
Headache	68	
Nausea and vomiting	52	
Neck pain	28	
Physical		
Fever	87	
Neck stiffness	80	
Altered mental status	69	
Focal neurological findings	21	
Rash	13	
Kernig sign (patient lying supine with hip flexed >90°)	9	100
Extension of knee from this position elicits resistance or pain in lower back or posterior thigh)		
Brdzinski sign (passive neck flexion in supine patient results in flexion of knees and hips)	–	–
Jolt accentuation of headache (patient turns head horizontally at a frequency of 2–3 rotations per second. Worsening headache represents positive sign)	97	60
Combination of Findings		
Classic triad (fever, neck stiffness, headache)	46	

UPDATE—individual findings are not sufficiently accurate to diagnose meningitis. Absence of all 3 signs of the classic triad of fever, neck stiffness,

CLINICAL FEATURES (CONT'D)

and altered mental status is **not** sufficiently sensitive to rule out a diagnosis of meningitis. Fever and neck stiffness are the most sensitive findings of the triad. Kernig and Brudzinski signs have low sensitivity but high specificity. Jolt accentuation of headache may be a useful adjunctive maneuver for patients with fever and headache

Attia et al. JAMA 1999;282(2)
Simel et al. The Rational Clinical Examination. McGraw-Hill; 2009

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, Cr/urea, INR, PTT, AST, ALT, ALP, bilirubin, fibrinogen, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S
- **IMAGING**—CXR, head CT (see below)
- **LUMBAR PUNCTURE**—(1) cell count and differential; (2) Gram stain, C&S and AFB; (3) cell count and differential; (4) protein, glucose, lactate; (5) PCR for HSV, VZV, enteroviruses; (6) cytology

DIAGNOSTIC AND PROGNOSTIC ISSUES

LUMBAR PUNCTURE—suspect bacterial infection if high neutrophils, low glucose, high protein, positive culture. Suspect viral infection if high lymphocytes, *normal* glucose, and normal/high protein

- **OPENING PRESSURE**—normal is 60–250 mmH₂O. Causes of elevated opening pressure include meningitis, pseudotumor cerebri, intracranial hemorrhage, tumors, and idiopathic
- **CELL COUNT AND DIFFERENTIAL**—normal WBC is <5/mm³. This can increase to 1000–5000/mm³ for bacterial meningitis (neutrophils mainly) and 50–1000/mm³ for viral meningitis (lymphocyte predominant). Other causes include seizure, intracerebral hemorrhage, tumor, and “traumatic tap” (correct by +1 WBC for every 500–1000 RBCs)
- **XANTHOCHROMIA**—lysed RBCs. Present in >90% of patients within 12 h of subarachnoid hemorrhage onset
- **GRAM STAIN**—sensitivity is 60–80% in untreated bacterial meningitis and 40–60% in partially treated cases

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **CULTURE**—gold standard with sensitivity of 70–85% in untreated bacterial meningitis and 50% in partially treated cases. Viral, TB, and fungal cultures can also be done
- **PROTEIN**—normal is 0.18–0.58 g/L. Significantly elevated in bacterial meningitis and obstruction, variably elevated in fungal and TB infections, and only sometimes elevated in viral infections. Other causes include tumors, intracranial hemorrhage, multiple sclerosis, and Guillain-Barré syndrome
- **GLUCOSE**—normal is 2/3 of serum level, up to 16.7 mM [300 mg/dL]. Significantly lower in bacterial meningitis, mildly lower in fungal and TB infections, and usually normal in viral infections

Ellenby et al. NEJM 2006;355(e12)

RATIONAL CLINICAL EXAMINATION SERIES: HOW DO I PERFORM A LUMBAR PUNCTURE AND ANALYZE THE RESULTS TO DIAGNOSE BACTERIAL MENINGITIS?

- **TECHNIQUE**—use of an **atraumatic needle** compared with a standard needle and use of a **26-gauge** standard needle compared with a 22-gauge standard needle have been shown to be associated with reduced risk of headache after lumbar puncture. **Reinsertion of the stylet** before needle removal should occur (ARR 11%). **Patients do not require bed rest** after the procedure

	LR+
CSF analysis	
CSF blood glucose ratio ≤ 0.4	18
CSF glucose >2.2 mmol/L [>40 mg/dL]	23
CSF WBC $\geq 500/\mu\text{L}$	15
CSF lactate ≥ 3.5 mmol/L [≥ 32 mg/dL]	21

Straus et al. JAMA 2006;296(16)

CT HEAD—indicated before LP if age >60, immunocompromised, history of CNS disease, seizures within 1 week, focal neurological abnormalities, papilloedema, altered mental status

PROGNOSIS—mortality rate is 19–26% for *S. pneumoniae* meningitis and 3–13% for *N. meningitidis* meningitis. Factors conferring poor prognosis include systemic compromise, ↓ level of consciousness, and *S. pneumoniae*

MANAGEMENT

ACUTE—ABC, O₂, IV, intubation. Droplet precautions for suspect *N. meningitidis* infection

EMPIRIC ANTIBIOTICS—**steroid** if acute bacterial meningitis and 15–20 min before first dose of antibiotics (*dexamethasone* 0.15 mg/kg or 10 mg IV q6h × 4 days). **Cefotaxime** 2 g IV q6h or **ceftriaxone** 2 g IV q12h + **vancomycin** 500–750 mg IV q6h if concerned about penicillin-resistant pneumococci. Add **ampicillin** 2 g IV q4h if age >50 for *Listeria* coverage. If neurosurgery/trauma, CSF shunt, or basilar skull fracture, give **meropenem** 1 g IV q6h plus **vancomycin**. If HSV encephalitis, give **acyclovir** 10 mg/kg IV q8h

SPECIFIC ANTIBIOTICS—***S. pneumoniae*** (penicillin G or ampicillin if MIC <0.1 µg/mL, ceftriaxone or cefotaxime ± vancomycin × 10–14 days if MIC >1.0 µg/mL), ***N. meningitidis*** (ceftriaxone, penicillin G or ampicillin × 7 days), ***L. monocytogenes*** (ampicillin or penicillin G, plus gentamicin × 21 days), ***H. influenzae*** (ampicillin, ceftriaxone, or cefotaxime × 7 days), **Enterobacteriaceae** (ceftriaxone or cefotaxime × 7 days)

SPECIFIC ENTITIES

CHRONIC MENINGITIS (>4 weeks symptoms and persistent CSF abnormalities)—consider TB, fungal infections, neurosarcoidosis, lymphoma, leptomeningeal carcinomatosis

RECURRENT MENINGITIS—**congenital pre-disposition** (myelomeningocele, dermal sinus), **acquired** (trauma, tumor, shunt), **immunologic**

SPECIFIC ENTITIES (CONT'D)

defects (complement defects, antibody defects, splenectomy)

HSV ENCEPHALITIS

- **PATHOPHYSIOLOGY**—usually infects the temporal lobe → subacute illness with fever, focal neurologic abnormalities, aphasia, mental status changes, and seizures. May have long-term sequelae
- **DIAGNOSIS**—LP (mild lymphocytic pleocytosis <500 cells/µL, erythrocytes, xanthochromia, ↑ protein, normal glucose, PCR for HSV1/HSV2), MRI (hyperintense lesion in the inferior medial temporal lobe, often extending into the insula)
- **TREATMENTS**—*acyclovir* 10 mg/kg/dose q8h × 14–21 days

WEST NILE VIRUS ENCEPHALITIS

- **PATHOPHYSIOLOGY**—*Flavivirus* West Nile virus transmitted by mosquitoes between late spring and early autumn
- **CLINICAL FEATURES**—wide spectrum from asymptomatic (30%) to severe neurologic disorder (0.5%). Fever, erythematous rash, meningitis, encephalitis, and flaccid paralysis. Risk of progression to severe neurological disease about 1/150, highest in the elderly
- **DIAGNOSIS**—LP (viral picture, PCR for West Nile virus), IgM antibody to West Nile virus in serum or CSF (samples from the acute and convalescent phases, submitted at least 2 weeks apart)
- **TREATMENTS**—supportive. Prevention is key (insect repellent, proper clothing)

Urinary Tract Infections and Sexually Transmitted Infections

Canadian Guidelines on Sexually Transmitted Infections

DIFFERENTIAL DIAGNOSIS OF DYSURIA**★SUV★**

SEXUALLY TRANSMITTED INFECTIONS—*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, HSV, HIV, trichomonas

URINARY TRACT INFECTIONS (urethritis, cystitis, pyelonephritis, perinephric abscess)—**bacterial** (★KEEPS★ *Klebsiella*, *E. coli*, *Enterococci*, *Proteus*, *Staphylococcus saprophyticus*)

VAGINAL INFECTIONS—*Candida albicans*, *Trichomonas*, bacterial vaginosis

PATHOPHYSIOLOGY OF URINARY TRACT INFECTIONS

COMPLICATED UTI—presence of functional or anatomic abnormality of the urinary tract (e.g. polycystic kidney disease, nephrolithiasis, neurogenic bladder, diabetes, immunosuppression, pregnancy, indwelling urinary catheter, recent urinary tract instrumentation)

UNCOMPLICATED UTI—absence of risk factors for complicated UTI. In women, uncomplicated UTIs are usually treated for 3 days (or 5–7 days with nitrofurantoin)

PATHOPHYSIOLOGY OF URINARY TRACT INFECTIONS (CONT'D)

PYELONEPHRITIS—fever, costovertebral angle tenderness, blood and urine cultures indicated

RISK FACTORS FOR UTI

- **YOUNG WOMEN**—frequent or recent sexual activity
- **ELDERLY WOMEN**—age, estrogen deficiency, incontinence, diabetes, cystoceles, previous GU surgery

PATHOPHYSIOLOGY OF CATHETER-ASSOCIATED BACTERIURIA—bacteria establish biofilm in or on catheter and enter bladder intra- or extraluminally. Common organisms include *E. coli* and enterococci. Responsible for 80% of urosepsis. Risk factors: duration of catheterization, poor catheter care, diabetes mellitus, female sex

CLINICAL FEATURES OF URINARY TRACT INFECTIONS

HISTORY—dysuria, urinary frequency, urgency, suprapubic or flank pain, hematuria, cloudy/foul urine odor. Symptoms less clear in older women (consider chronic dysuria, urinary incontinence, confusion, falls, delirium). Pyelonephritis may have fever, chills, flank pain, nausea/vomiting, sepsis if severe (multiple organ system dysfunction, acute renal failure, shock)

PHYSICAL—fever, costovertebral angle tenderness, abdominal/suprapubic tenderness, pelvic examination in sexually active women for cervical motion/uterine tenderness to exclude pelvic inflammatory disease, DRE in men to exclude prostatitis

INVESTIGATIONS FOR URINARY TRACT INFECTIONS

BASIC

- **LABS**—CBC, lytes, Cr/urea, urinalysis
- **MICROBIOLOGY**—urine C&S
- **IMAGING**—US

DIAGNOSTIC ISSUES FOR URINARY TRACT INFECTIONS

NUMBER OF BACTERIA—significant bacteria ($>10^5$ /mL) in clean catch suggests UTI (sens 50%). If using lower threshold to $>10^3$ /mL for women with symptoms, sensitivity increases and specificity only decreases slightly

URINALYSIS—nitrite or leukocyte esterase (sens 75%, spc 82%), pyuria (sens 95%, spc 71%),

DIAGNOSTIC ISSUES FOR URINARY TRACT INFECTIONS (CONT'D)

bacteria (sens 40–70%, spc 85–95%). Not necessary in women with typical symptomatic uncomplicated UTI (helpful if atypical presentation)

URINE CULTURE—not always needed if symptomatic and biochemical evidence (i.e. leukocyte esterase) of uncomplicated UTI. However, antimicrobial resistance is increasing, so culture and sensitivity may become more important

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS ADULT PATIENT WITH SUSPECTED BACTEREMIA REQUIRE BLOOD CULTURES?

	LR+	LR-
Chills in febrile patients	2.2	0.56
Shaking chills	4.7	–
Subjective fever	1.0	0.95
Temperature ≥ 38.0 °C	1.9	0.54
High clinical impression ($\geq 50\%$ probability of bacteremia)	2.3	–
Intermediate clinical impression (10–49%)	0.49	–
Low clinical impression ($\leq 10\%$)	0.48	–
Systemic inflammatory response syndrome (SIRS)	1.8	0.09
Shapiro clinical decision rule	1.3	0.08

Shapiro Decision Rule: blood cultures indicated if 1 major **or** 2 minor criteria. Major criteria (suspicion of endocarditis, temperature >39.4 °C, indwelling catheter), minor criteria (temperature 38.3–39.3 °C, age >65 years, chills, vomiting, SBP <90 mmHg, WBC $>18,000/\mu\text{L}$, creatinine >177 $\mu\text{mol/L}$)

APPROACH—pretest probability of true positive blood cultures is low (4.1–7.3%), but depends on the clinical context (low risk: cellulitis, community acquired pneumonia; intermediate risk: pyelonephritis; high risk: sepsis, acute bacterial meningitis, septic shock). Blood cultures should not be ordered for isolated fever/leukocytosis. The Shapiro decision rule may identify low-risk patients not requiring further investigation. These findings do not apply if there is a suspicion for endocarditis or in immunocompromised patients

Coburn et al. JAMA 2012;308(5)

MANAGEMENT OF URINARY TRACT INFECTIONS

UNCOMPLICATED UTI IN WOMEN—*trimethoprim-sulfamethoxazole* (DS-160/800 mg) 1 tab PO BID \times 3 days, *nitrofurantoin monohydrate/macrocrystals* 100 mg PO BID \times 5–7 days, *fosfomycin* 3 g PO \times 1 dose, *pivmecillinam* 400 mg PO BID \times 5–7 days

COMPLICATED UTI—treatment duration 7–14 days, empiric therapy based on severity and risk factors for resistance. Consider antipseudomonal carbapenem for ESBL and *Pseudomonas aeruginosa*, vancomycin for MRSA

RECURRENT UTI (consider if >3 –4 episodes of UTI/year)—**daily low-dose prophylaxis** (*trimethoprim-sulfamethoxazole* DS $\frac{1}{2}$ tab PO nightly \times 6 months, *nitrofurantoin* 50 mg or macrocrystals 100 mg PO nightly \times 6 months), **post-coital prophylaxis** (*trimethoprim-sulfamethoxazole* DS $\frac{1}{2}$ -1 tab PO post-coital, *nitrofurantoin* 50 mg PO or *macrocrystals* 100 mg PO post-coital), **patient-initiated treatment** (start standard dose of antibiotics with onset of UTI symptoms)

SYMPTOM CONTROL—*phenazopyridine* 100–200 mg PO TID \times 2 days

ACUTE UNCOMPLICATED PYELONEPHRITIS—treat empirically with oral fluoroquinolones \times 7 d (*ciprofloxacin* 500 mg PO BID or *levofloxacin* 750 mg PO daily). If isolate susceptible, may treat with trimethoprim-sulfamethoxazole, amoxicillin, or amoxicillin-clavulanate \times 14 d. Most healthy, non-pregnant women with pyelonephritis can be treated on an outpatient basis. Otherwise, treat with IV antibiotics, at least initially (aminoglycoside \pm ampicillin, third generation cephalosporin, or carbapenem)

CATHETER-ASSOCIATED BACTERIURIA—remove or replace catheter and initiate antibiotics for symptomatic infection; switch to intermittent catheterization

PREGNANCY AND UTI—urinalysis for all pregnant women at 12–16 weeks. Treat all bacteriuria ($\geq 10^5$ CFU/mL) with amoxicillin or nitrofurantoin \times 3–7 days even if asymptomatic as there is a 20–40% risk of pyelonephritis. Alternatives (cephalexin, cefpodoxime, fosfomycin, trimethoprim-sulfamethoxazole). Avoid fluoroquinolones

VAGINITIS

CANDIDA—vulvovaginitis with cheesy vaginal discharge, intense itch. Diagnosis by microscopy with 10% KOH showing hyphae and budding yeast, pH 4–4.5 (normal). Treat with vaginal

VAGINITIS (CONT'D)

antifungal cream (3–14 days) or *fluconazole* 150 mg PO \times 1 dose

TRICHOMONIASIS—profuse purulent greenish vaginal discharge, strawberry cervix. Diagnosis by microscopy showing motile trichomonads, pH 5–6. Treat with oral *metronidazole* 2 g as a single dose (treatment of sexual partners indicated)

BACTERIAL VAGINOSIS—gray, fishy-smelling vaginal discharge. Diagnosis made by amine odor when KOH added to the discharge, pH >4.5 and clue cells (vaginal epithelial cells coated with bacteria) seen on microscopy. Treat if symptomatic or pregnant with metronidazole or clindamycin, orally or vaginally

SEXUALLY TRANSMITTED INFECTIONS (STI)**URETHRITIS IN MEN/CERVICITIS IN WOMEN**

- PATHOPHYSIOLOGY**—*N. gonorrhoeae*, *C. trachomatis*, and other non-gonococcal (*Ureaplasma urealyticum*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, HSV)
- DIAGNOSIS**—Gram stain of discharge, urine for chlamydia/gonorrhea (nucleic acid amplification test, NAAT) or urethral/cervical swab for gonorrhea culture; offer syphilis and HIV testing
- TREATMENTS**—anti-gonococcal (*ceftriaxone* 125 mg IM \times 1 plus *azithromycin* 1 g PO \times 1), anti-chlamydial (*azithromycin* 1 g PO \times 1, or *doxycycline* 100 mg PO BID \times 7 days). If gonorrhea identified, empirically treat for both gonococcus and chlamydia since dual infection is common. Dual therapy is recommended for gonorrhea due to increasing incidence of resistance to third generation cephalosporins. Trace and treat all partners within the last 60 days

SYPHILIS

- PATHOPHYSIOLOGY**—*T. pallidum* infection. Risk factors include men who have sex with men (MSM), sex trade, HIV infection
 - PRIMARY SYPHILIS**—presents as chancre (painless, indurated, non-purulent ulcer) within 3–90 days
 - SECONDARY SYPHILIS**—develops within 2 weeks to 6 months, symptoms include fever, maculopapular rash, mucocutaneous lesions, alopecia, lymphadenopathy, meningitis, uveitis, and cranial neuritis
 - TERTIARY SYPHILIS**—develops after year(s) and may involve the heart (aortitis), eyes (iritis, Argyll Robertson pupil), bones/soft tissues (gummas), and neurologic system

**SEXUALLY TRANSMITTED INFECTIONS (STI)
(CONT'D)**

(general paresis, rapidly progressive dementia with psychotic features, and tabes dorsalis, which affects posterior columns of the spinal cord and the dorsal roots, leading to pain episodes, decreased vibration and proprioception, absent reflexes, and bowel/bladder dysfunction)

**SEXUALLY TRANSMITTED INFECTIONS (STI)
(CONT'D)**

- **DIAGNOSIS**—first-line diagnostic test of choice for a primary syphilitic chancre should be either direct fluorescent antibody (DFA) or PCR, if available. Otherwise, treponemal serologies are more sensitive and become positive earlier than non-treponemal serologies and would be preferred if primary syphilis is a consideration

Diagnostic Method	Test(s)	Utility
Direct visualization	Dark field microscopy	Traditional but availability is limited
Visualization with fluorescent Ab	DFA	Diagnosis of 1° syphilis. Sensitive/specific
Molecular testing	PCR	Diagnosis of 1° syphilis. Most sensitive/specific but not readily available
Treponemal serology (presence of Ab against TP)	FTA-ABS TPPA MHA-TP TP-EIA INNO-LIA	Diagnosis of syphilis Sensitive; however, does not differentiate venereal from non-venereal treponematoses
Non-treponemal serology (presence of Ab against cardiolipin/lecithin)	VDRL RPR	Screening RPR titer helpful in staging, check for reinfection, treatment monitoring

Abbreviations: *DFA* direct fluorescent antibody, *EIA* enzyme immunoassay, *FTA-ABS* fluorescent treponemal antibody-absorption, *MHA-TP* microhemagglutination assay for antibody to TP, *PCR* polymerase chain reaction, *RPR* rapid plasma reagin test, *TP* *Treponema pallidum*, *TPPA* TP particle agglutination assay, *VDRL* Venereal Disease Research Laboratory, *INNO-LIA* line immunoassay

**SEXUALLY TRANSMITTED INFECTIONS (STI)
(CONT'D)**

- **TREATMENTS**—for primary, secondary and early latent (<1 year) syphilis, *benzathine penicillin G* 2.4 M units IM × 1 (preferred) or *doxycycline* 100 mg PO BID × 2 weeks. For late latent (>1 year) syphilis, gummatous and cardiovascular syphilis, *benzathine penicillin G* 2.4 M units IM q7days × 3 weeks. For neurosyphilis or syphilitic eye disease, give *benzathine penicillin G* 3–4 M units q4h IV × 10–14 days. Follow-up is essential. Treatment failure is defined as persistent symptoms or failure of serologic test to decline by 4 fold within 6 months

PELVIC INFLAMMATORY DISEASE

- **PATHOPHYSIOLOGY**—includes endometritis, tubo-ovarian abscess, salpingitis, and pelvic peritonitis. Most commonly due to *N. gonor-*

**SEXUALLY TRANSMITTED INFECTIONS (STI)
(CONT'D)**

- *rhoeae*, *C. trachomatis*, *Mycoplasma hominis*, *U. urealyticum*; may involve endogenous (gut) organisms including anaerobes. Complications include infertility, ectopic pregnancy, chronic pelvic pain
- **CLINICAL FEATURES**—lower abdominal pain, abnormal vaginal bleeding/discharge, and dyspareunia may be mild and non-specific. Findings include lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness
- **DIAGNOSIS**—high index of clinical suspicion. Cervical swab and urine NAAT for chlamydia and gonorrhea. US Pregnancy test
- **TREATMENTS**—**outpatients** (*ceftriaxone* 250 mg IM × 1 and *doxycycline* 100 mg PO

**SEXUALLY TRANSMITTED INFECTIONS (STI)
(CONT'D)**

BID×14 days, or *levofloxacin* 500 mg PO daily×14 days); add *metronidazole* 500 mg PO BID×14 days if there are risk factors for anaerobic pathogens. **Inpatients** (*doxycycline* 100 mg PO q12h and *cefoxitin* 2 g IV

**SEXUALLY TRANSMITTED INFECTIONS (STI)
(CONT'D)**

q6h×14 days, or *clindamycin* 900 mg IV q8h and *gentamicin* 1.5 mg/kg IV q8h×14 days)

Canadian Guidelines on Sexually Transmitted Infections**Soft Tissue Infections****DIFFERENTIAL DIAGNOSIS**

DISCRETE LOCALIZED CUTANEOUS INFECTIONS—**superficial** (impetigo, folliculitis, furunculosis), **deep** (carbuncles, subcutaneous abscesses)

SPREADING DIFFUSE CUTANEOUS INFECTIONS (involves deeper dermis and subcutaneous tissues)—erysipelas, cellulitis

DEEP SOFT TISSUE INFECTIONS—necrotizing fasciitis (polymicrobial, *Streptococcus pyogenes*), gas gangrene (*C. perfringens*)

PATHOPHYSIOLOGY**RISK FACTORS FOR CELLULITIS**

- **COMPROMISED SKIN**—trauma, IDU, psoriasis, eczema, fungal disease (especially tinea pedis)
- **COMPROMISED SENSORY/PROPRIOCEPTIVE NERVES**—diabetic neuropathy
- **COMPROMISED BLOOD/LYMPHATIC VESSELS**—diabetes, malignancy, lymphatic or venous insufficiency, radiation, prior cellulitis

CELLULITIS—acute spreading infection involving the dermis and subcutaneous tissue, mostly caused by Staphylococci and group A *Streptococcus*. Usually presents as a swollen, erythematous plaque with ill-defined border (mark borders to identify progress)

ERYSIPELAS—superficial cellulitis involving the upper dermis and lymphatics, mostly caused by group A *Streptococcus*. Usually presents as a raised, erythematous plaque with well-demarcated border. It occurs more commonly in infants and elderly

RISK FACTORS FOR SKIN AND SOFT TISSUE INFECTIONS DUE TO MRSA/CA-MRSA—previous MRSA infection, hospitalization, or household contacts of known MRSA; street involved/shelters/incarceration, IDU, athletes, children/day care

PATHOPHYSIOLOGY (CONT'D)**COMMON PATHOGENS CAUSING CELLULITIS**

- **MOST COMMON**—*S. pyogenes* (β-hemolytic group A *Streptococcus*), *S. aureus*, other β-hemolytic streptococci (B, C, G, and F)
- **SURGICAL WOUND**—*S. aureus*, *S. pyogenes*
- **HUMAN BITE**—oral anaerobes, *Eikenella corrodens*
- **ANIMAL BITE**—*Pasteurella multocida*, *Capnocytophaga canimorsus*
- **TICK BITE**—*B. burgdorferi*, tularemia
- **FRESHWATER**—*Aeromonas hydrophila*
- **SEAWATER**—*V. vulnificus*
- **FISH EXPOSURE**—*Erysipelothrix rhusiopathiae*, *Streptococcus iniae*
- **HOT TUB**—*P. aeruginosa* folliculitis

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, lactate (if suspicion of necrotizing fasciitis)
- **MICROBIOLOGY**—swab of portal of entry or any open draining wound for Gram stain and C&S, blood C&S (indicated only if systemic symptoms)

MANAGEMENT

TREAT UNDERLYING CAUSE—**incision and drainage of abscesses**. **Elevation** of affected area if possible, compression and skin hydration.

Antibiotics for mild cellulitis (*cephalexin* 500 mg PO QID, *dicloxacillin* 500 mg PO QID, or *clindamycin* 150–300 mg PO QID×5–14 days); for **systemic toxicity or severe cellulitis** (*cefazolin* 1–2 g IV q8h, *ceftriaxone* 1 g IV q24h, *nafcillin* 1–2 g IV q4–6 h×7–14 days). For MRSA associated skin infections, consider *vancomycin* 1–2 g IV q12h, *trimethoprim/sulfamethoxazole* 1

MANAGEMENT (CONT'D)

DS tab PO BID, *daptomycin* 4–6 mg/kg IV daily, *tigecycline* 100 mg loading dose, then 50 mg IV q12h, *doxycycline* 100 mg PO BID, *linezolid* 600 mg PO/IV q12h. For **mild erysipelas**, consider *penicillin* 500 mg PO QID or *amoxicillin* 500 mg PO TID. For **severe erysipelas** with fevers and **chills**, consider *ceftriaxone* 1 g IV q24h or *cefazolin* 1–2 g IV q8h × 5–14 days

Daum *NEJM* 2007;357(4)

2014 IDDSA Update Guideline Skin Soft Tissue Infections

SPECIFIC ENTITIES

NECROTIZING FASCIITIS

- **TYPES**—**type 1** (polymicrobial infections including Enterococci, *E. coli*, non-group A *Streptococcus*, *Klebsiella*, anaerobes. Mixed infections occurring postoperatively or in those with diabetes or peripheral vascular disease, e.g. Fournier gangrene of perineum in diabetics), **type 2** (monomicrobial *S. pyogenes*; rarely, CA-MRSA. May occur at any age and in healthy hosts following minor trauma, penetrating injury, laceration, varicella, IDU, or childbirth)
- **PATHOPHYSIOLOGY (type 1)**—inoculation of ischemic or devitalized tissue → host immune system and antibiotics relatively ineffective → rapid spreading of infection to sur-

SPECIFIC ENTITIES (CONT'D)

rounding tissue → late signs include fever, crepitus, shock → complications include compartment syndrome, acute renal failure, sepsis. May be limb or life-threatening, requires urgent surgery. May develop over a few hours

- **ASSOCIATIONS**—host (age >50, cancer, alcoholism, immunocompromised, malnutrition, obesity), compromised skin (burns, trauma, postoperative infection), compromised blood vessels (peripheral vascular disease, diabetes)
- **CLINICAL FEATURES**—typically happens over body areas with limited fibrous tissue (trunk, extremities). Pain disproportionate to physical findings. Gangrenous skin changes, bullae, tense edema, and crepitus may be seen as late signs
- **DIAGNOSIS**—high index of suspicion (pain >> physical findings). Plain radiograph to check for gas with type 1 necrotizing fasciitis. CT or MRI may be useful. Early deep incisional biopsy is gold standard
- **TREATMENTS**—urgent **surgical debridement** of all necrotic tissue. Consider **IVIG** if significant hypotension in Group A *Streptococcus* necrotizing fasciitis. **Polymicrobial** (*piperacillin-tazobactam* 4.5 g IV q8h plus *vancomycin* 25 mg/kg IV q12h), **Streptococcus** (*penicillin G* 4 MU IV q4h plus *clindamycin* 600–900 mg IV q8h)

Osteomyelitis

CAUSES

HEMATOGENOUS (monomicrobial)—*S. aureus*, coagulase-negative staphylococci, Gram-negative bacilli (*P. aeruginosa*, *Serratia*, *E. coli*), TB, fungi

CONTIGUOUS SPREAD FROM SOFT TISSUE OR JOINTS (polymicrobial)—

S. aureus, coagulase-negative staphylococci, *S. pyogenes*, *Enterococcus*, Gram-negative bacilli, anaerobes

CONTIGUOUS SPREAD WITH GENERALIZED VASCULAR INSUFFICIENCY (polymicrobial)—

S. aureus, *Streptococcus*, *Enterococcus*, *Proteus mirabilis*, *P. aeruginosa*, anaerobes

DIRECT INOCULATION THROUGH TRAUMA OR SURGERY (monomicrobial or polymicrobial)—may involve skin or environmental commensal organisms

PATHOPHYSIOLOGY

ROUTE OF INFECTION

- **HEMATOGENOUS**—mainly central (vertebrae, sternoclavicular, sacroiliac) and sometimes long bones (femur, tibia, humerus)
- **CONTIGUOUS SPREAD FROM SOFT TISSUE INFECTIONS**—trauma, surgery, orthopedic prosthesis, decubitus ulcer
- **CONTIGUOUS SPREAD FROM SOFT TISSUE INFECTIONS WITH GENERALIZED VASCULAR INSUFFICIENCY**—ischemic ulcers, diabetic ulcers

RISK FACTORS FOR OSTEOMYELITIS

- **SYSTEMIC**—diabetes, sickle cell disease (*Salmonella*)
- **LOCAL**—vascular compromise (arterial insufficiency, neuropathy venous stasis), orthopedic surgery

CLINICAL FEATURES

DIABETIC FOOT ULCER—either probing of bone or ulcer area above 2 cm² is associated with ~90% chance of having underlying osteomyelitis (sens 66%, spc 85%, PPV 89%). Further noninvasive testing unlikely to improve diagnostic accuracy

HISTORY

- **ACUTE OSTEOMYELITIS** (<2 weeks)—typically associated with bone pain, tenderness,

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH DIABETES HAVE OSTEOMYELITIS OF THE LOWER EXTREMITY?

- **Wagner grading scale**

- 0—no open lesions; may have evidence of healed lesions or deformities
- 1—superficial ulcer
- 2—deeper ulcer to tendon, bone, or joint capsule
- 3—deeper tissues involved, with abscess, osteomyelitis, or tendinitis
- 4—localized gangrene of toe or forefoot
- 5—gangrene of foot (partial or total)

	LR+	LR–
Clinical gestalt		
Clinical judgment	9.2	0.70
Wagner grade >2	5.5	0.54
Physical		
Bone exposure	9.2	0.70
Positive probe to bone finding	6.4	0.39
Ulcer area >2 cm ²	7.2	0.48
Ulcer inflammation	1.5	0.84
Laboratory		
ESR ≥ 70 mm/h	11	0.34
Swab culture	1	1
Abnormal plain radiograph	2.3	0.63
Abnormal MRI	3.8	0.14

APPROACH—“An ulcer area >2 cm², a positive probe-to-bone test result, an ESR ≥70 mm/h, and an abnormal plain radiograph ... are helpful in diagnosing the presence of lower extremity osteomyelitis in patients with diabetes. A negative MRI result makes the diagnosis much less likely when all of these findings are absent.”

Butalia et al. JAMA 2008;299(7)

CLINICAL FEATURES (CONT'D)

warmth, swelling, fever, and chills. Hip, vertebrae, and pelvis tend to manifest fewer signs and symptoms

- **SUBACUTE OSTEOMYELITIS** (weeks to few months)—longer duration of above symptoms, but less severe. Over time, draining sinus tracts, deformity, instability, and vascular/neurologic changes may develop
- **CHRONIC OSTEOMYELITIS** (>few months)—similar to subacute osteomyelitis

INVESTIGATIONS**BASIC**

- **LABS**—CBC, ESR (monitor disease progress if elevated), urinalysis
- **MICROBIOLOGY**—blood C&S, urine C&S
- **IMAGING**—plain films (specific but insensitive), three-phase bone scan (sensitive), CT, MRI (most sensitive and specific, particularly spine and diabetic foot), indium-labeled WBC scan (specific), US, bone marrow scan, dual tracer scan

SPECIAL

- **ULCER PROBING**
- **BONE BIOPSY**—C&S, AFB, TB culture, fungal culture, histology; generally required for vertebral osteomyelitis (CT-guided biopsy can provide microbiological diagnosis to guide therapy)
- **ANKLE BRACHIAL INDEX**—ischemic ulcers suspected

DIAGNOSTIC ISSUES

PLAIN FILMS—soft tissue swelling and gas, cortical destruction, periosteal new bone formation, deformities, fractures, and soft tissue gas. May not detect osteomyelitis changes until after 2–3 weeks of infection. May help make diagnosis of osteomyelitis but never excludes it (sens 61%, spc 72%, PPV 80% for diabetic foot osteomyelitis)

BONE SCAN—more sensitive but less specific than plain films (sens 70–100%, spc 36% for diabetic foot osteomyelitis). Useful for ruling out osteomyelitis

INDIUM-LABELED LEUKOCYTE SCAN—better sensitivity and specificity (but still poor) than bone scans in diabetic foot. Since WBC accumulates in the marrow, the scan is less sensitive in

DIAGNOSTIC ISSUES (CONT'D)

areas with red marrow (vertebrae, pelvis). Excellent for fracture nonunion osteomyelitis (sens 91%, spc 97%)

MRI—provides best anatomic details, more sensitive and specific than bone scan. Imaging of choice for specific body sites (vertebrae, diabetic foot)

BONE BIOPSY—gold standard for osteomyelitis and generally required in vertebral osteomyelitis. Positive blood cultures and corresponding radiologic findings may support diagnosis and sometimes replace bone biopsy. Consider holding off antibiotic therapy if not life-threatening infection to facilitate identification of organisms. Organisms from superficial skin swabs have little correlation with the actual organisms growing inside the bone, except for *S. aureus*

MANAGEMENT

HEMATOGENOUS—for vertebral osteomyelitis, need blood and bone cultures, then start empiric antibiotics with *cloxacillin* 2 g IV q4–6 h or *cefazolin* 2 g IV q8h. Consider *vancomycin* 15 mg/kg IV q12h if high local MRSA rates. Once organism identified, treat with specific antibiotic (total 6–12 weeks of antibiotics guided by susceptibility from time of biopsy or definitive surgery, with at least 2 weeks of IV therapy). If failed therapy, consider bone/soft tissue debridement and another 4–6 weeks of antibiotics after definitive surgery

CONTIGUOUS SPREAD WITHOUT VASCULAR INSUFFICIENCY—after orthopedic surgery and specimen collection, start *vancomycin* 15 mg/kg IV q12h. For sternal osteomyelitis, give *vancomycin* 15 mg/kg IV q12h, then switch to specific antibiotics (total 6 weeks of antibiotics from time of definitive surgery, usually intravenous for the duration)

CONTIGUOUS SPREAD WITH VASCULAR INSUFFICIENCY—polymicrobial. Base therapy

MANAGEMENT (CONT'D)

on bone culture, empirical coverage should include anaerobes (e.g. carbapenems, piperacillin–tazobactam)

SPECIFIC ENTITIES**VERTEBRAL OSTEOMYELITIS**

- **PATHOPHYSIOLOGY**—usually results from disc-space seeding through hematogenous dissemination, seeding from urinary tract, trauma, extension of infection from adjacent structures, or as a complication of spine and disc surgery. Risk factors include extraspinal infection site, urinary tract instrumentation, vascular catheter, hemodialysis, intravenous drug abuse, cancer, and diabetes mellitus
- **CLINICAL FEATURES**—severe back pain, limited function, and fever (52%)
- **DIAGNOSIS**—MRI, blood cultures. Bone biopsy generally required for confirmation and microbiological diagnosis to guide therapy
- **TREATMENTS**—*cloxacillin* 2 g IV q4–6 h or *cefazolin* 2 g IV q8h. Consider *vancomycin* 15 mg/kg IV q12h if high local MRSA rates

PROSTHETIC JOINT INFECTIONS

- **PATHOPHYSIOLOGY**—most commonly due to coagulase-negative staphylococci
- **TREATMENTS**—debridement with retention of prosthesis may be possible with early-onset infection (within 3 months of surgery), short duration of symptoms (<3 weeks) with no sinus tract, a stable implant **and** a causative organism susceptible to quinolones (or trimethoprim–sulfamethoxazole) and rifampin, which are given for 3 months (hips) to 6 months (knees) after an initial course of appropriate IV antibiotic therapy for at least 2 weeks. If debridement and retention are not appropriate, removal of the infected prosthesis with one-stage or two-stage exchange; IV antibiotic therapy is also provided for 6 weeks following the initial surgery

Del Pozo et al. *NEJM* 2009;361(8)

Tuberculosis

2014 Canadian Tuberculosis Standards, 7th ed.

PATHOPHYSIOLOGY

ORGANISMS—genus *Mycobacterium* consists of >50 species. TB is caused by *M. tuberculosis* complex including *M. tuberculosis*, *M. bovis*, and others. The cell envelope contains mycolic acid → resists destaining by acid alcohol, thus termed acid fast bacilli

TRANSMISSION—TB transmission is almost exclusively airborne through inhalation of minute droplet nuclei. Therefore, lungs are the primary focus. However, any organ can become infected during the bacteremia that follows initial lung infection

LATENT TB INFECTION (LTBI)—follows initial infection; asymptomatic; detected by tuberculin skin test (TST) or interferon-gamma release assay (IGRA). Risk of active infection generally is 5% in the first 2 years with 5% risk of reactivation thereafter

FACTORS THAT INCREASE THE RISK OF INFECTION—1/3 of the world's population is infected with TB. Birth in endemic area (less commonly travel) is the major risk factor; other risk factors include Indigenous populations and racial/ethnic minorities, household/institutional contacts and crowding (healthcare workers, long-term care, correctional facilities, substance abuse, and shelters)

FACTORS INCREASING THE RISK OF REACTIVATION OF LTBI—HIV infection (most important risk factor, always test those with active TB for HIV), fibronodular disease on CXR, chronic renal failure, increasing age, malignancy, transplant/immunosuppression, silicosis, chronic steroid use, TNF- α inhibitors, alcohol abuse, malnutrition, liver or kidney disease, poorly controlled diabetes, smoking, gastrectomy, jejunoileal bypass

CLINICAL FEATURES

PRIMARY TB

- **SYMPTOMS**—fever, night sweats, pleuritic chest pain, chronic cough, anorexia, weight loss, fatigue, erythema nodosum
- **SIGNS**—often none. Primary TB usually involves the mediastinal lymph nodes (Ghon complex); hilar lymphadenopathy in the presence of *RML collapse* is the most common radiologic finding (2/3) with pleural effusion in 1/3. Lung infil-

CLINICAL FEATURES (CONT'D)

trates may be seen and involve lower lungs or middle lung fields most commonly with possible cavitation in areas of consolidation

REACTIVATION TB (active pulmonary)

- **SYMPTOMS**—subacute progressive cough, yellow-green sputum, hemoptysis (25%), chest pain/dyspnea (33%), fever/night sweats (50%), fatigue (50–66%), weight loss
- **SIGNS**—reactivation TB usually involves the apical-posterior segments of upper lobes (80–90%), cavitation (19–40%), hilar lymphadenopathy
- **ELDERLY WITH REACTIVATION TB**—presents with fever, night sweats, or hemoptysis less often. Lesions less often cavitory and less often TST positive

COMPLICATIONS OF PULMONARY TB—hemoptysis (rarely massive), pneumothorax (more common in endemic countries), bronchiectasis, and pulmonary destruction (rare)

Related Topic

Tuberculosis in Pregnancy (p. 470)

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, albumin, urinalysis
- **MICROBIOLOGY**—blood C&S with mycobacterial culture, sputum Gram stain/AFB/C&S, urine AFB/C&S, HIV serology
- **IMAGING**—CXR, CT chest

SPECIAL

- **TUBERCULIN SKIN TEST**—see Diagnostic Issues for details
- **INTERFERON GAMMA RELEASE ASSAYS**—QuantiFERON®-TB Gold In-Tube (QFT-GIT) assay, and T-SPOT® TB assay
- **PCR**
- **MOLECULAR FINGERPRINTING**—tracing outbreaks
- **SUSCEPTIBILITY TESTING**—1 extra week
- **THORACENTESIS**—if effusion. Send for fluid AFB and TB culture
- **PLEURAL BIOPSY**
- **CSF**—AFB, TB culture

DIAGNOSTIC ISSUES

TUBERCULIN SKIN TEST (TST)—gold standard for diagnosing **latent tuberculosis** (epidemiologic tool), but not sensitive or specific to include or exclude active pulmonary TB. Given as 5 units TST-S (purified protein derivative) intradermally, measure extent of induration after 48–72 h. Skin test reaction cutoffs and corresponding population groups when test considered positive (in North America) are as follows:

- **0–4 mm**—in general, considered negative; no treatment indicated unless child <5 years of age and high risk of TB infection
- **≥5 mm**—HIV positive, recent infectious TB contact within 2 years, CXR signs (fibronodular disease), immunosuppression (TNF α inhibitors, organ transplantation, glucocorticoid treatment equivalent of ≥ 15 mg/day prednisone $\times \geq 1$ month), end stage renal disease
- **≥10 mm**—all others, including TST conversion within 2 years, diabetes, malnutrition (<90% ideal body weight), cigarette smoking, daily alcohol consumption >3 drinks/day, silicosis, hematologic malignancies (leukemia/lymphoma) and certain carcinomas (e.g. head and neck, lung)

INTERFERON GAMMA RELEASE ASSAYS—in-vitro blood test of cell-mediated immune response from T-cell release of interferon gamma after stimulation by antigens. IGRA does not distinguish latent from active TB infection, should not be used for diagnosis of active TB. Sens >95%; not affected by prior bacillus Calmette-Guerin (BCG) vaccination. Most useful for evaluation of latent TB in those with +TST and previously vaccinated with BCG

SPUTUM SMEAR

- **UTILITY**—morning sputum $\times 3$ days (AFB, TB culture), induced sputum if necessary, bronchoscopic lavage if cannot obtain sputum. Three consecutive AFB-negative sputum samples support that patient is non-infectious and can come off isolation
- **LIMITATIONS**—smear only detects 50% of culture positive TB, and in non-endemic areas positive smear may represent non-TB mycobacterium
- **STAINING AGENTS**—standard is Ziehl-Neelsen (acid fast stain); auramine–rhodamine or auramine O fluorescence staining improves sensitivity but must be confirmed with acid fast

SPUTUM CULTURE—2–8 weeks in egg media, 4–14 days if radiometric (sens 80–85%, spc 98–99%)

DIAGNOSTIC ISSUES (CONT'D)

POLYMERASE CHAIN REACTION (PCR)—more useful in non-endemic countries to rule out other common mycobacteria. High specificity but variable sensitivity (if AFB positive, sens 94–96%, spc 99.7–100%. If AFB positive, sens 9–100%, spc 25–100%)

MANAGEMENT

LATENT TB INFECTION—**rifampin** 10 mg/kg to 600 mg maximum PO daily $\times 4$ months or **isoniazid** 5 mg/kg to 300 mg maximum PO daily $\times 9$ months. A “decision to tuberculin test is a decision to treat” with no age cutoff for treatment and regardless of BCG vaccination status. Exclude active TB with sputum culture and CXR before treatment. HIV, immunosuppressed, and newly infected patients should be priority for treatment of latent TB

PRIMARY OR REACTIVATION TB—in hospital, patients should be isolated in single rooms with negative air pressure. TB therapy should be undertaken in consultation with an expert. Susceptibility testing is necessary to guide treatment. Directly observed treatment (DOT) is the standard of care for all patients. TB therapy consists of an intensive phase of daily therapy followed by a continuation phase of twice- or thrice-weekly therapy. **★RIPE★** **Rifampin** 10 mg/kg or 600 mg PO daily, **isoniazid** 5 mg/kg or 300 mg PO daily, **pyrazinamide** 20–25 mg/kg PO daily $\times 8$ weeks. **Ethambutol** 15–20 mg/kg PO daily is added until drug susceptibility results are available. This is followed by isoniazid and rifampin daily, twice weekly, or three times weekly for 16 more weeks

TREATMENT ISSUES

VACCINATION WITH BCG (Bacillus Calmette-Guerin)—decreases miliary and meningeal TB by 75–86% and pulmonary TB by 50% in children. However, BCG leads to false-positive skin test, which may compromise contact tracing and decision to treat latent TB infection. Not routinely performed in areas with low endemic TB risk

DIRECTLY OBSERVED TREATMENT—most effective method to prevent multi-drug-resistant tuberculosis according to the WHO

MEDICATION DETAILS

- **RIFAMPIN (RIF)**—bactericidal. Side effects include hepatic toxicity (less than INH, but induces hepatic microsomal enzymes $\rightarrow \uparrow$ clearance and \downarrow effects of many drugs), flu-like symptoms, red-orange urine, sweat, tears

TREATMENT ISSUES (CONT'D)

- **ISONIAZID (INH)**—bactericidal and inexpensive. Side effects include hepatitis (↑ with increased age and alcohol use), peripheral neuropathy (↓ with pyridoxine 10 mg PO daily or 25 mg PO daily if HIV, diabetes, malnourished, renal failure, pregnancy, or breast feeding)
- **PYRAZINAMIDE (PZA)**—bactericidal at acidic pH in cells. Side effects include GI intolerance, hepatic injury, hyperuricemia due to ↓ renal excretion, arthralgias
- **ETHAMBUTOL**—mostly bacteriostatic. Main side effect is optic neuritis

DRUG MONITORING

- **BASELINE**—platelet, Cr, AST, ALP, bilirubin, uric acid (pyrazinamide), visual acuity, and red-green color discrimination (ethambutol)

TREATMENT ISSUES (CONT'D)

- **FOLLOW-UP**—symptoms of hepatotoxicity and visual disturbance

TREATMENT OF CO-INFECTION WITH TB AND HIV—similar treatment outcome with or without HIV, but treatment of active TB infection in HIV patients should be extended beyond 6 months if bacteriologic or clinical response is slow or suboptimal. Also beware of TB and HIV drug interactions (protease inhibitors and non-nucleoside reverse transcriptase inhibitors may cause toxic levels of rifampin, which should be replaced by rifabutin)

Approach to Gram Stain, Culture, and Sensitivity**GRAM-POSITIVE COCCI****CLUSTERS (catalase positive, staphylococci)**

- **COAGULASE POSITIVE**—*S. aureus*
- **COAGULASE NEGATIVE**—*S. epidermidis*, *S. saprophyticus*, *Staphylococcus hominis*, *Staphylococcus lugdunensis*, *Staphylococcus schleiferi*

PAIRS/CHAINS (catalase negative)

- **α-HEMOLYTIC STREPTOCOCCI**—*S. pneumoniae*, viridians group streptococci
- **β-HEMOLYTIC STREPTOCOCCI**—*S. pyogenes* (group A strep), *S. agalactiae* (group B strep), group C, F, G strep
- **ENTEROCOCCUS**—*E. faecalis*, *E. faecium*
- **OTHERS**—*Abiotrophia*, *Granulicatella* (“nutrient variant strep”), *Leuconostoc*, *Lactococcus*, *Aerococcus*

ANAEROBIC—*Peptostreptococcus*, *Streptococcus*, *Peptococcus*, *Anaerococcus*

GRAM-POSITIVE BACILLI

ACID FAST (*Mycobacterium*)—*M. tuberculosis*, *M. leprae*, *M. avium-intracellulare* complex, or non-tuberculous Mycobacteria (NTM, also known as mycobacteria other than TB [MOTT]). These organisms have Gram-positive-type cell walls, but do not stain Gram-positive due to the waxy mycolic acids in the cell envelope

SPORE FORMING

- **AEROBIC**—*Bacillus anthrax*, *Bacillus cereus*
- **ANAEROBIC**—*Clostridium perfringens*, *C. difficile*, *Clostridium botulinum*

GRAM-POSITIVE BACILLI (CONT'D)**NON-SPORE FORMING**

- **AEROBIC, FACULTATIVE, AEROTOLERANT**—*Corynebacterium*/diphtheroids, *Lactobacillus*, *Listeria*, *Gardnerella*, *Nocardia*
- **ANAEROBIC**—*Actinomyces*, *Cutibacterium*, *Eubacterium*

BRANCHING BACILLI—★ ABCD-LMN★

Actinomyces (acid fast negative), *Bacillus*, *Clostridium*, *Diphtheroids*, *Listeria*, *Lactobacillus*, *Mycobacterium* (modified and Ziehl–Neelsen acid fast), *Nocardia* (modified acid fast)

GRAM-NEGATIVE COCCI

NEISSERIA—*N. meningitidis* (diplococci), *N. gonorrhoeae* (diplococci), other *Neisseria*

MORAXELLA—*M. catarrhalis*

GRAM-NEGATIVE BACILLI**AEROBIC**

- **GLUCOSE FERMENTING AND LACTOSE FERMENTING**—a number of Enterobacteriaceae including *E. coli*, *Citrobacter*, *Enterobacter*, *Klebsiella*, *Serratia*
- **GLUCOSE FERMENTING BUT NON-LACTOSE FERMENTING**—*Shigella*, *Salmonella*, *Hafnia*, *Morganella*, *Proteus*, *Yersinia*, *Edwardsiella*, *Vibrio* (oxidase positive), *Aeromonas* (oxidase positive), *Pleisiomonas* (oxidase positive)
- **NON-GLUCOSE AND NON-LACTOSE FERMENTING**

GRAM-NEGATIVE BACILLI (CONT'D)

- **OXIDASE POSITIVE**—*Pseudomonas*, *Ralstonia*, *Burkholderia*, *Roseomonas*, *Sphingomonas*
- **OXIDASE NEGATIVE**—*Stenotrophomonas*, *Acinetobacter*, *Chryseomonas*

ANAEROBIC—*Bacteroides fragilis*, *Fusobacterium*, *Prevotella*, *Porphyromonas*

OTHERS—*Eikenella**, *Pasteurella* (cats), *Capnocytophaga* (dogs), *Kingella**, *Actinobacillus**, *Cardiobacterium**, *Haemophilus** (coccobacilli, pleomorphic), *Legionella* (BCYE agar), *Campylobacter* (boomerang)

*HACEK organisms in endocarditis

SPECIFIC ORGANISMS

NON-GRAM-STAINABLE—*Chlamydia*, *Mycoplasma*, *Ureaplasma*, *Rickettsia*, *Treponema*, *Coxiella*, *Ehrlichia*, *Mycobacteria*

ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE

GROUP A STREPTOCOCCAL INFECTIONS—resistant to clindamycin

STREPTOCOCCUS PNEUMONIAE—may develop resistance to penicillin by altered penicillin-binding protein

S. AUREUS (MSSA)—may develop resistance to penicillin by β -lactamase

PSEUDOMONAS—various intrinsic mechanisms conferring resistance. Need to treat with dual antibiotic therapy for serious infections if therapy for >2 weeks or if susceptibility not yet available

ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE (CONT'D)

VRE—vancomycin-resistant enterococci

MRSA—*S. aureus* that is resistant not only to penicillin, but also penicillinase-resistant penicillins (methicillin, nafcillin, oxacillin). In general, hospital MRSA strains have broader resistance (e.g. clindamycin, trimethoprim-sulfamethoxazole, tetracyclines) than community-associated MRSA strains (CA-MRSA). Risk factors for hospital MRSA infections include frequent hospital visits and contact with MRSA-infected individuals; CA-MRSA is associated with crowding, acute and chronic skin disease, poor hygiene, sharing of contaminated items, contact sports, and IDU

β -LACTAMASE-RESISTANT BACTERIA—constitutive (*E. coli**, *Klebsiella**, *Haemophilus*, *Neisseria*, *Bacteroides*), **inducible** (*S. aureus*, *Serratia*†*, *Providencia*†, *Pseudomonas*, *Indole-positive Proteus*†*, *Citrobacter*†*, *Enterobacter*†*, *Hafnia*†*, *Acinetobacter*†*, *Morganella*†*)

†★**SPIICE-HAM**★ organisms with inducible, chromosomally mediated cephalosporinases (AmpC type β -lactamases) are resistant to penicillins, first and second generation cephalosporins, cephamycins, and β -lactamase inhibitors

*These organisms may have extended spectrum β -lactamase (ESBL) resistant to all β -lactams except carbapenems

ANTIBIOTICS

Antibiotics	Mechanism	Gram-positive	Gram-negative	Anaerobes	Others	Renal adjustments
Penicillins						
Penicillin G 2–4 M units IV q4–6 h	Bactericidal, cell wall synthesis inhibition and lysis	++ Strep	Meningococcus	++	Syphilis	Yes (dose + interval)
Penicillin V 250–500 mg PO TID/QID		++ Strep		++		Yes (dose + interval)
Cloxacillin/nafcillin/oxacillin 1–2 g IV q4–6 h		++ <i>S. aureus</i>				No
Amino-Penicillins						
Ampicillin 1–2 g IV q4–6 h	Bactericidal, cell wall synthesis inhibition and lysis	+++Strep/Entero	+/-H. flu, +/-E. coli		<i>Listeria</i>	Yes (interval)

ANTIBIOTICS (CONT'D)

Antibiotics	Mechanism	Gram-positive	Gram-negative	Anaerobes	Others	Renal adjustments
Amoxicillin 250–1,000 mg PO TID		+++Strep/ Entero	+/-H. flu, +/-E. coli			Yes (interval)
Amox/clavulanate 875/125 mg PO BID		+++Strep/ Entero	++H. flu, E. coli	+++		Yes (interval)
Anti-pseudomonal Penicillins						
Piperacillin 3–4 g IV q4–6 h	Bactericidal, cell wall synthesis inhibition and lysis	++	++Pseudo	++		Yes (dose + interval)
Piperacillin/ Tazobactam 3.375 g q6h–4.5 g IV q8h		++Staph	++Pseudo/H. flu	+++		Yes (dose + interval)
Ticarcillin 3–4 g IV q4–6 h		++	++Pseudo	++		Yes (dose + interval)
Ticarcillin/ clavulanate 3.1 g IV q4–6 h		++	++Pseudo	+++		Yes (dose + interval)
Monobactam and Carbapenems						
Aztreonam 1–2 g IV q6–8 h	Bactericidal, cell wall synthesis inhibition and lysis		+++Pseudo	+++		Yes (dose)
Imipenem 500 mg IV q6h		+++	++Pseudo	+++		Yes (dose + interval)
Meropenem 1 g IV q8h		++	+++Pseudo	+++		Yes (dose + interval)
Ertapenem 1 g IV q24h		++	++(no Pseudo)	+++		Yes (dose)
Doripenem 500 mg IV q8h		++	+++	+++		Yes (dose + interval)
First-Generation Cephalosporins						
Cefazolin 1–2 g IV q8h	Bactericidal, cell wall synthesis inhibition and lysis	+++	+			Yes (interval)
Cephalexin 250–1000 mg PO QID		+++	+			Yes (interval)
Second-Generation Cephalosporins						
Cefuroxime 750–1500 mg IV q8h	Bactericidal, cell wall synthesis inhibition and lysis	++	++			Yes (interval)
Cefuroxime 125–500 mg PO BID		++	++			Yes (interval)
Cefprozil 250–500 mg PO q12h		++	++			Yes (interval)
Cefaclor 250–500 mg PO BID		++	++			Yes (interval)

ANTIBIOTICS (CONT'D)						
Antibiotics	Mechanism	Gram-positive	Gram-negative	Anaerobes	Others	Renal adjustments
Third/Fourth Generation Cephalosporins						
Cefoxitin 1–2 g IV q6–8 h	Bactericidal, cell wall synthesis inhibition and lysis	+++	+++	++		Yes (interval)
Cefotaxime 1–2 g IV q6–8 h		+++	+++			Yes (interval)
Ceftriaxone 1–2 g IV q24h		+++	+++			No
Ceftazidime 1 g IV q8–12 h		+++	+++Pseudo			Yes (interval)
Cefepime 1–2 g IV q12h		+	+++Pseudo			Yes (interval)
Cefixime 400 mg PO daily		+	++			Yes (interval)
Ceftaroline 600 mg IV q8–12 h		+++MRSA	+++			Yes (interval)
Aminoglycosides						
Gentamicin 5–7 mg/kg IV q24h	Bactericidal, binds to 30S and 50S ribosomes	Entero (syn)	+Pseudo			Yes (dose + interval)
Tobramycin 5–7 mg/kg IV q24h		+/-Entero (syn)	++Pseudo			Yes (dose + interval)
Amikacin 7.5 mg/kg q12h		+/-Entero (syn)	++Pseudo			Yes (dose + interval)
Streptomycin 15 mg/kg IM or IV q24h		Entero (syn)	++Pseudo	AFB, Plague		Yes (dose + interval)
Fluoroquinolones						
Ciprofloxacin 500 mg PO/400 mg IV BID	Bactericidal, inhibit DNA synthesis through inhibition of DNA gyrase and topoisomerase		+++Pseudo		AFB	Yes (interval)
Norfloxacin 400 mg PO BID			+++			Yes (dose ± interval)
Ofloxacin 200–400 mg PO BID			++		AFB	Yes (dose ± interval)
Levofloxacin 500–750 mg PO/IV daily		++	+++		AFB	Yes (dose ± interval)
Moxifloxacin 400 mg PO/IV daily		++	+++	++	AFB	Yes (dose ± interval)
Gemifloxacin 320 mg PO daily		++	+++		AFB	Yes (dose ± interval)
Macrolides						
Azithromycin 250 mg PO daily	Bacteriostatic, binds to 50S ribosomes	+	+H. flu/Legion		++ <i>Mycoplasma</i> and <i>Chlamydia</i> for all macrolides	No
Clarithromycin 250–500 mg PO BID		+	+H. flu/Legion			Yes (dose)

ANTIBIOTICS (CONT'D)

Antibiotics	Mechanism	Gram-positive	Gram-negative	Anaerobes	Others	Renal adjustments
Erythromycin 250–500 mg PO q6–12 h		+	+Legion			No
Tetracyclines						
Doxycycline 100 mg PO/IV q12h	Bacteriostatic, binds to 30S ribosomes		+		+Chlamydia	No
Minocycline 50–100 mg PO daily-BID		+	+		+Chlamydia	No
Tetracycline 500 mg PO QID			+		+Chlamydia	Avoid
Tigecycline 100 mg IV, then 50 mg q12h		+++MRSA, VRE	++Acinetobacter		+Chlamydia	No
Sulfa						
Sulfamethoxazole/ Trimethoprim 1–2	Bactericidal, blocks DNA synthesis	+	++Steno, +PJP			Yes (interval)
SS/DS tab PO BID (also available IV)						
Clindamycin						
Clindamycin 150–450 mg PO QID or 300–600 mg IV q6–12 h	Bacteriostatic, binds to tRNA complex	++		+++		No
Metronidazole						
Metronidazole 500 mg PO/IV q12h	Bactericidal, DNA breakage		<i>H. pylori</i> , <i>Gardnerella vaginalis</i>	+++C. diff	++protozoa	No
Glycopeptides						
Vancomycin 15 mg/ kg IV q12h	Bactericidal, interferes with peptidoglycan and RNA synthesis	+++				
		<i>S. epidermidis</i> , MRSA, Enteroc		++C. diff		Yes (interval)
Oxazolidinones						
Linezolid 600 mg PO/ IV q12h	Bactericidal (Strep) and bacteriostatic (Staph, Enteroc), binds to 50S ribosomes	++MRSA, VRE		+	+++AFB	No
Streptogramins						
Quinupristin/ Dalfopristin 7.5 mg/kg IV q8h via central line	Inhibits late + early protein synthesis	++MRSA, VRE (not <i>E. faecalis</i>)		+		No

ANTIBIOTICS (CONT'D)

Antibiotics	Mechanism	Gram-positive	Gram-negative	Anaerobes	Others	Renal adjustments
Lipopeptides						
Daptomycin 4–6 mg/kg q24h	Bactericidal, disrupts cell membrane	++MRSA, VRE		+		Yes (interval)

Abbreviations: *SS* single strength, *DS* double strength

VANCOMYCIN TOXICITY AND DOSING

TOXICITY—rash, infusion-related red man syndrome, rarely nephrotoxicity (especially when combined with aminoglycoside), and ototoxicity. However, serum vancomycin levels do not predict toxicity

LOADING DOSE—15–20 mg/kg (usually 1–1.5 g) IV

MAINTENANCE DOSE—30 mg/kg (actual body weight) per day divided into 2–4 doses (maximum usually 1.5 g/dose). New recommendations to use area under curve (AUC)/minimum inhibitory concentration (MIC) for drug monitoring with target AUC 400–600 mg^h/L when treating serious MRSA infections but this is not available in all laboratories

- **START**—monitoring after steady state, i.e. usually after third dose, or after second dose if dosing interval >48 h. Monitor only if treatment duration >14 days in patients with stable renal function and mild/moderate infection, or treatment duration >4 days in patients with unstable renal function or severe infection
- **TROUGH LEVELS**—obtained 30–60 min before next scheduled dose. Should be at least 6.9–10.4 μmol/L [10–15 μg/mL]; adjust to 10.4–13.8 μmol/L [15–20 μg/mL] for serious infections (endocarditis, osteomyelitis)
- **PEAK LEVELS**—does not correlate for efficacy or toxicity and therefore should not be monitored
- **ADJUSTMENTS**—dosing interval is dependent on renal function (CrCl >100 mL/min, q12h; 80–100 mL/min, q18h; 60–80 mL/min, q24h; 40–60 mL/min, q36h; 25–40 mL/min q48h; <25 mL/min, single dose then measure serum concentration and give PRN). Changes in dose without changes in interval will result in proportional changes in both peak and trough serum drug concentrations. Prolongation of dosing interval will also reduce both, particularly trough level

2020 ASHSP/IDSA/PIDS/SIDP Revised Guideline Vancomycin MRSA Infections

PENICILLIN ALLERGY

HISTORY—characterize reaction (age when reaction occurred, timing of reaction after penicillin administration, type of reaction, route of administration, reason for penicillin, any other medications at the time, resolution), any similar antibiotics since

CROSS-REACTIVITY—incidence of cross-reactivity to cephalosporins when patient has penicillin allergy by history is <2%. It is often safe to use these medications, with the first dose monitored. If safety unclear, skin testing provides reassurance. For patients with a history of penicillin allergy, those with positive and negative skin test have 5.6% and 1.7% chance of developing cross-reactivity with cephalosporin, respectively

TYPES OF ALLERGIC REACTIONS

★**ACID**★ Antibody-mediated (IgE), Cytotoxic (antibody-dependent), **Immune-complex-mediated**, Delayed hypersensitivity reaction

- **TYPE I**—immediate <1 h, drug-specific IgE mediated, anaphylaxis, hypotension, laryngeal edema, wheezing, angioedema, urticaria
- **TYPE II**—>72 h, IgG and complement mediated, increased clearance of RBC and platelets by lymphoreticular system
- **TYPE III**—>72 h, IgG and IgM immune complexes mediated, serum sickness, tissue injury
- **TYPE IV**—>72 h, contact dermatitis
- **OTHERS**—>72 h, maculopapular or morbilliform rashes

APPROACH—detailed history of a patient's reaction to penicillin is most helpful tool for excluding true penicillin allergy. Patients with a concerning history of type I penicillin allergy and have a compelling need for penicillin-containing drug should undergo skin testing. Negative skin test result decreases the likelihood of a life-threatening reaction

Approach to Empiric Antibiotics

GENERAL APPROACH

CHOICE OF EMPIRIC ANTIBIOTIC—based on the most likely and deadly organisms for each type of infection. Thus, a good understanding of the pathophysiology of each infection and the **local resistance pattern of various organisms is essential**

CULTURE AND SUSCEPTIBILITY—should always be performed to facilitate targeted antibiotic treatment except for mild infections. However, the specific organism may not be identified even if multiple cultures are taken. In this case, the clinician must rely on clinical judgment and continue treatment with empiric antibiotic(s)

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES

SEPSIS—appropriate choice depends on the suspected source. For pulmonary source, azithromycin plus ceftriaxone or respiratory fluoroquinolone. For hospital acquired pneumonia, anti-pseudomonal agent such as piperacillin-tazobactam or ceftriaxone. For urinary source, ceftriaxone, carbapenem, fluoroquinolone or aminoglycoside. For intra-abdominal source, piperacillin-tazobactam or a carbapenem. Duration of treatment is at least 7–14 days with rationalization of antibiotics when susceptibility results available. See p. 118 for details

MENINGITIS (*S. pneumoniae*, *N. meningitidis*, *Listeria*, HSV)—ceftriaxone/cefotaxime + vancomycin + dexamethasone ± ampicillin (depending on age and risk factors). Add acyclovir if CSF suggests viral picture or presence of confusion to suggest encephalitis. Duration of treatment is 7–21 days. See p. 257 for details

COMMUNITY-ACQUIRED PNEUMONIA (*S. pneumoniae*, *Klebsiella*, *Mycoplasma*)—macrolides, ceftriaxone or respiratory fluoroquinolones. Duration of treatment is usually 7 days. See p. 9 for details

ASPIRATION PNEUMONIA (anaerobes, Staph, GNB)—ceftriaxone or levofloxacin plus metronidazole. Duration of treatment is usually 7 days. See p. 9 for details

ICU/VENTILATOR-ASSOCIATED PNEUMONIA (GNB, *Pseudomonas*)—piperacillin-tazobactam or carbapenem. Duration of treatment is usually 7 days. See p. 107 for details

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

ENDOCARDITIS (*S. aureus*, *S. viridans*, *Enterococcus*) Duration of treatment is highly variable. See AHA guidelines and p. 65 for details

- **NATIVE VALVE DISEASE**—vancomycin plus ceftriaxone or gentamicin
- **PROSTHETIC VALVE DISEASE**—vancomycin plus gentamicin plus rifampin

Hoehn et al. *NEJM* 2013;368(15)

Wang et al. *JAMA* 2018;320(1)

ACUTE BLOODY DIARRHEA (*Salmonella*, *Shigella*, *Campylobacter*)—may or may not require treatment with ciprofloxacin. Duration of treatment is 3 days. See p. 137 for details

ANTIBIOTIC-ASSOCIATED DIARRHEA (*C. difficile*)—oral vancomycin. Duration of treatment is 10–14 days. See p. 138 for details

PERITONITIS/INTRA-ABDOMINAL SEPSIS (coliforms, anaerobes)—piperacillin-tazobactam, carbapenem, or ceftriaxone plus metronidazole. Treat until WBC/peritonitis resolved

FEVER IN SPLENECTOMIZED PATIENT (*H. influenza*, *N. meningitidis*, *S. pneumoniae*, *Capnocytophaga canimorsus*)—cefotaxime/ceftriaxone. Duration of treatment is usually 10–14 days. See p. 165 for further information

URINARY TRACT INFECTION (*E. coli*, *Klebsiella*, *Enterococcus*, *Proteus*, *S. saprophyticus*)—nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomicin. Duration of treatment is 3 days if uncomplicated UTI, otherwise 10–14 days. See p. 259 for details

CELLULITIS (*Staphylococcus*, *Streptococcus*)—cefazolin, cloxacillin, or cephalixin. Vancomycin, doxycycline or TMP/SMX if MRSA suspected. Duration of treatment is usually 7–10 days. See p. 263 for details

HUMAN BITE (Gram-positive, *Eikenella*, anaerobes)—amoxicillin-clavulanate, or clindamycin plus ciprofloxacin

DIABETIC FOOT (polymicrobial)—amoxicillin-clavulanate or piperacillin-tazobactam (depending on severity). Consider surgical consult if necrotic tissue or abscess. See p. 265 for details

NECROTIZING FASCIITIS—surgical treatment is mandatory. For type I infection piperacillin-tazobactam + vancomycin or ceftriaxone + metronidazole + vancomycin. For *Streptococcus*, penicillin G plus clindamycin. See p. 264 for details

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

OSTEOMYELITIS (Gram-positive, Gram-negative, anaerobes)—for Gram-positive coverage, cefazolin or vancomycin. For Gram-negative coverage, ceftriaxone. Important to get a microbiologic diagnosis to guide definitive therapy (consider bone biopsy if blood or tissue cultures non diagnostic). Duration of

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

therapy usually at least 6 weeks. See p. 264 for details

SEPTIC ARTHRITIS—vancomycin + cefazolin for empiric coverage as generally caused by Gram-positive bacteria. Important to get a microbiologic diagnosis to guide definitive therapy. Usual duration 4 weeks. See p. 293 for details

Hepatitis B

See HEPATITIS B (p. 147)

Hepatitis C

See HEPATITIS C (p. 148)

Herpes Simplex Virus Infection

See HERPES SIMPLEX VIRUS (p. 405)

Human Immunodeficiency Virus[HIV/AIDS Treatment Guidelines/ Clinical Info](#)Ghosh et al. *Lancet* 2018;392(10148)**RISK FACTORS FOR HIV INFECTION****SEXUAL CONTACT**

PARENTERAL—IDU, transfusion or unsafe needle use in healthcare settings in the developing world, health workers

MATERNAL-FETAL—in-utero, delivery, breast feeding

ACUTE HIV INFECTION

STRAINS—HIV1 globally; HIV2 mainly in West Africa

SYMPTOMS—acute febrile “mononucleosis-like” illness, lymphadenopathy, pharyngitis, rash and headache within 1–6 weeks post-exposure. Hematologic (lymphopenia, thrombocytopenia) and liver enzyme abnormalities

DIAGNOSIS—ELISA assay (sens ~100%, spc <100%) → if positive, repeat ELISA → if positive, Western blot for confirmation → if indeterminate, repeat Western blot. If during window period

ACUTE HIV INFECTION (CONT'D)

within 2 weeks postexposure, consider viral load testing

BASIC WORKUP FOR THE NEWLY DIAGNOSED

- **HIV STATUS**—viral load, CD4 count, genotypic antiretroviral drug resistance testing
- **BASELINE**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, TSH, glucose, fasting lipid profile, lipase, CK, HLA B*5701 (for abacavir hypersensitivity), βhCG, CXR, ECG, urinalysis
- **CO-EXISTING/OPPORTUNISTIC INFECTIONS**—HAV serology, HBV testing (HBsAg, HBsAb, HBcAb. If HBsAg or HBcAb positive, check HBV DNA as well), HCV testing (anti-HCV). If anti-HCV positive, check HCV RNA and FibroScan® to assess liver fibrosis. Pap smear, anal screening for HPV in MSM, chlamydia and gonorrhea screen, syphilis testing, TST or IGRA, *Toxoplasma* serology, CMV serology

NATURAL HISTORY OF HIV

VIRAL LOAD—rate of progression (speed of train). Indicates activity of viral replication. Critical measure of effect of antiretroviral therapy, once started

CD4 COUNT—progress and stage of disease (distance to crash). Indicates relative health of immune system and risk of opportunistic complications

FOLLOW-UP—viral load and CD4 count (usually 3–6 month intervals once viral load is suppressed)

AIDS—CD4 <200/mm³ or any AIDS-defining diseases

- **BACTERIAL**—MAC, TB, recurrent *Salmonella* sepsis
- **VIRAL**—CMV retinitis, chronic HSV, PML
- **FUNGAL**—esophageal candidiasis, extrapulmonary coccidioidomycosis, histoplasmosis or cryptococcosis
- **PARASITIC**—*Pneumocystis jirovecii* pneumonia (PJP), toxoplasmosis, chronic cryptosporidiosis or isosporiasis
- **HIV**—HIV encephalopathy, wasting syndrome
- **NEOPLASMS**—Kaposi sarcoma, CNS lymphoma, non-Hodgkin lymphoma, cervical carcinoma

MAJOR CAUSES OF DEATH IN HIV PATIENTS—varies by geographic location and CD4 count. Includes: AIDS (30%), liver disease (14%), accidents and overdose (15–20%) cardiovascular disease (9%), non-AIDS cancers (8%)

CD4 COUNT AND PATHOLOGIES IN HIV PATIENTS

CD4 count (/mm ³)	>500	200–500	100–200	<100
Kaposi sarcoma	+	+	+	+
Bacterial	+	+	+	+
TB	+	+	+	+
HSV	+	+	+	+
<i>Candida</i>		+	+	+
<i>Coccidioides</i>		+	+	+
<i>Histoplasma</i>		+	+	+
PJP			+	+
<i>Cryptococcus</i>				+
<i>Toxoplasma</i>				+
CMV				+
MAC				+
CNS				+
lymphoma				+

CNS LESIONS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **BRAIN ABSCESS**—toxoplasma (CD4 <100/mm³, usually multiple ring-enhancing lesions), tuberculosis (any CD4), *Cryptococcus* (CD4 <100/mm³), *Histoplasma* (CD4 <500/mm³), aspergillosis
- **CNS LYMPHOMA** (CD4 <100/mm³)
- **PROGRESSIVE MULTI-FOCAL LEUKOENCEPHALOPATHY** (PML, CD4 <100/mm³)—reactivation of JC virus, hypodense white matter lesion (non-enhancing on MRI)

DIAGNOSIS—CBC, lytes, urea, Cr, blood C&S, toxoplasma IgG antibodies, EBV PCR, JC virus PCR, CT/MR head, PET scan (CNS lymphoma has higher activity than abscess), brain biopsy (if suspect CNS lymphoma). The combination of (1) multiple ring enhancing lesions, (2) positive antitoxoplasmosis antibodies, and (3) lack of toxoplasma prophylaxis in a HIV patient with CD4 count <100/mm³ has 90% PPV for diagnosing toxoplasma

TREATMENT OF TOXOPLASMOSIS—pyrimethamine plus either sulfadiazine or clindamycin

CHRONIC MENINGITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **CRYPTOCOCCUS** (CD4 <100/mm³)—ubiquitous fungus. High opening pressure (>200 cmH₂O)
- **BACTERIAL MENINGITIS** (any CD4)—*N. meningitidis*, *S. pneumoniae*, *Listeria*, Gram-negative bacilli
- **VIRAL MENINGITIS** (any CD4)—HSV encephalitis

DIAGNOSIS—CBC, lytes, urea, Cr, blood C&S, serum cryptococcal antigen (sens 95% for *Cryptococcus*), CT head, lumbar puncture (for *Cryptococcus* and cryptoantigen)

TREATMENT OF CRYPTOCOCCUS—induction with *amphotericin B* 0.7 mg/kg IV daily plus *flucytosine* 25 mg/kg PO QID, switch to *fluconazole* 400 mg PO daily × 2 months for consolidation, followed by *fluconazole* 200 mg PO daily as maintenance. Management of increased intracranial pressure may be needed (neuroimaging to rule out concomitant space-occupying lesions, repeated LP to decrease ICP)

RESPIRATORY INFECTIONS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **COMMUNITY-ACQUIRED PNEUMONIA** (any CD4)—most common cause is *S. pneumoniae*. Others include *Moraxella*, *H. influenzae*
- **TUBERCULOSIS** (any CD4)—170 × increased risk in HIV patients. May be extrapulmonary

RESPIRATORY INFECTIONS IN HIV PATIENTS (CONT'D)

- **NON-TB MYCOBACTERIUM**—MAC (CD4 <100/mm³, pulmonary involvement alone is rare, usually disseminated)
- **FUNGAL** (CD4 <500/mm³)—*Histoplasma*, *Coccidioides*, *Cryptococcus*
- **PNEUMOCYSTIS JIROVECI PNEUMONIA** (PJP, CD4 <200/mm³)

DIAGNOSIS—CBC, lytes, urea, Cr, LDH (↑ in PJP but non-specific), blood C&S and mycobacterial culture, sputum C&S and AFB, ABG (for PaO₂ and A-a gradient), urine C&S, CXR, bronchoscopy (lavage, biopsy)

TREATMENT OF PJP—trimethoprim-sulfamethoxazole 15 mg of TMP/kg PO/IV divided q8h daily × 21 days. If severe disease (PaO₂ ≤ 70 mmHg or A-a gradient ≥ 35 mmHg on room air), add prednisone 40 mg PO BID × 5 days, then 40 mg PO daily × 5 days, then 20 mg PO daily × 11 days. Alternatives to trimethoprim-sulfamethoxazole include dapsone plus trimethoprim, or clindamycin plus primaquine, pentamidine IV. Use atovaquone in patients with G6PD deficiency

ESOPHAGITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
 - **CANDIDA** (CD4 <500/mm³)—50–70%
 - **HSV** (any CD4)—5–10%
 - **CMV** (CD4 <100/mm³)—5–15%
- **NON-INFECTIOUS**—GERD, pill esophagitis, neoplasms
- **IDIOPATHIC** (any CD4)—10–30%

DIAGNOSIS—empiric therapy (fluconazole), endoscopy with cultures for fungus, virus, and biopsy for histopathology

HEPATITIS/CHOLANGITIS/PANCREATITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
 - **TB** (any CD4)
 - **MYCOBACTERIUM AVIUM COMPLEX** (MAC, CD4 <100/mm³)—*M. avium*, *M. intracellulare*
 - **VIRUSES**—HBV, HCV, CMV
 - **PARASITES**—*Cryptosporidium*, *Microsporidium*, *Cyclospora*
- **ALCOHOL**
- **DRUGS**—antiretrovirals, antibiotics (sulfa, isoniazid, rifampin, ketoconazole, fluconazole)

HEPATITIS/CHOLANGITIS/PANCREATITIS IN HIV PATIENTS (CONT'D)

DIAGNOSIS—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, lipase, INR, cultures and serologies, US abd, CT abd, ERCP

COLITIS/DIARRHEA IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
 - **BACTERIAL**—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, EHEC, EIEC, *C. difficile*
 - **TB** (any CD4)
 - **MYCOBACTERIUM AVIUM COMPLEX** (MAC, CD4 <100/mm³)—*M. avium*, *M. intracellulare*
 - **CMV** (CD4 <100/mm³)
 - **PARASITIC** ★**MAGIC**★—*Microsporidium*, *Entamoeba*, *Giardia*, *Isospora*, *Cryptosporidium*
- **MEDICATIONS**—antiretrovirals, antibiotics
- **AIDS ENTEROPATHY**—diagnosis of exclusion

DIAGNOSIS—CBC, lytes, urea, Cr, stool C&S, stool O&P with acid fast staining, stool MAC, *C. diff* toxin, fecal WBC, *Cryptosporidium*, microsporidium

TREATMENT OF MAC—clarithromycin 500 mg PO BID or azithromycin 600 mg PO daily, plus ethambutol 15 mg/kg PO daily, plus rifabutin 600 mg PO daily for at least 12 months and at least 6 months of immune reconstitution (CD4 >100–200/mm³)

AIDS-ASSOCIATED MALIGNANCIES

AIDS-DEFINING MALIGNANCIES

- **KAPOSI SARCOMA** (any CD4)—strongly associated with HHV8. Lesions may involve skin, oral mucosa, lungs, and GI tract. Treat with liposomal doxorubicin. Lesions may also resolve with antiretroviral treatment
- **NON-HODGKIN LYMPHOMA** (CD4 <100/mm³)—diffuse large B-cell lymphoma, primary effusion lymphoma (associated with HHV8 and EBV), and plasmablastic lymphomas. Treat with combination chemotherapy (CHOPR)
- **PRIMARY CNS LYMPHOMA** (CD4 <100/mm³)—strongly associated with EBV. Treat with radiation and/or high-dose methotrexate or intrathecal chemotherapy
- **CERVICAL CARCINOMA** (any CD4)—strongly associated with HPV. Treat with surgery, radiation, and/or chemotherapy (cisplatin)

AIDS-ASSOCIATED MALIGNANCIES (CONT'D)

NON-AIDS-DEFINING MALIGNANCIES—increased incidence of Hodgkin lymphoma, multiple myeloma, anogenital cancer, testicular cancer (seminoma), and basal cell carcinoma in HIV patients. Lung cancer, colorectal cancer, melanoma, squamous cell carcinoma of skin, and head and neck cancer may also be increased

EDUCATION, PROPHYLAXIS, AND IMMUNIZATION FOR HIV PATIENTS

EDUCATION AND COUNSELING—patient MUST be told to reveal HIV status to sexual partners (reportable disease). Advise regarding condom use and safe sex practices. Risk reduction strategies should be explored for substance abuse (e.g. avoid sharing needles or other drug paraphernalia), tobacco use, and other social issues. HIV is a chronic disease that can be **successfully treated**

PJP PROPHYLAXIS—for patients with CD4 <200/mm³. *Trimethoprim-sulfamethoxazole* SS 1 tab PO daily, or *trimethoprim-sulfamethoxazole* DS 1 tab PO daily, or *trimethoprim-sulfamethoxazole* DS 1 tab PO three times a week. If allergic, desensitize or use dapsone or inhaled pentamidine

TOXOPLASMOSIS PROPHYLAXIS—for patients with positive *Toxoplasma* serology and CD4 <100/mm³. *Trimethoprim-sulfamethoxazole* DS 1 tab PO daily. If allergic, dapsone plus pyrimethamine plus folinic acid are alternatives

MAC PROPHYLAXIS—for patients with CD4 <50/mm³. *Azithromycin* 1200 mg PO once weekly

HISTOPLASMOSIS PROPHYLAXIS—for patients with CD4 <150/mm³ and living in endemic area. *Itraconazole* 200 mg PO daily

TB PROPHYLAXIS—for patients with positive TST reaction (induration ≥5 mm) and not treated for TB previously. *Isoniazid* 5 mg/kg/day PO to max 300 mg/day, or 900 mg thrice weekly × 9 months. *Rifampin* 600 mg PO daily × 4 months restricted to exposures to INH-resistant, RIF-susceptible isolates. Should be followed by a TB specialist

VACCINATIONS

- **GIVE**—Prevnar followed by pneumococcal polysaccharide vaccine at least 8 weeks later. Pneumococcal vaccine should be repeated every 5 years up to 3 doses. Hepatitis B vaccine (if non-immune), hepatitis A vaccine (if non-

EDUCATION, PROPHYLAXIS AND IMMUNIZATION FOR HIV PATIENTS (CONT'D)

immune and especially if homosexual), influenza vaccine annually are all recommended

- **GENERALLY AVOID**—live vaccines (oral polio, varicella, measles-mumps-rubella, or yellow fever immunizations) if CD4 count is <200/mm³

Related Topics

Hepatitis B (p. 147)
Hepatitis C (p. 148)
HIV in Pregnancy (p. 470)
Needle Stick Injury (p. 290)
Tuberculosis (p. 267)

ANTIRETROVIRAL THERAPY FOR HIV PATIENTS

NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)—zidovudine (ZDV, AZT), stavudine (d4T), didanosine (ddI), lamivudine (3TC), abacavir (ABC), tenofovir (TDF), and emtricitabine (FTC). Major side effects include hepatic steatosis, lactic acidosis, neuropathy, anemia, pancreatitis, and renal disease

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)—efavirenz (EFV), nevirapine (NVP), etravirine (ETR) and rilpivirine (RPV). Major side effects include rash, Stevens-Johnson syndrome, hepatitis, and CNS complications

PROTEASE INHIBITORS (PI)—saquinavir (SQV), indinavir (IDV), nelfinavir (NFV), lopinavir-ritonavir (LPV/RTV), fosamprenavir (FPV), atazanavir (ATV), tipranavir (TPV), and darunavir (DRV). Major side effects include hyperglycemia, fat redistribution syndrome, insulin resistance, and GI intolerance

INTEGRASE INHIBITORS—raltegravir, dolutegravir, elvitegravir

FUSION INHIBITOR (FI)—enfuvirtide (T-20)

CCR5 ANTAGONIST—maraviroc

EXAMPLES OF PREFERRED HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) REGIMENS (Clinicalinfo.HIV.gov)

- **BICTEGRAVIR/TENOFOVIR ALAFENAMIDE/EMTRICITABINE**
- **DOLUTEGRAVIR/ABACAVIR/LAMIVUDINE**—only for individuals who are HLA-B*5701 negative and without chronic HBV coinfection

ANTIRETROVIRAL THERAPY FOR HIV PATIENTS (CONT'D)

- **DOLUTEGRAVIR OR RALTEGRAVIR**—plus (emtricitabine or lamivudine) plus (tenofovir alafenamide or tenofovir disoproxil fumarate)
- **DOLUTEGRAVIR/LAMIVUDINE**—except for individuals with HIV RNA >500,000 copies/mL, HBV co-infection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

THERAPEUTIC DECISIONS IN HIV

GOALS OF HIV THERAPY—durable suppression of HIV viral load to undetectable levels, reduction in HIV related morbidity, improvement in quality of life, prolongation of survival, restoration of immune function, and prevention of HIV transmission

APPROACH—start treatment in all patients regardless of CD4 count. Even those with CD4 count >500 are likely to benefit from ART

RESPONSE—successful if viral load ↓ by 2 logs after 8 weeks and ↓ to <50 copies/mL after 6 months of therapy. Need to continue therapy or may develop viral load rebound or drug resistance. If failure, consider non-adherence and/or resistance. Resistance testing should be performed, and the regimen should be changed based on resistance profile

2016 IAS-USA Recommendations Antiretroviral Drugs HIV Infection

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) IN HIV PATIENTS

PATHOPHYSIOLOGY—delayed (1 week to several months) inflammatory response as the immune system is restored by antiretrovirals, leading to acute, paradoxical deterioration of pre-existing infections (TB, MAC, PJP, histoplasma, HCV, HBV). Clinical features highly variable. IRIS is a diagnosis of exclusion after considering drug reactions, non-adherence, new onset or progression of opportunistic infection. May occur in up to 25% of patients with opportunistic infections started on HAART (e.g. lymphadenopathy after starting antiretrovirals in patients with

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS) IN HIV PATIENTS (CONT'D)

disseminated MAC or worsening CXR and fever in patients with TB)

TREATMENTS—supportive, continue antiretrovirals, corticosteroids

VIRAL HEPATITIS IN HIV CO-INFECTED PATIENTS

HEPATITIS B

- **PATHOPHYSIOLOGY**—HIV/HBV co-infection rate is up to 20–30% in Asia/sub-Saharan Africa where transmission is mostly vertical or between young children and 5–10% in the USA and Europe where transmission is mostly via IDU and sexual contact. Co-infection associated with progression to end-stage liver disease
- **DIAGNOSIS**—for patients with isolated HbCAb, 10–45% have occult HBV infection with detectable levels of HBV DNA
- **PREVENTION**—hepatitis B vaccination of family and sexual partners
- **TREATMENTS**—long-term combination therapy with a nucleoside analogue and nucleotide analogue (e.g. tenofovir plus either emtricitabine or lamivudine) is recommended in co-infected patients. US and AFP recommended every 6 months for hepatocellular carcinoma screening

HEPATITIS C

- **PATHOPHYSIOLOGY**—HIV/HCV co-infection rate up to 70–95% for patients with IDU and hemophilia and 1–12% for MSM. Coinfection results in more aggressive HCV, with more rapid progression to liver failure and hepatocellular carcinoma
- **DIAGNOSIS**—HCV AB and RNA. FibroScan® or APRI can be done to determine degree of fibrosis and need for monitoring for HCC
- **PREVENTION**—risk reduction and safer needle use
- **TREATMENTS**—all coinfecting patients should be offered treatment for hepatitis C infection as treatment is now well tolerated and accessible, high likelihood of achieving sustained virologic response (see p. 148)

Influenza

Glazen *NEJM* 2008;359(24)

DIFFERENTIAL DIAGNOSIS

VIRAL—influenza A/B, parainfluenza, RSV, metapneumovirus, adenovirus, enterorhinovirus, coronavirus (seasonal and pandemic)

BACTERIAL PNEUMONIA—*S. pneumoniae*, *S. aureus*, *Haemophilus*, *Moraxella*

ATYPICAL—*Mycoplasma*, *Chlamydia*, *Legionella*, TB, community-acquired MRSA

PATHOPHYSIOLOGY

CLASSIFICATION—influenza A, B. Influenza A classified into subtypes based on the combination of two surface glycoproteins: neuraminidase (1 of 9 subtypes) and hemagglutinin (1 of 16 subtypes), e.g. H1N1, H1N2, and H3N2. Influenza A subtypes and influenza B further classified into various strains that arise due to antigenic drift

HOSTS—influenza B viruses mainly affect humans. Influenza A can infect both humans and animals, including wild birds, poultry, pigs, dogs, and horses. Some influenza A strains are highly pathogenic and can cause severe disease in specific hosts, while others are associated with low pathogenicity

ANTIGENIC DRIFT—a gradual change in viral RNA sequence that occurs in both influenza A and B. This process is due to random point mutations in the genes encoding neuraminidase or hemagglutinin, creating strains of virus with new surface glycoproteins. Thus, antibodies against previous strains are ineffective. Can result in seasonal epidemics

ANTIGENIC SHIFT—an abrupt and significant emergence of novel viral strains. Only happens with influenza A. Antigenic shift occurs through mixing of human influenza A and animal (e.g. pig, bird) influenza A virus genes to create a new influenza A subtype through genetic reassortment (e.g. swine flu, avian flu). Rarely, avian strains of influenza may directly infect humans. Antigenic shift generates new virus and triggers pandemics as the majority of the population has no immunity against this new virus

PANDEMIC (worldwide outbreak)—based on the following criteria: (1) emergence of a new subtype of influenza A virus, (2) this virus is able to infect humans, (3) this virus can spread easily from person to person in a sustained manner

PATHOPHYSIOLOGY (CONT'D)

DISTINGUISHING FEATURES BETWEEN INFLUENZA A, B,

	Influenza A	Influenza B
Hosts	Humans, Birds, Mammals	Humans only
Antigenic shift	Yes, creating new subtypes	No
Antigenic drift	Yes, creating new strains	Yes
Epidemics	Yes	Yes
Pandemics	Yes	No

CLINICAL FEATURES

HISTORY—acute onset of systemic symptoms, such as fever, headache, myalgia, arthralgia, fatigue, and respiratory symptoms such as cough, dyspnea, and sore throat. Clinical findings of influenza-like illness (ILI) cannot be used to confirm/exclude diagnosis; use epidemiologic data and treat empirically or obtain rapid influenza test to assist with management decisions

COMPLICATIONS—**respiratory** (bacterial pneumonia), **muscular** (rhabdomyolysis, myositis), **neurologic** (encephalitis, aseptic meningitis, transverse myelitis, Guillain-Barré syndrome)

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis
- **MICROBIOLOGY**—nasopharyngeal swab for rapid assays (variable sensitivity/specificity), RT-PCR (preferred), or DFA (direct fluorescent antigen detection). Blood C&S, sputum Gram stain/AFB/C&S, urine C&S
- **IMAGING**—CXR

SPECIAL

- **LUMBAR PUNCTURE**—if neurologic symptoms
- **ABG**

MANAGEMENT

PREVENTION IS KEY—annual vaccination is recommended for all individuals. Highly recommended for those at risk for severe disease: ≥ 50 years, children 6–24 months or taking long-term

MANAGEMENT (CONT'D)

salicylates, any chronic medical condition, pregnant women, healthcare workers, household contacts of those at risk, and residents of chronic care facilities. Depending on the match between vaccine and circulating virus, the efficacy can range from 70% to 90% for a good match and 20% to 50% for poor matches

TREATMENT—neuraminidase inhibitors (*oseltamivir* 75 mg PO BID×5 days, or *zanamivir* 10 mg inhaled BID×5 days) are active against influenza A and B. Antiviral treatment is most effective when started within 48 h of symptom onset. Treatment decreases symptom duration by one day, reduces viral shedding, may reduce complications in those at risk. Inhaled zanamivir relatively contraindicated in patients with asthma or chronic respiratory conditions. Household contacts of infected patients should be vaccinated, may be given prophylaxis (*oseltamivir* 75 mg PO daily). Resistance to oseltamivir occurs in some strains of influenza A and amantadine or rimantadine may have a role. Treatment of secondary bacterial pneumonia with antibiotics

TREATMENT ISSUES

NEURAMINIDASE INHIBITORS—neuraminidase plays an important role for viral release from the host cell. Oral oseltamivir and inhaled zanamivir are active against both influenza A and influenza B

ADAMANTANES—block replication of influenza A RNA through inhibition of M2 protein ion channels. Amantadine and rimantadine are inactive against influenza B and resistance is now widespread in influenza A

VACCINE PRODUCTION—every February/March, WHO makes recommendations regarding the four strains (2 A and 1 or 2 B) of influenza viruses that are most likely to cause outbreaks in the fall/winter in the upcoming season. Vaccines are then produced based on this decision. There are both trivalent (active against 2 strains of influenza A and 1 strain of influenza B) and quadrivalent vaccines (2 strains of influenza A and 2 strains of influenza B) available

Antiviral Agents

Antiviral agents	Mechanism	HSV, VZV	CMV	Influenza A	Influenza B
Acyclovir 200–800 mg PO BID 5 × /day; 5–10 mg/kg IV q8h	Nucleoside analogues—activated by viral thymidine kinase, inhibit viral DNA polymerase (vDNAp); also incorporated into viral DNA and act as a chain terminator	++			
Valacyclovir 500–1000 mg PO daily–TID		++			
Famciclovir 250–1000 mg PO BID		++			
Penciclovir 10 mg/g topically q2h × 4 days	Applied topically for treatment of oral cold sores	++			
Ganciclovir 5 mg/kg IV q12h or 1000 mg PO TID (maintenance)	Nucleoside analogue that inhibits viral DNA polymerase	++	++		
Valganciclovir 900 mg PO daily–BID		++	+++		

Antiviral agents	Mechanism	HSV, VZV	CMV	Influenza A	Influenza B
Foscarnet 90 mg/kg IV q12–24 h	Pyrophosphate analogue that inhibits viral DNA polymerase	++	+++		
Cidofovir 5 mg/kg IV q week	Nucleoside analogue that inhibits viral DNA polymerase	++	+++		
Amantadine 100 mg PO BID	Inhibits M2 Protein (ion channel) of influenza A, blocking uncoating of virus genome within newly infected cells			++	
Rimantadine 100 mg PO BID				++	
Zanamivir 10 mg INH q12–24 h	Neuraminidase Inhibitors. Block release of influenza virus from infected cells			++	++
Oseltamivir 75 mg PO daily–BID				++	++

Coronavirus

This section addresses the ongoing coronavirus 19 (COVID-19) pandemic, caused by the SARS-CoV-2 virus. Data regarding the presentation, treatment, and prevention of COVID-19 is rapidly changing and the editors recommend consulting the most recent local guidance for management decisions

DIFFERENTIAL DIAGNOSIS

VIRAL PNEUMONIA—influenza A/B, parainfluenza, RSV, metapneumovirus, other coronaviruses, adenovirus, rhinovirus

BACTERIAL PNEUMONIA—*S. pneumoniae*, *S. aureus*, *Haemophilus*, *Moraxella*

ATYPICAL PNEUMONIA—*Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, TB, *Legionella*, non-TB mycobacteria

OTHER INFECTIOUS—pertussis, upper respiratory infections, ARDS from non-pulmonary source

NON-INFECTIOUS—heart failure decompensation, asthma, COPD exacerbation, PE, cryptogenic organizing pneumonia, aspiration pneumonitis, hypersensitivity pneumonitis, drug reaction, GERD, cocaine-induced lung injury, vasculitis

PATHOPHYSIOLOGY

CLASSIFICATION—SARS-CoV-2 virus is an enveloped, RNA virus in the *Coronaviridae* family, similar to MERS-CoV (Middle Eastern Respiratory

PATHOPHYSIOLOGY (CONT'D)

Syndrome, 2012) and SARS-CoV (Severe Acute Respiratory Syndrome, 2002)

TRANSMISSION—transmitted through respiratory droplets by individuals speaking, coughing, or sneezing. Also transmitted through fomites and aerosols. Initial zoonotic vector was the bat with possible intermediate transmission through the pangolin. First isolated from China's Wuhan province, where both zoonotic and human-to-human spread likely occurred. Vertical transmission from mother to infant is very uncommon

PATHOGENESIS—virus spike protein binds to the ACE2 receptor on nasal and bronchial epithelial cells to gain cellular entry. Type 2 alveolar epithelial cells are enriched in ACE2 receptors, hence the predominance of lower respiratory symptoms. Direct lymphocyte infection and destruction as well as activation of the innate immune response with proinflammatory factors suppressing lymphopoiesis cause lymphopenia. In severe infection, the pulmonary epithelial-endothelial barrier is compromised, causing neutrophilic invasion of the alveoli, then pulmonary edema with decreased diffusing capacity. Coagulopathy and fulminant DIC may also occur

INCUBATION AND INFECTIVITY—may incubate for up to 14 days. Median time to symptoms

PATHOPHYSIOLOGY (CONT'D)

is 4–5 days. Viral shedding may occur 2–3 days prior to symptoms but has been reported as early as 12 days prior to symptoms. Median time from initial symptoms to critical illness is 10 days. True asymptomatic infection is uncommon; 97.5% of those with a positive test result will become symptomatic

CLINICAL FEATURES

HISTORY—fever, cough, and fatigue are the most common symptoms. Other symptoms include headache, myalgias, pharyngitis, rhinorrhea, dyspnea, hemoptysis, nausea, vomiting, diarrhea, anosmia (high specificity), ageusia, altered mental status

PHYSICAL—maculopapular viral exanthem, conjunctivitis, urticaria, vasculitic lesions including livedo reticularis, purpura, and chilblains (“COVID toes”)

RISK FACTORS FOR SEVERE DISEASE—cardiac disease including CAD and HF, CKD, COPD, frailty, obesity, malignancy, sickle cell disease, solid-organ transplant recipients on immunosuppression, type 2 diabetes mellitus. Possible risk factors: moderate-to-severe asthma, CVD, cystic fibrosis, HIV, HTN, other immunosuppression, liver disease, pregnancy, IPF, thalassemia, tobacco use

COMPLICATIONS—bacterial co-infection (7%), viral co-infection (3%), acute kidney injury (5%), neurologic (CVA), hematologic (VTE, DIC), arrhythmia, myocarditis

PROGNOSIS—80% mild infection; 15% may need hospitalization and 5% critical care

- **PREDICTION TOOLS**—COVID-GRAM (CXR, age, dyspnea, unconsciousness, hemoptysis, comorbidities, cancer history, LDH, bilirubin, neutrophil-lymphocyte ratio); CALL score (comorbidities, age, lymphocyte count, LDH)
- **MORTALITY AND RECOVERY**—mortality increases with age (<0.1% if <18 years, 30% if >85 years). Recovery 2 weeks with mild illness but longer if severe disease
- **REINFECTION**—possible with emergence of multiple strains of SARS-CoV-2

INVESTIGATIONS

BASIC

- **LABS**—CBC (neutrophil/lymphocyte ratio, lymphopenia, thrombocytopenia), lytes, urea, Cr, AST, ALT, CRP, bilirubin, LDH, troponin
- **MICROBIOLOGY**—nasopharyngeal, nasal, or oropharyngeal swab for NAAT, blood C&S, sputum NAAT/Gram stain/C&S/AFB, urine culture
- **IMAGING**—CXR

INVESTIGATIONS (CONT'D)

SPECIAL

- **ABG**
- **COAGULOPATHY**—D-dimer, INR/PTT, fibrinogen
- **IMAGING**—CT chest, lung US
- **BAL/ETT ASPIRATE**—or other lower respiratory tract specimens for NAAT
- **LUMBAR PUNCTURE**
- **COVID-19 SEROLOGY**—consider testing immunocompromised and unvaccinated patients who may be candidates for Regen-COV (seronegative patients more likely to benefit)

MANAGEMENT

PREVENTION

- **PUBLIC HEALTH MEASURES**—masking, eye protection and handwashing reduce transmission in healthcare facilities, long-term care, and community settings. Physical distancing and mass gathering restrictions slow community transmission in the community. Contact tracing, testing and isolation measures important for suspected and confirmed cases, masking to limit pre-symptomatic transmission
- **IMMUNIZATION**—multiple types of vaccines in development including **inactivated whole virus** vaccines, **protein-based** vaccines (fragment of protein/protein shell to generate immune response), **viral vector** vaccines (virus genetically engineered to produce coronavirus proteins to generate immune response but cannot cause disease), and **RNA/DNA** vaccines (e.g. using messenger RNA, which is translated into target spike protein that elicits immune response). Four vaccines have been Health Canada approved for use (BNT162b2 [mRNA vaccine by Pfizer], mRNA1273 [mRNA vaccine by Moderna], ChAdOx1-S [adenovirus vector vaccine by Astra Zeneca] and Ad26.CoV2-S [adenovirus vector vaccine by J&J/Janssen])

TREATMENT SETTING

- **INFECTION CONTROL PRECAUTIONS**—contact and droplet isolation for all patients with suspected or confirmed COVID-19 infection. N95 is recommended for care of patients undergoing aerosol-generating medical procedures (AGMP). Cohort patients within specific units/facilities when possible, minimize inter-facility transfer
- **DISCONTINUING INFECTION CONTROL**—precautions may be discontinued when patients have been afebrile for >24 hours, had symptom onset >14 days prior, and respiratory symptoms improving. Repeat testing to remove precautions not indicated as PCR-based testing positive for many weeks but does not represent infectivity

MANAGEMENT (CONT'D)

- **PPE REQUIREMENTS**—surgical face mask, eye protection, disposable gloves, and gown required for contact and droplet precautions along with appropriate hand hygiene. N95 or equivalent respirator required for airborne precautions
- **AEROSOL GENERATING MEDICAL PROCEDURES**—intubation, bronchoscopy, NIPPV, bag-valve-mask ventilation. High-flow/humidified oxygen via nasal cannula, CPR, airway suctioning, sputum induction, nebulized medications may generate aerosols

TREATMENTS

- **OXYGENATION**—titrate supplemental oxygen to maintain SpO₂ 92–96%. High-flow nasal cannula is preferred over NIPPV. Early involvement of ICU services if decompensation occurs. Follow ARDS management for critically ill, ventilated patients including prone positioning, conservative fluids, and low tidal volume
- **ANTIMICROBIALS**—empiric treatment for bacterial pneumonia and influenza as per local guidance and seasonal patterns only if clinical suspicion for a pulmonary infection other than COVID-19 remains after clinical assessment
- **CORTICOSTEROIDS**—*dexamethasone* 6 mg PO/IV daily for 10 days or until discharge from hospital for patients requiring supplemental oxygen. Reduces mortality
- **ANTIVIRAL THERAPIES**
 - **REMDESIVIR**—causes premature termination of RNA transcription. *Remdesivir* 200 mg IV on day one, then 100 mg IV daily on days 2–10 for patients on mechanical ventilation or ECMO, or days 2–5 for patients on supplemental oxygen alone (may be extended to 10 days if no improvement or ended on day of discharge if < 5 days). May shorten time to clinical improvement. Limited by availability
 - **MOLNUPIRAVIR (LAGEVRIO)**—inhibits viral genome replication. *Molnupiravir* 800 mg PO every 12 hours for 5 days for patients with mild-moderate symptoms for < 5 days and at high risk for progression to severe COVID-19 (hospitalization or death). Reduced composite death/hospitalization outcome in interim analysis of MOVE-OUT
 - **NIRMATRELVIR WITH RITONAVIR (PAXLOVID)**—viral protease inhibitor with CYP inhibitor. *Nirmatrelvir* 300 mg with *ritonavir* 100 mg PO twice daily for 5 days for patients with mild-moderate symptoms for < 5 days and at high risk for progression to severe COVID-19 (hospitalization or death). Reduced compos-

MANAGEMENT (CONT'D)

- ite death/hospitalization outcome in interim analysis of EPIC-HR
- **ADJUNCTIVE THERAPY**—for patients with severe disease and high oxygen requirements or ventilation on dexamethasone and remdesivir, consider adding *baricitinib* (selective Janus kinase 1 and 2 inhibitor) 4 mg PO daily x 14 days or *tocilizumab* (monoclonal antibody against IL-6) 8 mg/kg IV x 1 dose
- **NEUTRALIZING ANTIBODIES**—monoclonal antibodies targeting the COVID-19 spike protein. For patients with mild-moderate symptoms at high risk for progression to severe COVID-19 (hospitalization or death) and/or those who either have significant immunosuppression preventing adequate serologic response to vaccination or who are unvaccinated and have a negative COVID-19 serologic test, consider one of the following: *casirivimab-imdevimab* (REGEN-COV) 1.2–1.2 g or 0.6–0.6 g IV x 1 dose; or *sotrovimab* (Xevudy) 500 mg IV x 1 dose. Each COVID-19 variant has a different susceptibility to neutralizing antibodies. Check the latest susceptibility reporting for efficacy against variants of interest

OTHER TREATMENT ISSUES

- **ANTICOAGULATION**—thromboprophylaxis with LMWH or sequential compression devices for inpatients. Consider therapeutic-dose LMWH for non-ICU inpatients with low risk of bleeding for the duration of hospitalization (increased survival to hospital discharge without need for organ support)
- **PALLIATIVE CARE**—assess patient frailty on admission. Distinguish between resource rationing and appropriateness of a therapy when explaining treatment decisions to patients. Consider appropriate pharmacotherapy for symptom control and goals of care discussions (see p. 431)
- **THERAPEUTIC MYTHS**
 - **HYDROXYCHLOROQUINE/CHLOROQUINE**—no evidence of benefit for treatment or prophylaxis, with or without azithromycin. Risk of cardiac arrhythmia
 - **IVERMECTIN**—for treatment of parasitic worms, head lice and rosacea. No evidence of benefit for treatment or prevention of COVID-19. High doses of ivermectin may lead to hypotension, ataxia, seizures and death
 - **RAAS BLOCKERS (ACE INHIBITOR OR ARB)**—no evidence of harm. Do not stop if patients appropriately on these medications
 - **NSAIDs**—no evidence of specific harm in COVID-19 patients

Fungal Infections

GENERAL APPROACH

CLASSIFICATION—fungal infections can be classified into 3 main categories: yeasts, molds (“filamentous fungi”), and dimorphic fungi

- **YEASTS**—grow as single cells (via budding) and include *Candida*, *Malassezia*, *Rodotorula*, *Trichosporon*
- **MOLDS**—filamentous fungi grow as hyphae (via sexual and asexual reproduction) and include *Aspergillus*, *Mucormycetes* (formerly *Zygomycetes*), *Fusarium*, and dematiaceous (pigmented) fungi. Ubiquitous in the environment (e.g. soil, decaying vegetation, water, air). Infection may cause blood vessel invasion, thrombosis, and obstruction. Clinical syndromes include cerebral parenchymal infections, pulmonary parenchymal infections, hepatosplenic abscesses, and otitis externa
- **DIMORPHIC FUNGI**—exist as both molds and yeasts and include *Coccidioides*, *Histoplasma*, *Blastomyces*, and *Cryptococcus*. At low temperatures, found as multicellular molds (which release spores that are inhaled). In warm temperatures (e.g. inside the body), inhaled spores germinate into yeasts, which are infectious to the patient, but no longer contagious (i.e. these patients do not require isolation)

CANDIDIASIS

PATHOPHYSIOLOGY—*C. albicans* (“germ-tube positive” with pseudohyphae) or non-*albicans* species (“germ-tube negative,” e.g. *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida krusei*, *Candida auris*), mostly in patients with hematological malignancy, neutropenia, immunosuppressed, IDU, or those in the ICU with hemodialysis, broad-spectrum antibiotics, surgery, central venous catheters, or parenteral nutrition

CLINICAL FEATURES—localized mucocutaneous infections (thrush and vaginitis), serious focal infections (endophthalmitis, meningitis, osteomyelitis), or disseminated infection (candidemia) with pustular skin lesions, retinal lesions. Candiduria is common in ICU patients, but usually represents colonization unless patient is symptomatic

TREATMENTS

- **OROPHARYNGEAL**—*nystatin* suspension (500,000 U) or *nystatin pastilles* (200,000 U) 4 × daily, *fluconazole* 100 mg PO/IV daily × 1–2 weeks
- **ESOPHAGITIS**—*fluconazole* 400 mg loading dose, then 200 mg PO/IV daily × 14 days
- **CANDIDURIA**—remove catheter, indications for treatment include kidney transplant recipients,

CANDIDIASIS (CONT'D)

prior to cystoscopy or invasive GU procedure, neonates, severe illness, *fluconazole* 200 mg PO/IV daily × 2 weeks

- **ACUTE DISSEMINATED CANDIDEMIA**—remove all intravascular devices. *Fluconazole* 800 mg IV loading dose, then 400 mg PO/IV daily × 2 weeks (minimum), or one of the echinocandins, including *caspofungin* 70 mg then 50 mg IV daily, *micafungin* 100 mg IV daily, or *anidulafungin* 200 mg loading, then 100 mg IV daily × 2 weeks (minimum) after last positive culture for *C. albicans*. Echinocandin is preferred for initial therapy in neutropenic patients. Almost all (>95%) *C. albicans* are sensitive to fluconazole. Some laboratories report *C. albicans* as “*C. albicans* complex” because of structural resemblance between *C. albicans* and *Candida dubliniensis*. This is of no clinical significance because *albicans* and *dubliniensis* have the same susceptibility patterns. Susceptibility patterns for other non-*albicans* infections may significantly differ. Consider echinocandin for non-*albicans* candidiasis
- **CANDIDA AURIS**—an emerging hospital acquired pathogen that can cause candidemia, otitis and disseminated disease. Often resistant to fluconazole and requires treatment with an echinocandin

2016 IDSA Update Guideline Candidiasis

ASPERGILLOSIS

MICROBIOLOGY—genus contains >185 species including *Aspergillus fumigatus* (80% of clinical infections), *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillus terreus*

PATHOPHYSIOLOGY—mostly in patients with neutropenia, organ or stem cell transplants, advanced AIDS, corticosteroids. Invasive aspergillosis has mortality of >50%

CLINICAL FEATURES—spectrum of pulmonary involvement includes colonization, pulmonary aspergilloma (“fungal ball”), allergic bronchopulmonary aspergillosis (ABPA), chronic necrotizing aspergillus pneumonia (CNPA), and invasive aspergillosis. Second most common cause of fungal endocarditis (after *Candida*). Cutaneous involvement may follow trauma or dissemination from respiratory tract

DIAGNOSIS—often difficult and may require biopsy with culture and histology. Check quantitative immunoglobulin, aspergillus IgG and IgE, galactomannan levels (suggestive of invasive aspergillosis). CT chest may show multiple nodular

ASPERGILLOSIS (CONT'D)

lesions (halo sign = nodule with surrounding hemorrhage, air crescent sign = necrosis and cavitation). Sputum fungal culture and eosinophils, bronchoalveolar lavage, or lung biopsy. The galactomannan assay is relatively specific for invasive aspergillosis, and, in the right clinical context, provides adequate evidence of invasive pulmonary disease. This assay can be done on serum or BAL specimens

TREATMENTS—*voriconazole* 6 mg/kg q12h × 24 h then 4 mg/kg IV q12h or 200 mg PO BID until resolved, Alternatives include *caspofungin* 70 mg then 50 mg IV q24h, lipid-formulation *amphotericin B* 3–5 mg/kg IV daily, *micafungin* 100–150 mg IV daily, *posaconazole* 200 mg PO QID then 400 mg BID after clinical stabilization. Some species, especially *A. terreus*, are resistant to amphotericin. *Aspergillus* is the only filamentous fungus that can be treated with echinocandins

2016 IDSA Update Guideline Aspergillosis

MUCORMYCOSES (FORMERLY CALLED ZYGOMYCOSIS)

MICROBIOLOGY—large group of filamentous fungi including *Rhizopus*, *Absidia*, *Rhizomucor*, *Mucor*, and *Cunninghamella*

PATHOPHYSIOLOGY—mostly affecting immunocompromised patients and those with diabetes. Prognosis extremely poor

CLINICAL FEATURES—CNS, pulmonary, GI, and cutaneous involvement. Infection can cause devastating rhino-orbital-cerebral and pulmonary infections

TREATMENTS—antifungal therapy frequently needs to be combined with surgical debridement. Empiric treatment options include lipid formulations of *amphotericin B* and *posaconazole*. Note that susceptibility testing of *Mucormycetes* (formerly *Zygomycetes*) is not always reliable, and that *caspofungin* and “azoles” (apart from *posaconazole*) are not generally effective

HISTOPLASMOSES

PATHOPHYSIOLOGY—*H. capsulatum* endemic along St. Lawrence seaway and in Midwestern states located along the Ohio and Mississippi River valleys. Symptoms typically occur in patients who are immunocompromised or exposed to a large inoculum

CLINICAL FEATURES—usually asymptomatic. Pulmonary manifestations may mimic sarcoidosis and include pneumonia (localized or diffuse), granuloma/cavitary lung lesions, and hilar and mediastinal lymphadenopathy. Pericarditis, arthritis, arthralgia and erythema nodosum may also occur without pulmonary symptoms. Disseminated disease may

HISTOPLASMOSES (CONT'D)

present with hepatosplenomegaly, pancytopenia, oropharyngeal ulcers, skin, and CNS involvement

DIAGNOSIS—fungal culture of blood and tissue, urine antigen, *Histoplasma* serology, and histopathology. *Histoplasma* is predominantly an intracellular pathogen; therefore cultures need to be placed in “isolator tube” (containing cell lysis product)

TREATMENTS—*itraconazole* 200 mg PO TID × 3 days, then 200 mg PO daily—BID, lipid formulation of *amphotericin B* (preferred for ill patients)

2007 IDSA Update Guidelines Histoplasmosis

CRYPTOCOCCOSIS

MICROBIOLOGY—dimorphic but unlike other dimorphic fungi (e.g. *Histoplasma*, *Blastomyces*, and *Coccidioides*), *Cryptococcus* is ubiquitous and not geographically isolated. *Cryptococcus neoformans* has two varieties: var. *neoformans* and var. *gattii*

PATHOPHYSIOLOGY

- **C. NEOFORMANS**—almost invariably in immunocompromised patients including HIV with CD4 < 100/mm³, transplantation, hematologic malignancies, chronic kidney diseases, diabetes mellitus, cirrhosis, or corticosteroid use. This pathogen is inhaled, then disseminates with predilection for CNS with meningitis more common than focal parenchymal infections
- **C. GATTII**—seen more commonly in immunocompetent hosts and paradoxically uncommon in immunosuppressed hosts. Symptomatic infection is usually pulmonary ± focal parenchymal brain infection

CLINICAL FEATURES—CNS (chronic meningitis), pulmonary, and cutaneous involvement (but may involve any organ)

TREATMENTS—**CNS infection** (lumbar puncture to lower intracranial pressure, *amphotericin B* plus *flucytosine*, followed by *fluconazole*), **pulmonary or cutaneous infection** (*fluconazole* or *itraconazole*)

2010 IDSA Update Guidelines Cryptococcal Disease

COCCIDIOIDOMYCOSIS

PATHOPHYSIOLOGY—endemic to lower deserts of southern Arizona, central California, southwestern New Mexico, and west Texas in USA. Also Mexico, Central and South America. Peak incidence from May–July and October–December. Affects mostly patients with immunosuppression

CLINICAL FEATURES—an acute pulmonary infection that is often asymptomatic, but can cause a flu-like illness or pneumonia. Pulmonary

COCCIDIOIDOMYCOSIS (CONT'D)

symptoms include chest pain, cough, fever, and hemoptysis if cavitary lesions. Radiologically, unilateral infiltrate and hilar adenopathy are common. Cutaneous symptoms include erythema nodosum and erythema multiforme. Most common sites of dissemination are skin, bone, and meninges

DIAGNOSIS—fungal culture and serology. Note that *Coccidioides* is a level 3 pathogen. Therefore, cultures should be processed in **high-level isolation unit** and labeled carefully to avoid iatrogenic infection of laboratory personnel
TREATMENTS—usually resolves spontaneously if uncomplicated disease. Antifungal therapy may need to be combined with surgery for certain pulmonary infections. *Fluconazole* 400 mg PO daily, *itraconazole* 200 mg PO daily (duration dependent on site of infection and may last months to years). *Coccidioides* meningitis should be treated with amphotericin B

2016 IDSA Guideline Coccidioidomycosis

BLASTOMYCES

PATHOPHYSIOLOGY—mostly found in north-west Ontario, the Great Lakes, and some Eastern states (e.g. Ohio, Mississippi River valley). Infection occurs by inhalation of aerosolized spores from soil
CLINICAL FEATURES—asymptomatic infection is common. Pulmonary symptoms of acute or chronic pneumonia (incubation time 45–100 days). Extrapulmonary dissemination to skin, bone/joint, GU tract, usually associated with pulmonary disease

DIAGNOSIS—fungal culture. Presence of “broad-based budding yeast” in clinical specimens strongly suggests *Blastomyces*

TREATMENTS—amphotericin B or lipid formulation for moderate-to-severe disease or CNS involvement. Itraconazole for mild disease or step-down but has poor blood–brain barrier penetration; alternatives are voriconazole or fluconazole

2008 IDSA Update Guideline Blastomycosis

INDICATIONS FOR VORICONAZOLE

INVASIVE ASPERGILLOSIS—first line treatment for invasive and CNS

INVASIVE CANDIDIASIS—second or third line treatment for patients who are refractory or intolerant of fluconazole (first line for some)

FUNGEMIA—empiric treatment for fungi not yet speciated where neither amphotericin B nor fluconazole can be used

FEBRILE NEUTROPENIA—empiric antifungal treatment for patients with suspected aspergillus infection

INDICATIONS FOR CASPOFUNGIN/MICAFUNGIN

INVASIVE ASPERGILLOSIS—third line treatment for patients who are refractory or intolerant of voriconazole (first line) or amphotericin B (second line)

INVASIVE CANDIDIASIS—second line treatment for patients who are refractory or intolerant of fluconazole (first line for some)

FUNGEMIA—empiric treatment for fungi not yet speciated where neither amphotericin B nor fluconazole can be used

FEBRILE NEUTROPENIA—empiric antifungal treatment

TREATMENT DEFINITIONS

REFRACTORY—persistence of positive cultures or lack of clinical response despite ≥ 5 days of therapy and removal of catheter if applicable

INTOLERANCE—serum creatinine doubling from baseline and $\geq 450 \mu\text{mol/L}$ [$\geq 5.1 \text{ mg/dL}$], tripling of serum creatinine from baseline, creatinine clearance $\leq 40 \text{ mL/min}$ or concomitant administration of nephrotoxins, documented allergy, or intolerable infusion reactions

Antifungal Agents

	Mechanism	<i>Candida</i>	<i>Cryptococcus</i>	<i>Aspergillus</i>	Other molds ^a	Dimorphic ^b	Mucoromycota ^c	Renal adjustments
Azoles								
Fluconazole ^d 100–400 mg PO/ IV daily	Inhibits CP450 (convert lanosterol to ergosterol on cell membrane)	++C. alb	+++			+		Yes (dose)
Itraconazole ^e 100–200 mg PO daily–BID		+++		++	++	++		No
Voriconazole ^f 4 mg/ kg IV q12h or 200 mg PO BID		+++		+++	++Fusa/ Scedo	++		No but avoid IV form

Antifungal Agents (Cont'd)

	Mechanism	<i>Candida</i>	<i>Cryptococcus</i>	<i>Aspergillus</i>	Other molds ^a	Dimorphic ^b	Mucormycota ^c	Renal adjustments
Posaconazole 200 mg PO QID		+++	+++	+++	+++Fusa	++	+++	No
Amphotericin B^d								
Amphotericin B 0.3–1 mg/kg IV q24h	Binds to ergosterol on cell wall, causing cell leakage	+++	+++	++	+	+++	+++	Yes (interval)
Liposomal AmphoB 3–5 mg/kg IV q24h		+++	+++	++	+	+++	+++	Yes (interval)
AmphoB colloidal dispersion		+++	+++	++	+	+++	+++	Yes (interval)
AmphoB lipid complex 5 mg/kg IV q24h		+++	+++	++	+	+++	+++	Yes (interval)
Echinocandin^e								
Caspofungin 70 mg then 50 mg IV q24h	Inhibits synthesis of β-1,3-d-glucan on cell wall	+++		+++	+Scedo	+/-		No
Micafungin 150 mg IV q24h		+++		+++				No
Anidulafungin 200 mg then 100 mg IV q24h		+++		+++				No
5-Flucytosine 5 Flucytosine	Inhibits synthesis of DNA (thymidylate synthetase)	+++	+++				++	Yes (dose)

^aother than *Aspergillus*, *Fusarium*, *Scedosporium*, and *Pseudallescheria boydii* are all examples of molds

^bdimorphic fungi include *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, and *Sporothrix schenckii*

^c*Mucormycota* fungi include *Rhizopus*, *Mucor*, and *Absidia*

^dfluconazole is ineffective against some *Candida*, molds, and *Mucormycetes* (formerly *Zygomycetes*)

^eitraconazole is ineffective against some *Candida*, *Scedosporium*, and *Mucormycetes* (formerly *Zygomycetes*). It has activity against *Cryptococcus*, but has less CSF penetration than fluconazole

^fvoriconazole is ineffective against some *Candida*, *Scedosporium*, and *Mucormycetes* (formerly *Zygomycetes*). It has activity against *Cryptococcus*, but has less CSF penetration than fluconazole

^gamphotericin B is ineffective against molds (*Fusarium*, *Scedosporium*, *Trichosporium*, *Aspergillus terreus*), *C. guilliermondii* and *C. lusitanae*

^hcasprofungin is ineffective against *Mucormycetes* (formerly *Zygomycetes*), *Cryptococcus*, and *Fusarium* but probably has activity against other molds

Infection Control

NOSOCOMIAL INFECTIONS

DEFINITION—infections acquired in hospital that occur between 48 and 72 h after admission and up to 72 h after discharge (up to 30 days for surgical procedures)

URINARY TRACT INFECTIONS—secondary to urinary catheters. Infection rates are 1–5%, up to 100% for long-term catheterization. Complications include cystitis, prostatitis, pyelonephritis, and urosepsis

VENTILATOR-ASSOCIATED PNEUMONIAS—secondary to mechanical ventilation (after >48 h, p. 107)

NOSOCOMIAL INFECTIONS (CONT'D)

BACTEREMIA—secondary to peripheral central venous catheters. Infection rates are 1–5%

SURGICAL SITE INFECTIONS

PREVENTION STRATEGIES—hand washing critical! Education, isolation, and surveillance are important. Practice routine/standard/universal precautions with the use of gloves when handling all body fluids except sweat. Always use sterile technique when inserting urinary and central venous catheters. Minimize NG tube insertion and keep patient head of bed 30–45° if intubated. Ensure receipt of prophylactic antibiotics prior to surgical procedures.

NOSOCOMIAL INFECTIONS (CONT'D)**ISOLATION**

- **AIRBORNE** (negative pressure room with high-efficiency particulate aerator filter, fit tested N95 respirator for personal protection)—varicella, TB, measles
- **DROPLET** (mask within 3–6 ft; eye protection, gown and gloves)—*H. influenza B*, *N. meningitidis*, invasive group A strep (for first 24 hours of appropriate antibiotics) influenza, coronavirus, RSV, pertussis, parainfluenza, adenovirus, human metapneumovirus and other respiratory viruses
- **CONTACT** (glove, gown, wash hands)—*C. difficile*, VRE, MRSA, carbapenem-resistant organism (CRO), ESBL

N. MENINGITIDIS PROPHYLAXIS

- **CHEMOPROPHYLAXIS**—for exposures in last 7 days with *ciprofloxacin* 500 mg PO \times 1 dose or *rifampin* 600 mg PO BID \times 2 days can be used to reduce the risk of *N. meningitidis* in “close contacts.” Vaccines not recommended for primary prophylaxis post-exposure, but may be useful for epidemic control on a population basis
- **CLOSE CONTACTS**—defined as healthcare workers with direct exposure to respiratory secretions (e.g. mouth-to-mouth resuscitation or intubation), household members, intimate contacts, children in school environments, coworkers in the same office, young adults in dormitories, and recruits in training centers. Not recommended for most medical personnel (i.e. those without direct exposure to patient’s oral secretions) or for casual or indirect contacts (e.g. school or workmates)

NEEDLE STICK INJURY

PREVENTION—routine/standard/universal precautions (gloves, gowns, masks if risk of exposure of body fluids), never recap needles, education

NEEDLE STICK INJURY (CONT'D)

PRE-EXPOSURE PROPHYLAXIS—immunization (hepatitis B vaccine at 0, 1, 6 months)

RISK OF TRANSMISSION—depends on the mechanism of exposure, source patient characteristics, pre and post-exposure prophylaxis

- **HBV**—6–30% if source positive
- **HCV**—1.8% if source positive
- **HIV**—0.3% if source positive

POST-EXPOSURE PROCEDURE

- **SOURCE PATIENT TESTING**—HBV, HCV, HIV
- **EXPOSED PERSON BASELINE TESTING**—HBV, HCV, HIV (ELISA, Western), CBC, lytes, urea, Cr, AST, ALT, ALP, bili
- **HBV PROPHYLAXIS**—HB Ig (only if source patient is HBsAg positive or unknown and the exposed person is unvaccinated) and start vaccination for HBV
- **HIV PROPHYLAXIS**—antiretroviral therapy for 30 days (if source patient HIV positive or source patient unknown and high risk). Therapy should include dolutegravir and tenofovir/emtricitabine. If source patient ARV resistance testing known, post-exposure procedure can be tailored accordingly. Treatment started within 4 h
- **COUNSELING**—protective sexual intercourse, hold blood donation and breastfeeding, side effects of prophylactic medication(s), follow-up in 2 weeks

PROPHYLAXIS FOR OTHER INFECTIOUS

AGENTS—diphtheria (penicillin or erythromycin), pertussis (trimethoprim–sulfamethoxazole, erythromycin), rabies (rabies immune globulin, vaccine), varicella zoster (varicellazoster immune globulin, vaccine), hepatitis A (immune globulin, vaccine)

PRE-EXPOSURE PROPHYLAXIS—PrEP for prevention of HIV infection indicated in those at high risk for infection. Treatment generally consists of tenofovir/emtricitabine given daily with quarterly follow up for HIV Ab, and other STI testing

Immunization for Adults

Canadian Immunization Guide:
Vaccination of Specific Populations

NOTE—Vaccination schedule varies by jurisdiction. Please consult local guidelines for recommendations.

Immunization for Adults (Cont'd)				
Vaccine	Type	Schedule	Indications	Contraindications
Viral vaccines				
Measles SC	Live	0, +1 months (if high risk)	All adults not previously immunized in childhood	Preg, immunocomp.
Mumps SC	Live	0, +1 months (if high risk)	All adults not previously immunized in childhood	Preg, immunocomp.
Rubella SC	Live	0, +1 months (if high risk)	All adults not previously immunized in childhood	Preg, immunocomp.
Polio IM/SC	Inactivated	–	Not routinely recommended for adults	–
HBV IM	Recombinant	0, +1 months, +6 months	All adults not previously immunized in childhood, particularly high-risk groups for parenteral or sexual exposure, chronic liver disease (e.g. chronic HCV/HBV), chronic renal disease, healthcare workers, MSM, household and sexual contacts of those with chronic HBV, those with or evaluated for STDs	–
HAV IM	Inactivated	0, +6 months	Travelers (esp. developing world), chronic liver disease (e.g. chronic HCV/HBV), MSM, ?food handlers	–
Influenza IM	Inactivated	Annually (Oct)	Available and recommended for all adults	
Varicella SC	Live	0, 1–2 months	All who have not had chicken pox by adulthood, especially healthcare workers	Preg, immunocomp.
Herpes zoster SC	Live	1 dose	Adults >60 years. Note this vaccine has higher dose of attenuated virus than varicella vaccine	Preg, immunocomp, no history of varicella
HPV IM	Recombinant	0, +1–2 months, +6 months	Females aged 9–26 years (licensed also for males in some countries) Controversial as outcomes data pending	–
Bacterial vaccines				
Pertussis	Cellular	1 dose	All adults not previously immunized in childhood; single dose of acellular pertussis vaccine combined with tetanus/diphtheria (Tdap) recommended for adults aged 19–64	–

Immunization for Adults (Cont'd)

Vaccine	Type	Schedule	Indications	Contraindications
Td (tetanus, diphtheria) IM	Toxoid, inactivated	0, +2 months, +6–12 months, q10 year	All adults not previously immunized in childhood (see Tdap under Pertussis)	–
Pneumococcal IM/SC	Polysaccharide	0, +5 year	Adults >65 years, >6 months–50 years with chronic disease, pregnancy, splenectomy, malignancy, smokers	–
Haemophilus type B	Conjugated	1 dose	Splenectomy	–
Meningococcal SC	Polysaccharide	1 dose	Splenectomy, college dormitory students, lab workers, travelers to endemic areas	–

PRINCIPLES

RISK FACTORS FOR SPECIFIC ORGANISMS

- **HBV**—household contacts/sexual partners of hepatitis patients, IDU, homosexual, multiple sexual partners, tattoo, piercing, transfusions, healthcare workers (prior to vaccine era), residents/workers of institutions for mentally ill or criminals, birth in endemic country
- **HCV**—sexual partners (controversial), IDU, tattoo, piercing, transfusions, residents/workers of institutions for mentally ill or criminals

PRINCIPLES (CONT'D)

- **PNEUMOCOCCAL, MENINGOCOCCAL, H. INFLUENZAE**—splenectomy

CONTRAINDICATIONS

- **ALL VACCINES**—anaphylaxis, severe illness
- **LIVE VACCINES**—pregnancy, immunocompromised (B-cell depleting therapies, high dose corticosteroids, monoclonal biologic agents, AIDS but not HIV, malignancies)

SIDE EFFECTS—local erythema, fever



Septic Arthritis

DIFFERENTIAL DIAGNOSIS OF MONOARTHRITIS

★ ICU RN ★

INFECTIONS

- **BACTERIAL**—Gonococci, *Staphylococcus aureus*, *Streptococcus*, Enterobacteriaceae, *Borrelia burgdorferi*, Syphilis, Whipple disease, mycobacteria
- **VIRAL**—HIV, HBV, parvovirus, rubella, mumps, enterovirus, adenovirus
- **FUNGAL**—*Cryptococcus*, *Blastococcus*
- **OSTEOMYELITIS/OSTEONECROSIS EXTENDING TO JOINT**

CRYSTAL—gout, pseudogout, hydroxyapatite, basic calcium phosphate

UNCLASSIFIED

- **OSTEOARTHRITIS**
- **HEMARTHROSIS**—coagulopathy, thrombocytopenia, pigmented villonodular synovitis, trauma
- **NON-ARTHRITIS**
 - **BONE**—osteomyelitis, avascular necrosis, fracture
 - **SOFT TISSUE**—tendonitis, ligament tear, bursitis, myositis, meniscus tear

RHEUMATOLOGIC (early stage, unusual presentation as monoarthritis)

- **SEROPOSITIVE ★ PSSR ★**—Polymyositis, Palindromic rheumatism, SLE, Scleroderma, Rheumatoid arthritis
- **SERONEGATIVE ★ PEAR ★**—Psoriatic arthritis, Enteric arthritis, Ankylosing spondylitis, Reactive arthritis
- **SARCOIDOSIS, POLYMYALGIA RHEUMATICA**

NEOPLASTIC—chondrosarcoma, osteoid osteoma, metastasis

PATHOPHYSIOLOGY

RISK FACTORS—50% of sexually active adults with septic arthritis are due to gonococcal infections. Most patients with risk factors for septic arthritis listed below are due to non-gonococcal

PATHOPHYSIOLOGY (CONT'D)

infections (*S. aureus*, Streptococci, Gram-negative bacilli)

- **COMORBIDITIES**—diabetes, chronic kidney disease, rheumatologic disease, cancer
- **TREATMENT RELATED**—immunosuppressive therapy (glucocorticoids, cytotoxic agents), prosthetic joint
- **SPECIFICS**—IDU (more axial joints with MRSA, Gram-negative especially *Pseudomonas*), endocarditis (sterile fluid as autoimmune process)

GNONOCOCCAL ARTHRITIS—less destructive and better outcomes than non-gonococcal arthritis. Synovial fluid Gram stain + in <10% and culture often negative

COMPLICATIONS—osteomyelitis (30%), permanent joint damage, sepsis

CLINICAL FEATURES

HISTORY—arthritis (location, duration, pain, range of motion, function), adenopathy, fever, rash, oral ulcers, alopecia, Raynaud phenomenon, photosensitivity, sicca, trauma, recent infections, cervical/urethral discharge, sexual encounters, diarrhea, recent travel, past medical history (pre-existing joint disease, gout, rheumatoid arthritis, SLE, IBD, psoriasis, diabetes, IDU), medications (anticoagulants)

PHYSICAL—vitals (fever), joint examination (tenderness, swelling, range of motion). Look for nail pitting, onycholysis, tophi, rheumatoid nodules, track marks, psoriasis, keratoconjunctivitis sicca, uveitis, conjunctivitis, episcleritis, murmurs, urethral discharge, and penile ulcers. Soft tissue injuries (bursitis, tendonitis, muscles) usually have decreased active range of motion but normal passive range of motion, while both active and passive range of motion would be affected in joint diseases. Pelvic examination to inspect the cervix and to look for pelvic inflammatory disease

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES:
DOES THIS ADULT PATIENT HAVE SEPTIC
ARTHRITIS?

Investigations	Sens (%)	Spc (%)	LR+	LR-
Elevated WBC	90	36	1.4	0.28
Elevated ESR	95	29	1.3	0.17
Elevated CRP	77	53	1.6	0.44
Synovial fluid analysis				
WBC >100,000/mL	29	99	28	0.71
WBC >50,000/mL	62	92	7.7	0.42
WBC >25,000/mL	77	73	2.9	0.32
PMN \geq 90%	73	79	3.4	0.34

APPROACH—“when evaluating a patient with a painful, peripheral, swollen joint, the underlying pathology of a monoarthritis may be difficult to diagnose by clinical history and examination alone due to nonspecific symptoms and signs. Identifiable risk factors and arthrocentesis are most helpful in predicting septic arthritis. In particular, synovial WBC count and percentage of polymorphonuclear cells provide the best utility in identifying septic arthritis while waiting for Gram stain and culture test results. There is no evidence that a patient’s symptoms or the physical examination are useful for predicting non-gonococcal bacterial arthritis.”

Margaretten et al. *JAMA* 2007;297(13)

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, uric acid, ANA, RF, ESR, CRP, INR, PTT
- **IMAGING**—joint X-ray (chondrocalcinosis in pseudogout; the presence of crystals does not rule out sepsis) +/- MRI or bone scan
- **ARTHROCENTESIS**—★3C★ (Cell count with diff, Culture and Gram stain, Crystals)

SPECIAL

- **INFECTIOUS WORKUP**—urethral/rectal swabs, blood C&S

DIAGNOSTIC ISSUES

GOLDEN RULE—patients with monoarthritis have septic arthritis until proven otherwise. Joint infection is a rheumatologic emergency as permanent damage can occur. Presence of crystal does not rule out infection. In up to 75% of patients with septic arthritis, a focus of infection may be found

DIAGNOSTIC ISSUES (CONT'D)

ARTHROCENTESIS FLUID ANALYSIS

	Normal	Non- Infectious	Infectious	Septic
WBC (/mm ³)	<200	200–2000	2000–50,000	>50,000
PMNs	<25%	<25%	25–50%	>50%

JOINT ASPIRATIONS/INJECTIONS—for diagnostic and sometimes therapeutic reasons. Overlying infection at site of injection is absolute contraindication. Relative contraindications: significant hemostasis defects and bacteremia

- **KNEE**—flex 10–15°, enter either medially or laterally immediately beneath the undersurface of the patella slightly above midway
- **ANKLE**—foot perpendicular to leg, medial approach immediately medial to the extensor hallucis longus tendon. Lateral approach just distal to fibula
- **WRISTS**—flex slightly. Medial approach at dorsal surface between the distal ulna and the carpal bones. Lateral approach at dorsum just distal to the end of the radius, between the extensor tendons of the thumb
- **ADVERSE EFFECTS OF ASPIRATIONS/INJECTIONS**—hypersensitivity to anesthetic, pain, infection, tendon rupture, subcutaneous atrophy, post-injection flare, systemic steroid absorption, hemorrhage, steroid arthropathy

Thomsen et al. *NEJM* 2006;354(e19)

MANAGEMENT

ALWAYS ASPIRATE BEFORE PROCEEDING
TO TREATMENT

SYMPTOM CONTROL—NSAIDs/opioids for pain

TREAT UNDERLYING CAUSE—**joint drainage by therapeutic arthrocentesis, arthroscopic or surgical drainage** (if joint inaccessible to needle drainage, organism resistant to antibiotics, or no clinical response in 3–4 days). **Empiric** (if not at risk for sexually transmitted disease, *nafcillin* 2 g IV q4h or *vancomycin* 1 g IV q12h, plus *ceftriaxone* 1 g IV q24h. If at risk of sexually transmitted disease, *ceftriaxone* 1 g IV q24h + *azithromycin* 1g PO x 1 day if Gram stain negative). **Gonococcal** (*ceftriaxone* 1 g IV q24h). **Lyme arthritis** (*amoxicillin* 500 mg PO TID, *doxycycline* 100 mg PO BID, or *cefuroxime* 500 mg PO BID x 28 days)

Gout

2020 ACR Guidelines Management of Gout 2020

CAUSES

DECREASED URATE EXCRETION (90%)

- **RENAL DISEASE**
- **DRUGS** ★**CAN'T LEAP**★—Cyclosporine, Alcohol, Nicotinic Acid, Thiazides, Loop diuretics, Ethambutol, ASA (low dose), Pyrazinamide

INCREASED URATE PRODUCTION (10%)

- **METABOLIC SYNDROME**—obesity, hyperlipidemia, hypertension
- **INCREASED METABOLISM**—alcohol, hemolytic anemia, psoriasis, Lesch–Nyhan syndrome
- **NEOPLASTIC**—myeloproliferative disease, lymphoproliferative disease, chemotherapy

PATHOPHYSIOLOGY

IMBALANCE—decreased urate excretion and/or increased urate production → uric acid crystals deposited in joints, skin, and kidneys → arthritis, tophi, and renal failure. Gout almost never occurs in pre-menopausal women (estrogen promotes higher urinary fractional excretion of urate)

PRECIPITANTS—surgery, dehydration, fasting, binge eating/drinking, exercise, trauma

CLINICAL FEATURES

SYMPTOMS

- **ARTHRITIS**—mono/oligo and asymmetric, especially first MTP joint. Podagra, inflammation of the first MTP joint, is the presenting symptom in 75% of gout patients. However, the first MTP is also commonly affected in pseudogout, psoriatic arthritis, sarcoidosis, osteoarthritis, and trauma
- **TOPHI**—yellowish-white nodular urate crystals collection in subcutaneous tissues (particularly colder extremities such as ear, fingers, olecranon bursa, ulnar aspect of forearm), bone, tendons (Achilles), cartilage, and joints. Generally painless but may lead to erosions
- **KIDNEYS**—urolithiasis (radiolucent), uric acid nephropathy (reversible acute renal failure secondary to acute lysis), urate nephropathy (chronic renal failure secondary to interstitial deposits)

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, uric acid (sens 75%), AST, ALT, ALP, bilirubin, TSH, urinalysis, 24-h urine uric acid collection (<800 mg/day suggests ↓ excretion)
- **IMAGING**—joint X-ray, dual energy CT, MSK US
- **ARTHROCENTESIS**—★**3C**★ (Cell count with diff, Culture and Gram stain, Crystal, for gout, sens 85%, spc 100%)

SPECIAL

- **TOPHUS ASPIRATION**

DIAGNOSTIC ISSUES

SERUM URIC ACID LEVELS—may be falsely lowered in an acute attack

JOINT X-RAY—soft tissue swelling, normal joint space, erosions (“punched out” and sclerotic lesions with overhanging edge)

JOINT ULTRASOUND—double contour sign, visible tophi

JOINT FLUID—ALWAYS confirm diagnosis with a synovial fluid aspirate if possible. Microscopy shows predominantly neutrophilic infiltrate with some intracellular monosodium urate crystals (needle shaped, negative birefringence, i.e. yellow when parallel to plane of polarized light)

MANAGEMENT

ACUTE—**NSAIDs** (first line, avoid if renal/hepatic failure; *naproxen* 375–500 mg PO BID × 3 days, then 250–375 mg PO BID × 4–7 days; *indomethacin* 25–50 mg PO TID × 3 days, then 100 mg PO div BID–QID × 4–7 days; *celecoxib* 200 mg PO BID × 1 day, then 100 mg PO BID × 6–10 days). **Systemic corticosteroids** (avoid if joint sepsis not excluded; *prednisone* 30–60 mg PO daily × 3 days, then ↓ 10–15 mg daily × 3 days until discontinuation, *triamcinolone* 50 mg IM × 1 dose). **Intra-articular corticosteroids** (for mono- and oligoarthritis only. *Methylprednisolone* 40–80 mg intra-articularly once). **Colchicine** 0.6 mg PO daily-BID during acute attack (avoid approach of giving colchicine q1h until development of diarrhea). Low dose colchicine regimens (≤1.8 g daily) as effective and are better tolerated than higher dose regimens. **Anakinra** (anti-IL1R) 100 mg subcutaneously daily × 3 days

MANAGEMENT (CONT'D)

LONG-TERM MANAGEMENT—purine-restricted diet (↓ red meats, ↓ seafood, ↑ low-fat dairy products, ↑ fruit and vegetables) have limited supportive evidence. Avoidance of beer and sugar-laden beverages. Xanthine oxidase inhibitors: **Allopurinol** 50–300 mg PO daily (first line, xanthine oxidase inhibitor, renal dose adjustment required; continue allopurinol if already on it prior to acute attack). **Febuxostat** 80 mg PO daily can be used in patients intolerant of allopurinol or with mild-to-moderate renal failure; however, need to discuss increased CV risk. **Probenecid** 250–1000 mg PO BID (first line uricosuric, ↓ renal urate reabsorption; ensure normal renal function and use with caution in G6PD deficiency). **Colchicine** 0.6 mg PO BID×6 months (for prophylaxis against recurrent attacks only. Do not give colchicine IV)

TREATMENT ISSUES

LONG-TERM THERAPY—consider if patients have frequent attacks (≥2/year, tophaceous deposits, CKD, history of urolithiasis)

ALLOPURINOL OR FEBUXOSTAT TREATMENT—start colchicine or NSAIDs prior to allopurinol and overlap therapy to prevent precipitating flare. Allopurinol alone can cause an abrupt decrease in serum uric

TREATMENT ISSUES (CONT'D)

acid → breakdown and release of synovial urate crystal deposits → inflammation. Aim to decrease serum uric acid level below 357 μmol/L [6 mg/dL]. Do not start or stop allopurinol during an acute attack

SPECIFIC ENTITIES

CALCIUM PYROPHOSPHATE DEPOSITION DISEASE (CPPD, pseudogout)—associated with normal urate levels and chondrocalcinosis that may be visible radiographically. Rhomboid crystals, positive birefringence (blue when parallel to polarized light, yellow when perpendicular). Risk factors: old age, advanced osteoarthritis, neuropathic joint, gout, hyperparathyroidism, hemochromatosis, diabetes, hypothyroidism, hypomagnesemia, and trauma

BASIC CALCIUM PHOSPHATE CRYSTALS (BCPC)—crystals appear snowball-like with Alizarin Red S stain. Implicated in bursitis, inflammation superimposed on osteoarthritis, and calcinosis cutis in systemic sclerosis and CREST

DIALYSIS PATIENTS—develop destructive arthritis and tendonitis from calcium oxalate, monosodium urate, calcium pyrophosphate, and basic calcium phosphate crystals. Amyloidosis may also contribute to arthritis

Polyarticular Joint Pain and Fever**DIFFERENTIAL DIAGNOSIS**

★RICE★

RHEUMATOLOGIC

- **SEROPOSITIVE**—SLE, rheumatoid arthritis
- **SERONEGATIVE**—psoriatic arthritis, enteric arthritis, reactive arthritis, ankylosing spondylitis
- **VASCULITIS**—granulomatosis with polyangiitis, Behçet disease, Still disease

INFECTIONS

- **BACTERIAL**—septic (gonococci), meningococci, endocarditis, Lyme disease, Whipple disease, mycobacteria
- **VIRAL**—parvovirus, rubella, HBV, HCV, HIV, EBV
- **FUNGAL**
- **POST-INFECTIOUS/REACTIVE**—enteric infections (*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*), genitourinary infections

DIFFERENTIAL DIAGNOSIS (CONT'D)

(*Chlamydia*), rheumatic fever, inflammatory bowel disease

CRYSTAL—gout, pseudogout

ETC

- **MALIGNANCIES**—acute leukemia
- **SARCOIDOSIS**—Lofgren syndrome
- **FAMILIAL MEDITERRANEAN FEVER**
- **POLYMYALGIA RHEUMATICA**

CLINICAL FEATURES**DISTINGUISHING FEATURES**

- **TEMPERATURE >40 °C (>104 °F)**—Still disease, bacterial arthritis, SLE
- **FEVER PRECEDING ARTHRITIS**—viral arthritis, Lyme disease, reactive arthritis, Still disease, bacterial endocarditis
- **MORNING STIFFNESS**—RA, PMR, Still disease, some viral/reactive arthritis

CLINICAL FEATURES (CONT'D)

- **MIGRATORY ARTHRITIS**—rheumatic fever, gonococemia, meningococemia, viral arthritis, SLE, acute leukemia, Whipple disease
- **EPISODIC RECURRENCE**—palindromic rheumatism, Lyme disease, crystal-induced arthritis, IBD, Whipple disease, familial Mediterranean fever, Still disease, SLE
- **PAIN DISPROPORTIONATELY GREATER THAN EFFUSION**—rheumatic fever, familial Mediterranean fever, acute leukemia, AIDS
- **EFFUSION DISPROPORTIONATELY GREATER THAN PAIN**—tuberculosis arthritis, bacterial endocarditis, IBD, giant cell arteritis, Lyme disease
- **SYMMETRIC SMALL JOINT SYNOVITIS**—RA, SLE, viral arthritis
- **LEUKOCYTOSIS** ($>15 \times 10^9/L$)—bacterial arthritis, bacterial endocarditis, Still disease, systemic vasculitis, acute leukemia
- **LEUKOPENIA**—SLE, viral arthritis
- **POSITIVE RHEUMATOID FACTOR**—RA (sens 70%, spc 70%), viral arthritis, tuberculosis arthritis, bacterial endocarditis, SLE, sarcoidosis, systemic vasculitis
- **POSITIVE ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES**—RA (not sensitive but highly spc 95%)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, uric acid, TSH, ESR, CRP, RF, anti-CCP, ANA,

Rheumatoid Arthritis**DIFFERENTIAL DIAGNOSIS OF INFLAMMATORY POLYARTHRITIS****★RICE★****RHEUMATOLOGIC (>6 weeks)**

- **SEROPOSITIVE ★PSSR★**—Polymyositis, Palindromic rheumatism, SLE, Scleroderma, Sjögren syndrome, Rheumatoid arthritis
- **SERONEGATIVE ★PEAR★**—Psoriatic arthritis, Enteric arthritis, Ankylosing spondylitis, Reactive arthritis, undifferentiated
- **VASCULITIS**—granulomatosis with polyangiitis, Behçet disease, Still disease

INFECTIONS (<6 weeks)

- **BACTERIAL**—sepsis, endocarditis, Lyme disease, Whipple disease, mycobacteria

INVESTIGATIONS (CONT'D)

- serologies (*B. burgdorferi*, streptococci, parvovirus, HBV, HCV, HIV), c-ANCA, urinalysis
- **IMAGING**—CXR, X-rays of affected joints

SPECIAL

- **ARTHROCENTESIS**—★3C★ (Cell count with diff, Culture and Gram stain, Crystal)

MANAGEMENT**TREAT UNDERLYING CAUSE SYMPTOM CONTROL****SPECIFIC ENTITIES****ADULT-ONSET STILL'S DISEASE**

- **PATHOPHYSIOLOGY**—unknown. Most consider this a diagnosis of exclusion
- **DIAGNOSIS**—major criteria: fever $\geq 39^\circ C$ [$\geq 102.2^\circ F$] (quotidian vs. diquotidian), salmon color maculopapular rash, arthralgia/arthritis ≥ 2 weeks, leukocytosis. Minor criteria: pharyngitis, lymphadenopathy, abnormal liver enzymes, hepatomegaly/splenomegaly, negative ANA, and negative RF. Need at least 2 major criteria and 3 minor criteria to make diagnosis (sens 93%). Important to exclude infections, malignancy, and acute rheumatologic disease. Significantly elevated serum ferritin
- **TREATMENTS**—NSAIDs, corticosteroids, methotrexate, recombinant IL-1 receptor antagonist (anakinra); IL-6 antagonist

DIFFERENTIAL DIAGNOSIS OF INFLAMMATORY POLYARTHRITIS (CONT'D)

- **VIRAL**—parvovirus, rubella, HBV, HCV, HIV
- **FUNGAL**
- **POST-INFECTIONUS/REACTIVE**—enteric infections, genitourinary infections, rheumatic fever, inflammatory bowel disease

CRYSTAL—gout, pseudogout, hydroxyapatite, basic calcium phosphate**ETC**

- **MALIGNANCIES**—leukemia
- **SARCOIDOSIS**—Lofgren syndrome
- **FAMILIAL MEDITERRANEAN FEVER**
- **POLYMYALGIA RHEUMATICA**

PATHOPHYSIOLOGY**CLASSIFICATION OF ARTHRITIS**

- **MONOARTHRITIS**—1 joint involved
- **OLIGOARTHRITIS**—2–4 joints involved
- **POLYARTHRITIS**— ≥ 5 joints involved

PATHOPHYSIOLOGY—T-helper 1 mediated process \rightarrow proteases produced by synovial cells destroy proteoglycans in the articular cartilage \rightarrow irreversible damage 6 months to 1 year from disease onset

POSSIBLE TRIGGERS—viruses (parvovirus, EBV, HTLV), super-antigens (from bacteria/viruses), autoantigens (QKRAA)

RISK FACTORS—age >50 , female (3:1), first-degree relative with rheumatoid arthritis, smoking, low socioeconomic status, genetic (HLA DR4)

CLINICAL FEATURES

JOINT SYMPTOMS—symmetric polyarthritis with joint pain, swelling, redness, morning stiffness (>1 h), and dysfunction

- **HANDS**—MCP, PIP, and wrist joints most commonly involved. Deformities include boutonnière, swan neck, Z (thumb), ulnar deviation at MCP joint, volar subluxation of proximal phalanx from MCP head, radial deviation of carpus, compression of the carpal bones, subluxation at the wrist
- **FEET**—MTP joints involved. Deformities include valgus of the ankle and hindfoot, pes planus, forefoot varus and hallux valgus, cock-up toes
- **LEGS**—knees (80%), ankles (80%), hips (50%)
- **ARMS**—shoulders (60%), elbows (50%), acromioclavicular (50%)
- **ATLANTOAXIAL**—subluxation may lead to spinal cord compression (cervical myelopathy with hand weakness/numbness)
- **TEMPOROMANDIBULAR** (30%)
- **OTHERS**—related disorders include Baker cyst, tenosynovitis, carpal tunnel syndrome

EXTRA-ARTICULAR MANIFESTATIONS—

- only in seropositive patients
- **RHEUMATOID NODULES** (20%)
 - **PULMONARY**—pleural effusion (exudative, low glucose), pulmonary nodules (Caplan syndrome), acute interstitial pneumonitis, bronchiolitis obliterans
 - **CARDIAC**—valvular abnormalities, myocarditis, pericardial effusion, constrictive pericarditis
 - **GI**—elevated transaminases (especially ALP), nodular hyperplasia (portal hypertension, hypersplenism)

CLINICAL FEATURES (CONT'D)

- **HEMATOLOGIC**—anemia of chronic disease, Felty syndrome (triad of seropositive rheumatoid arthritis, neutropenia and splenomegaly; often associated with anemia and thrombocytopenia). Patients at risk for leukemia, lymphoma
- **NEUROLOGIC**—peripheral sensory neuropathy (not motor), myelopathy from cervical vertebral subluxation
- **OPHTHALMIC**—keratoconjunctivitis sicca (Sjögren syndrome), scleritis, episcleritis
- **DERMATOLOGIC**—vasculitis (digital arteritis, cutaneous ulceration, visceral arteritis)
- **OTHERS**—amyloidosis

CONSTITUTIONAL SYMPTOMS—fatigue (40%), fever (low grade), sweats, weight loss, myalgia

DISTINGUISHING FEATURES BETWEEN INFLAMMATORY AND NON-INFLAMMATORY ARTHRITIS

	Inflammatory	Non-inflammatory
Classic example	RA	OA
Morning stiffness	>1 h	+/-
Resting Activity	Worsens	Improves
Synovitis, redness	Improves	Worsens
Fever, weight loss	+	-
ESR, CRP, platelets	+	No change

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, ESR, CRP, RF (IgM), anti-CCP (more specific), ANA, urinalysis
- **IMAGING**—X-rays of affected joints (particularly hands, knees, and ankles; soft tissue swelling, periarticular osteopenia, narrowing of joint space, marginal bony erosions, subluxation, joint destruction, bony ankylosis); MSK US

SPECIAL

- **INFECTIOUS WORKUP**—serologies (parvovirus, HBV, HCV, EBV, CMV, *B. burgdorferi*)

INVESTIGATIONS (CONT'D)

- **ARTHROCENTESIS**—★**3C's**★ (Cell count with diff, Culture and Gram stain, Crystal). Cannot make definite diagnosis of rheumatoid arthritis from arthrocentesis

DIAGNOSTIC AND PROGNOSTIC ISSUES

ACR CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS—add score of categories A to D, with a score of $\geq 6/10$ classified as definite RA

- JOINT INVOLVEMENT**—one large joint (0), 2–10 large joints (1), 1–3 small joints with or without involvement of large joints (2), 4–10 small joints with or without involvement of large joints (3), >10 joints with at least 1 small joint (5);
- SEROLOGY**—negative RF and negative citrullinated protein antibodies (ACPA) (0), low-positive RF or low-positive ACPA (2), high-positive RF or high-positive ACPA (3);
- ACUTE PHASE REACTANTS**—normal CRP and normal ESR (0), abnormal CRP or abnormal ESR (1);
- DURATION OF SYMPTOMS**—<6 weeks (0), ≥ 6 weeks (1)

PROGNOSIS—increased number of joints involved, rheumatoid nodules, erosions, elevated inflammatory markers and seropositivity all suggest more severe disease

MANAGEMENT

SYMPTOM CONTROL—**physical therapy, diet** (Ω -3 fatty acids). **Joint protection** (range of motion exercises, orthotics, splints). **NSAIDs** (antiinflammatory dose). **Intraarticular steroid injections** (if severe pain). **Patient education DISEASE-MODIFYING AGENTS OF RHEUMATOID DISEASE (DMARDs)**—**single agent** (methotrexate with folic acid, sulfasalazine, hydroxychloroquine, cyclosporine). **Combination triple therapy** (methotrexate plus sulfasalazine plus hydroxychloroquine). **Selective pyrimidine synthesis inhibitor** (leflunomide). **TNF α inhibitors** (infliximab, etanercept, adalimumab, golimumab, certolizumab). **B-cell inhibitor** (rituximab, an anti-CD20 monoclonal antibody). **T-lymphocyte activation inhibitor** (abatacept), **IL-6 inhibition** (tocilizumab, sarilumab). **JAK inhibitors** (tofacitinib, baricitinib, upadacitinib, peficitinib). **Surgical intervention**

SPECIFIC ENTITIES**RESPIRATORY DISEASES IN RHEUMATOID ARTHRITIS**

- **AIRWAY**—cricoarytenoid arthritis with central airway obstruction, bronchiectasis, obliterative bronchiolitis, chronic small airway obstruction
- **PARENCHYMA**—pneumonia, interstitial fibrosis, bronchiolitis obliterans with organizing pneumonia, rheumatoid nodules, rheumatoid pneumoconiosis, apical fibrobullous disease, drug-related pneumonitis and fibrosis (methotrexate, gold, penicillamine, NSAIDs, cyclophosphamide, azathioprine, sulfasalazine)
- **VASCULAR**—pulmonary hypertension, vasculitis
- **PLEURAL**—pleuritis, pleural effusion, pleural thickening

PALINDROMIC RHEUMATISM—episodic arthritis with one or more joints being affected sequentially for hours to days, and symptom-free periods in between for days to months. May be anti-CCP positive and occasionally progresses to other rheumatic disorders (RA, SLE). Treatment with hydroxychloroquine can be useful

SJÖGREN SYNDROME

- **PATHOPHYSIOLOGY**—CD4 lymphocytic infiltration of salivary and lacrimal glands
- **CAUSES**—**primary** (sicca plus episodic, non-deforming polyarthritis), **secondary** (RA, SLE, scleroderma, polyarteritis nodosa, polymyositis, HIV)
- **CLINICAL FEATURES**—sicca (dry eyes and dry mouth, impaired taste, parotid gland enlargement, dental caries), dyspareunia, arthralgia, arthritis, and constitutional symptoms. May be associated with Raynaud phenomenon, cutaneous vasculitis, cerebritis, CNS vasculitis, stroke, distal renal tubular acidosis, and peripheral neuropathy. Increased risk of non-Hodgkin lymphoma
- **INVESTIGATIONS**—CBC, quantitative Ig, RF, ANA, ENA (SS-A, SS-B), urinalysis. Labial minor salivary gland biopsy. Schirmer test. Check for secondary causes
- **TREATMENTS**—symptomatic (artificial tears, *pilocarpine* 5 mg PO QID), hydroxychloroquine for extraglandular complications, rituximab may have a role

LOFGREN SYNDROME—usually a benign self-limited form of sarcoidosis. Tetrad of erythema nodosum, hilar lymphadenopathy, arthritis (ankles and sometimes knees), and fever. Treatment with NSAIDs

Seronegative Spondyloarthropathies

DIFFERENTIAL DIAGNOSIS OF OLIGOARTHRITIS

★RICE★

RHEUMATOLOGIC (>6 weeks)

- **SEROPOSITIVE** ★PSSR★—Polymyositis, Palindromic rheumatism, SLE, Scleroderma, Rheumatoid arthritis
- **SERONEGATIVE** ★PEAR★—Psoriatic arthritis, Enteric arthritis, Ankylosing spondylitis, Reactive arthritis, undifferentiated
- **VASCULITIS**—granulomatosis with polyangiitis, Behçet disease, Still disease

INFECTIONS (<6 weeks)

- **BACTERIAL**—sepsis, endocarditis, Lyme disease, Whipple disease, mycobacteria
- **VIRAL**—parvovirus, rubella, HBV, HCV, HIV
- **FUNGAL**
- **POST-INFECTIOUS/REACTIVE**—enteric infections, urogenital infections, rheumatic fever, inflammatory bowel disease

CRYSTAL—gout, pseudogout, hydroxyapatite, basic calcium phosphate

ETC

- **MALIGNANCIES**—leukemia
- **SARCOIDOSIS**—Lofgren syndrome
- **FAMILIAL MEDITERRANEAN FEVER**
- **POLYMYALGIA RHEUMATICA**

CLINICAL FEATURES

CARDINAL FEATURES

- **DISTRIBUTION**—male preponderance, age 20–40
- **SPONDYLOARTHROPATHY**—spondylitis, sacroiliitis, morning stiffness >30 min
- **OLIGOARTHRITIS**—asymmetric, usually involving hands and below waist, <5 joints
- **ENTHESOPATHY**—inflammation at the sites of insertion of ligaments, tendons, joint capsule, and fascia to bone, with destruction and new bone formation. This results in Achilles tendonitis, plantar fasciitis, tenosynovitis, and dactylitis/sausage digits
- **SEROLOGY**—HLA-B27 positive, rheumatoid factor negative

BACK EXAMINATION

- **INSPECTION**—swelling, erythema, atrophy, scars, and loss of thoracic kyphosis and cervical/lumbar lordosis

CLINICAL FEATURES (CONT'D)

- **RANGE OF MOTION**—check gait and flexion, extension, lateral bending, rotation
- **PALPATION**—tenderness over spinous processes and sacroiliac joints
- **SPECIAL TESTS**—Modified Schober test (place mark 5 cm below and 10 cm above the spine at level of PSIS/L5 with patient standing. A distance increase of <5 cm [<2 in.] between the marks with the patient bending forward suggests limited lumbar flexion), finger-to-floor distance, occiput to-wall distance. FABER test (SI joint stability) and straight leg raising test (sciatica)
- **EXTRAARTICULAR CHANGES**—nail pitting, onycholysis, psoriasis, tenosynovitis, dactylitis, synovitis, acute uveitis, aortic regurgitation, apical pulmonary fibrosis, chin to chest distance, occiput-to-wall distance, decreased chest expansion resulting in functional restrictive lung disease, cauda equine compression, and enthesitis (costochondritis, patellar and Achilles tendonitis, plantar fasciitis). Also assess for extraintestinal manifestations of inflammatory bowel disease

DISTINGUISHING FEATURES BETWEEN VARIOUS SERONEGATIVE SPONDYLOARTHROPATHIES

- **PSORIATIC ARTHRITIS**—history of psoriasis, DIP involvement, nail changes
- **ENTEROPATHIC ARTHRITIS**—history of IBD, pyoderma gangrenosum
- **ANKYLOSING SPONDYLITIS**—back involvement, ankylosis
- **REACTIVE ARTHRITIS**—history of urethritis/cervicitis/diarrhea, eye involvement
- **UNDIFFERENTIATED**—does not fit any of the above

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, urea, Cr, ESR, CRP, urinalysis, RF
- **IMAGING**—X-rays of affected joints (lumbosacral spine, peripheral) +/- MRI (bone marrow edema)

INVESTIGATIONS (CONT'D)**SPECIAL**

- **INFECTIOUS WORKUP**—HIV serology (if suspect reactive arthritis), chlamydial PCR (if suspect reactive arthritis), stool culture (if suspect reactive arthritis)
- **HLA-B27**—association with seronegative spondyloarthropathy, most commonly ankylosing spondylitis (only order once)
- **ARTHROCENTESIS**—★**3C**★ (Cell count with diff, Culture and Gram stain, Crystal)

DIAGNOSTIC ISSUES**EUROPEAN SPONDYLOARTHROPATHY**

STUDY GROUP CRITERIA—one of inflammatory spinal pain or synovitis (asymmetric or predominantly in the lower limbs) plus one of positive family history, psoriasis, inflammatory bowel disease, urethritis/cervicitis/acute diarrhea (within 1 month prior to arthritis), alternating buttock pain, enthesopathy, sacroiliitis (sens 75%, spc 87%)

SPECIFIC ENTITIES**ANKYLOSING SPONDYLITIS (AS)**

- **CLINICAL FEATURES**—chronic inflammatory low back, hip, knee, shoulder, and +/- peripheral joint pain. Morning stiffness lasting > 30 minutes. Loss of lumbar lordosis and thoracic kyphosis with significant decreased range of motion and chest expansion, positive Schober test and occiput-to-wall test. Extraarticular manifestations include anterior uveitis, enthesitis, dactylitis, C1-2 subluxation, restrictive lung disease, aortic regurgitation, conduction abnormalities, and secondary amyloidosis. Imaging reveals sacroiliitis/spondylitis, bamboo spine (syndesmophytes), shiny corners (squaring and increased density anteriorly of vertebral bodies), and whiskering (new bone and osteitis at tendon and ligament insertions). MRI showing bone marrow edema and structural abnormalities (sclerosis, fat metaplasia, erosions, ankylosis)
- **ASAS CLASSIFICATION CRITERIA FOR AXIAL SPONDYLOARTHRITIS** (sens 80%, spc 83%)—patients should have ≥ 3 months of back pain, age of onset <45 years and either
 - A. Sacroiliitis on imaging **and** at least 1 AS feature (i.e. inflammatory back pain, arthritis, enthesitis, uveitis, dactylitis, psoriasis,

SPECIFIC ENTITIES (CONT'D)

- IBD, good response to NSAIDs, family history of AS, HLA-B27 positive, and elevated CRP) **or**
- B. HLA-B27 positive **and** at least 2 other AS features
- **ASAS CLASSIFICATION CRITERIA FOR PERIPHERAL SPONDYLOARTHRITIS (SENS 78%, SPC 82%)**—peripheral arthritis +/- or enthesitis +/- or dactylitis and either
 - A. At least 1 of: uveitis, psoriasis, IBD, preceding infection, HLA-B27, sacroiliitis on imaging **or**
 - B. At least 2 of: arthritis, enthesitis, dactylitis, inflammatory back pain (ever), family history of SpA
 - **TREATMENTS**
 - **AXIAL**—NSAIDs first line (avoid if renal/hepatic failure; *naproxen* 500 mg PO BID; *ibuprofen* 800 mg PO TID; *celecoxib* 200 mg PO BID), TNF antagonists (etanercept, infliximab, adalimumab, golimumab, certolizumab), anti-IL-17 agents (secukinumab, ixekizumab), JAK inhibitors (tofacitinib, upadacitinib). Physical therapy
 - **PERIPHERAL**—NSAIDs, intra-articular glucocorticoids, DMARDs (sulfasalazine recommended over methotrexate), TNF antagonist
- ENTEROPATHIC ARTHRITIS**
- **PATHOPHYSIOLOGY**—10–20% of IBD patients (more common in Crohn disease than ulcerative colitis). May be first sign of IBD (especially if joint pain with anemia)
 - **CLINICAL FEATURES**—spondylitis, sacroiliitis, morning stiffness, and large joint arthritis correlates with the activity of IBD. Other extraintestinal manifestations of IBD include fever, clubbing, uveitis, iritis, anemia, jaundice (primary sclerosing cholangitis), aphthous ulcers, arthritis, erythema nodosum, pyoderma gangrenosum, DVT, and amyloidosis
 - **TREATMENTS**
 - **TYPE I ARTHROPATHY**—acute, pauciarticular peripheral arthritis \pm spondylitis and sacroiliitis, associated with flares. Usually self-limited and resolves with treatment of IBD (but not axial arthritis)

SPECIFIC ENTITIES (CONT'D)

- **TYPE II ARTHROPATHY**—polyarticular peripheral arthritis that does not parallel bowel disease. Consider sulfasalazine, methotrexate, azathioprine, and glucocorticoids. Avoid NSAIDs if possible (worsens bowel symptoms)

PSORIATIC ARTHRITIS

- **PATHOPHYSIOLOGY**—patients with psoriatic arthritis usually have psoriasis, although psoriasis can be in a first degree relative. Arthritis may appear after (70%), before (15%), or at the same time (15%) as skin lesions
- **CLINICAL FEATURES**—variable pattern of arthritis (distal DIP joints, asymmetric oligoarthritis of lower limbs, symmetric polyarthritis, arthritis mutilans, spondyloarthritis), enthesitis (Achilles tendonitis, plantar fasciitis, tenosynovitis, dactylitis), nail changes (pits, onycholysis), dactylitis, pitting edema and uveitis (usually chronic, bilateral, posterior). Imaging reveals co-existence of erosive changes and new bone formation in the distal joints with lysis of the terminal phalanges, fluffy periostitis, “pencil-in-cup” appearance, and the occurrence of both joint lysis and ankylosis in the same patient. Rheumatoid factor positive in 2–10%, CCP positive in 8–16%, HLA-B27 positive in 40–60% if axial involvement
- **CASPAR CRITERIA**—requires 1 major and 3 minor criteria
 - **MAJOR**—presence of musculoskeletal inflammation (inflammatory arthritis, enthesitis, back pain)
 - **MINOR**—skin psoriasis, nail lesions, dactylitis, negative rheumatoid factor, and juxta-articular bone formation on X-ray
- **TREATMENTS**—methotrexate, sulfasalazine, leflunomide, anti-TNF agents, anti-IL 12/23 (ustekinumab), anti-IL 17 (secukinumab, ixekizumab, brodalumab), CTLA4-Ig (abatacept), JAK inhibitor (tofacitinib)

SPECIFIC ENTITIES (CONT'D)**REACTIVE ARTHRITIS****★CAN'T SEE, CAN'T PEE, CAN'T CLIMB A TREE★**

- **PATHOPHYSIOLOGY**—preceding/ongoing infectious disorders such as urethritis (*Chlamydia*), diarrhea (*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*) or HIV, usually within 6 weeks. Overall, 75% achieve remission within 2 years (about one-third of them may experience intermittent relapses), and 25% develop chronic disease (with 5–10% developing ankylosing spondylitis)
- **CLINICAL FEATURES**—acute asymmetric oligoarthritis (spondylitis, sacroiliitis, lower limbs), morning stiffness, and enthesitis (Achilles tendonitis, plantar fasciitis, chest wall changes, and sausage fingers/toes). Other important findings include genital lesions (circinate balanitis with shallow painless ulcers on the glans or urethral meatus, urethritis, prostatitis), skin lesions (keratoderma blennorrhagica with vesicles that progress to macules, papules and nodules on palms and soles), eye lesions (conjunctivitis, iritis [acute, unilateral, photophobia, pain, redness, impaired vision]), bowel inflammation (acute enterocolitis, chronic ileocolitis), and cardiac abnormalities (aortic regurgitation, conduction abnormalities). Imaging is non-specific but can show periosteal spurs, sacroiliitis
- **ACR DIAGNOSTIC CRITERIA**—episode of arthritis of more than 1 month with urethritis and/or cervicitis, episode of arthritis of more than 1 month and either urethritis or cervicitis, or bilateral conjunctivitis, episode of arthritis, conjunctivitis, and urethritis, episode of arthritis of more than 1 month, conjunctivitis, and urethritis
- **TREATMENTS**—NSAIDs (pain control), sulfasalazine, anti-TNF agents, methotrexate, leflunomide. Most patients will enter remission within 6–12 months

Back Pain**DIFFERENTIAL DIAGNOSIS****MECHANICAL**

- **TRAUMA**—sprain, strain, fracture
- **FRACTURE**—compression, traumatic
- **SPONDYLOSIS**—disc, annulus, facet
- **SPONDYLOLISTHESIS**

DIFFERENTIAL DIAGNOSIS (CONT'D)**INFLAMMATORY**

- **RHEUMATOLOGIC**—psoriatic arthritis, enteric arthritis, ankylosing spondylitis, reactive arthritis

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **MALIGNANCY**—multiple myeloma, epidural metastasis, leptomeningeal metastasis
- **INFECTIONS**—epidural abscess

REFERRED PAIN

- **GI**—pancreatitis, cholecystitis
- **RENAL**—stones, pyelonephritis, abscess
- **PELVIC**
- **AORTIC ANEURYSM RUPTURE**

CLINICAL FEATURES**RATIONAL CLINICAL EXAMINATION SERIES: WHAT CAN THE HISTORY AND PHYSICAL EXAMINATION TELL US ABOUT LOW BACK PAIN?**

HISTORY—**history** of cancer, unexplained weight loss, pain duration >1 month, failure to improve with conservative therapy are all relatively specific for cancer pain. **IDU** or **urinary infection** suggests spinal infection. Back pain in **young men** raises possibility of ankylosing spondylitis. **Failure to improve** with rest is sensitive for systemic conditions. **Sciatica** or **pseudoclaudication** suggests neurological involvement. **Bladder dysfunction** and **saddle anesthesia** suggest cauda equina syndrome

PHYSICAL—**vertebral tenderness** (sensitive but not specific) and **fever** suggest spinal infection. **Straight leg raising** should be assessed bilaterally in sciatica or neurogenic claudication. In addition to back examination, **tone, strength, reflexes and sensory examination** of lower limbs should be done

UPDATE—positive sit-to-stand test predicts upper lumbar herniation (LR+ 26, LR- 0.35). Positive crossed straight leg raise predicts disk herniation (LR+ 1.6–5.8, LR- 0.59–0.90)

Deyo et al. *JAMA* 1992;268(6)

Simel et al. *The Rational Clinical Examination* McGraw-Hill; 2009

INVESTIGATIONS**BASIC**

- **IMAGING**—spine X-ray should be obtained if red flag features but age-related degenerative changes may be unrelated to symptoms

SPECIAL

- **IMAGING**—CT spine, MRI spine (if surgery), myelogram (gold standard but seldom used)
- **MYELOMA WORKUP**—CBC, lytes, urea, Cr, ESR, serum protein electrophoresis, urinary protein electrophoresis, serum free light chain assay

INVESTIGATIONS (CONT'D)**Related Topics**

Ankylosing Spondylitis (p. 301)
Radiculopathy (p. 347)
Spinal Cord Compression (p. 243)

DIAGNOSTIC FEATURES**DISTINGUISHING FEATURES BETWEEN INFLAMMATORY AND MECHANICAL BACK PAIN**

	Inflammatory	Mechanical
Age	Younger	Older
Onset	Insidious	Abrupt
Duration	>3 months	Shorter
AM stiffness	++	+/-
Resting	Worsens	Improves
Activity	Improves	Worsens
Sacroiliac joints	++	-

MANAGEMENT

SYMPTOM CONTROL—pain control

TREAT UNDERLYING CAUSE—flexion and extension exercises

Carette et al. *NEJM* 2005;353(4)

SPECIFIC ENTITIES

SPINAL CORD COMPRESSION—compression of spinal cord (upper motor neuron findings). Lower limb weakness, increased tendon reflexes in legs, sensory loss usually 1–5 levels below cord lesion with sacral sparing

CAUDA EQUINA SYNDROME—compression of lumbosacral nerve roots (lower motor neurons, mostly below L1 level). Symptoms include lower limb weakness, depressed tendon reflexes in legs, and sacral paresthesia

SCIATICA (LUMBOSACRAL RADICULOPATHY)—pain radiating in the dermatomal distribution. The classic features are aching pain in the buttock and paresthesias radiating into the posterior thigh and calf or into the posterior lateral thigh and lateral foreleg. Radiating pain below the knee is more likely to indicate a true radiculopathy than radiation only to the posterior thigh

SPONDYLOLISTHESIS—forward slipping of one vertebra on another, usually as a result of repeated stress on pars interarticularis. Symptoms include sciatica and low back pain, although it can also be asymptomatic

SPECIFIC ENTITIES (CONT'D)

Disc/ Root	Pain	Sensory	Weakness	Reflex
C4–5 (C5)	Medial scapula, lateral upper arm	Shoulder	Deltoid, supraspinatus, infraspinatus	Supinator
C5–6 (C6)	Lateral forearm, thumb, and index finger	Thumb and index finger	Biceps, brachioradialis, wrist extension	Biceps
C6–7 (C7)	Medial scapula, posterior arm, dorsum of forearm, third finger	Posterior forearm, third finger	Triceps, wrist flexion, finger extension	Triceps
C7–T1 (C8)	Shoulder, ulnar side of forearm, fifth finger	Fifth finger	Intrinsic hand muscles, thumb flexion, and abduction	None
L3–4 (L4)	Anterior thigh	Lateral leg to medial malleolus	Hip flexion, dorsiflexion, and inversion	Knee
L4–5 (L5)	Posterior lower limb	Lateral leg, dorsal foot including first web space	Hip extension and abduction, dorsiflexion, plantarflexion, and ankle eversion and inversion	None
L5–S1 (S1)	Posterior lower limb, often to ankle	Posterior leg, lateral foot	Hip extension and abduction, dorsiflexion, plantarflexion, and ankle eversion	Ankle
S2–S4	Sacral or buttock, radiate to posterior leg or perineum	Perineum (sacral paresthesia)	Bowel and bladder dysfunction	None

SPECIFIC ENTITIES (CONT'D)

DISC HERNIATION—prolapse of nucleus pulposus through the annulus, due to intervertebral pressure and degeneration of the ligamentous fibers. Occurs more commonly in younger patients. If the prolapsed material presses on a nerve root, may cause inflammation and sciatic symptoms. Over 95% of herniated discs affect L4–5 or L5–S1 interspace. Most herniated discs resolve in 1–2 weeks with conservative treatment

SPINAL STENOSIS

- **PATHOPHYSIOLOGY**—narrowing of the spinal canal, with compression of nerve roots → exerts pressure on venules around nerve roots → ischemic nerve injury causing back pain and neurologic symptoms
- **CAUSES**—degenerative disc disease, osteoarthritis of facet joints with osteophyte and cyst

SPECIFIC ENTITIES (CONT'D)

formation, ligamentum flavum hypertrophy, and spondylolisthesis. Laminectomy, spinal fusion, trauma, Cushing syndrome, Paget disease, and acromegaly are also associated with spinal stenosis

- **CLINICAL FEATURES**—neurogenic claudication characterized by worsening back and/or lower extremity pain with walking, relieved with flexion, sitting or walking up hill. Neurologic examination may reveal motor/sensory deficits in lower extremities
- **DIAGNOSIS**—CT/MRI spine, lumbar myelogram
- **TREATMENTS**—pain control (acetaminophen, NSAIDs, opioids (for selected patients), lumbar epidural corticosteroid injections), decompression surgery with laminectomy and partial facetectomy. Physiotherapy consultation

Systemic Lupus Erythematosus

PATHOPHYSIOLOGY

POPULATION—typically affects women aged 15–45

PATHOGENESIS—antibody-immune complex deposition in kidneys (glomerulonephritis), auto-antibodies against cell surface antigens on hematopoietic progenitor cells (anemia, neutropenia,

PATHOPHYSIOLOGY (CONT'D)

thrombocytopenia), antiphospholipid antibodies (thrombosis)

ACR CLASSIFICATION CRITERIA—requires one clinical criterion and score of >10 in patients with positive ANA. Within each domain, count highest weighted criterion

PATHOPHYSIOLOGY (CONT'D)**Clinical Domains**

Constitutional: fever (2)
 Hematologic: leukopenia (3), thrombocytopenia (4), autoimmune hemolysis (4)
 Neuropsychiatric: delirium (20), psychosis (3), seizure (5)
 Mucocutaneous: non-scarring alopecia (2), oral ulcers (2), subacute cutaneous **or** discoid (4), acute cutaneous SLE (6)
 Serosal: pleural or pericardial effusion (5), acute pericarditis (6)
 MSK: joint involvement (6)
 Renal: proteinuria >5g/24h (4), Class II or V lupus nephritis (8), class III or IV lupus nephritis (10)

Immunology Domains

Antiphospholipid antibodies: anti-cardiolipin **or** anti-B2GP1 **or** lupus anticoagulant (2)
 Complements: low C3 or C4 (3), low C3 and C4 (4)
 SLE-specific antibodies: anti-dsDNA ab **or** anti-Smith ab (6)

CLINICAL FEATURES

JOINT SYMPTOMS—symmetric non-erosive polyarthritis with joint pain, swelling, redness, morning stiffness (>1 h), and dysfunction

- **HANDS**—Jaccoud arthritis (joint deformities are unusual), fingers and wrists
- **LEGS**—knees more commonly affected
- **AVASCULAR NECROSIS**—hip, shoulder, and knee may be affected

EXTRA-ARTICULAR MANIFESTATIONS

- **PULMONARY**—pleuritis, pulmonary hypertension, PE, alveolar hemorrhage, shrinking lung syndrome (dyspnea, pleuritic chest pain, progressive reduction in lung volume, elevated diaphragms)
- **CARDIAC**—pericarditis, myocarditis, Libman-Sacks endocarditis
- **RENAL**—proteinuria or active sediment, glomerulonephritis
 - **ISN CLASSIFICATION OF LUPUS NEPHRITIS**—class I (asymptomatic), class II (mesangial proliferative); class III (focal proliferative; nephritic syndrome with proteinuria); class IV (diffuse proliferative; nephritic syndrome and nephrotic syndrome); class V (membranous glomerulonephritis; nephrotic syndrome); class VI (advanced glomerulosclerosis; uremia)
 - **SEVERITY**—VI > IV > III > II > I. Consider aggressive treatment for class III/IV
- **GI**—mesenteric thrombosis and vasculitis, transaminitis/hepatitis

CLINICAL FEATURES (CONT'D)

- **HEMATOLOGIC**—anemia of chronic disease, autoimmune hemolytic anemia, lymphopenia, thrombocytopenia, lymphadenopathy, antiphospholipid antibody syndrome
- **NEUROLOGIC**—aseptic meningitis, transverse myelitis, stroke, seizures, organic brain syndrome, psychosis, depression, peripheral neuropathy
- **DERMATOLOGIC**—photosensitivity, malar rash (nasolabial folds spared), discoid lupus (erythematous papules/plaques with central hypopigmentation, atrophic scarring involving scalp and exposed skin), mucosal ulcers (oral, vaginal, nasal septal), alopecia, livedo reticularis, palpable purpura, Raynaud

SEROLOGIC—ANA (sens >99%), anti-dsDNA (very specific), anti-Smith (very specific), SSA/Ro, SSB/La, RNP, antiphospholipid antibody (sens 40%)

CONSTITUTIONAL SYMPTOMS—fatigue, fever (high grade), lymphadenopathy, weight loss, myalgia

LUPUS EXACERBATIONS—typically with fatigue, arthritis, mucocutaneous, renal, neurologic, and/or dermatologic involvement. Individual patients usually have a fixed pattern of presentation. Precipitants include UV exposure, medication non-adherence, infections, and pregnancy. Always consider other causes such as infections, medication side effects (steroids), and embolism

INVESTIGATIONS

BASIC

- **BLOOD TESTS**—CBC, lytes, urea, Cr, ESR, CRP, ANA (sensitive), anti-dsDNA (specific for SLE), C3, C4
- **URINE TESTS**—urinalysis, urine protein to Cr ratio

SPECIAL

- **INFLAMMATORY WORKUP**—ENA (anti-Smith), anti-SSA/SSB (especially in pregnancy, associated with neonatal lupus and congenital complete heart block), antiphospholipid antibodies (anticardiolipin, lupus anticoagulant, anti- β_2 glycoprotein 1), cryoglobulins
- **INFECTIOUS WORKUP**—serologies (parvovirus, HBV, HCV, EBV, CMV)
- **ARTHROCENTESIS**—★**3C**★ (Cell count with diff [>2000 WBC/mm³], Culture and Gram stain, Crystal. Cannot make definite diagnosis of SLE from arthrocentesis)

MANAGEMENT

HYDROXYCHLOROQUINE—consider for all patients with SLE (5mg/kg/day), unless there is a contraindication to treatment

SYMPTOM CONTROL—**cutaneous lupus** (photoprotection, topical agents [steroids, calcineurin inhibitors], prednisone). **Arthritis** (NSAIDs, steroids, methotrexate, belimumab). **Nephritis** (class III/IV induction with steroids plus cyclophosphamide [CYC] or mycophenolate mofetil [MMF]; alternative treatment with calcineurin inhibitor [CNI]; class V + nephrotic proteinuria MMF, alternative treatment with IV CYC or CNI (+/- MMF), Maintenance with MMF or azathioprine). **Neuropsychiatric** (steroids +/- CYC). **Serositis** (NSAIDs, steroids). **Thrombocytopenia** (steroids, IVIG, rituximab, splenectomy). **Avoid exogenous estrogen**

2019 EULAR/ACR Classification Criteria SLE

SPECIFIC ENTITIES

UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE—syndrome in which patient has some clinical features of systemic autoimmune rheumatic disease (RA, SLE, Sjögren syndrome, scleroderma, inflammatory myopathies) and positive ANA but does not meet criteria for specific diagnosis

OVERLAP SYNDROME—meets diagnostic criteria for >1 systemic autoimmune disease (SLE, systemic sclerosis, inflammatory myopathy, RA, Sjögren syndrome)

SPECIFIC ENTITIES (CONT'D)

MIXED CONNECTIVE TISSUE DISEASE—a specific overlap syndrome with clinical features of SLE, scleroderma, inflammatory myopathy, and antibodies to RNP. Characteristically, Raynaud phenomenon, myositis, and synovitis are present

DRUG-INDUCED SYSTEMIC LUPUS

- **PATHOPHYSIOLOGY**—some drugs may trigger production of autoantibodies (e.g. ANA), which may cause or precipitate drug-induced lupus in susceptible individuals
- **CAUSES**—procainamide, hydralazine, quinidine, D-penicillamine, diltiazem, atenolol, anti-TNF agents (infliximab, etanercept, adalimumab, golimumab), captopril, carbamazepine, chlorpromazine, enalapril, ethosuximide, hydrochlorothiazide, isoniazid, lithium, methyl dopa, minocycline, minoxidil, phenytoin, primidone, statins, sulfasalazine, trimethadione
- **CLINICAL FEATURES**—compared to systemic lupus, drug-induced lupus has the following features: middle age presentation, no gender difference, affects Caucasians, acute onset, less cutaneous, renal, neurologic, and hematologic involvement, but equal joint, hepatic, and constitutional symptoms. Usually anti-histone antibody positive, anti-Smith negative, anti-dsDNA negative and normal complement levels
- **TREATMENTS**—discontinue offending drug if possible, NSAIDs, may require short course of corticosteroids, hydroxychloroquine for more prolonged symptoms

RAYNAUD PHENOMENON

- **PATHOPHYSIOLOGY**—exaggerated acral vasoconstriction to cold, emotional stress, or exercise. Triphasic changes from white to blue to red
- **CAUSES**—**primary** (isolated Raynaud), **secondary** (rheumatologic [SLE, scleroderma, dermatomyositis, polymyositis, RA, mixed connective tissue disease], traumatic [vibrational injury, frostbite, carpal tunnel], drugs [ergots, cocaine, β -blockers, bleomycin, vinblastine, interferon], hyperviscosity [leukemia, thrombocytosis, polycythemia, cryoglobulinemia, cold agglutinins], occlusive arterial disease, hypothyroidism, infections [parvovirus B19, bacterial endocarditis], complex regional pain syndrome)
- **CLINICAL FEATURES**—usually symmetric episodes, sharply demarcated color changes of

SPECIFIC ENTITIES (CONT'D)

skin and severe pain of the digits lasting 10–15 min. Secondary causes more likely if age >40, male, ulcerations, asymmetric, involvement proximal to digits and abnormal capillary nailfold

- **TREATMENTS**—trigger avoidance (cold, stress, smoking, sympathomimetic drugs). Terminate attacks early (place hands in warm water). Dihydropyridine calcium channel blockers (*nifedipine* 10–60 mg PO TID, *amlodipine* 5–20 mg PO daily), topical nitrates, ASA, phosphodiesterase inhibitors. Anticoagulation (if antiphospholipid antibodies or surgical interventions required)

SYSTEMIC SCLEROSIS (SCLERODERMA)

- **PATHOPHYSIOLOGY**—extensive fibrosis of skin, blood vessels, and internal organs (GI, lungs, renal, cardiac). Four subtypes: diffuse systemic sclerosis (progressive systemic sclerosis), limited systemic sclerosis (formerly known as **★CREST★** syndrome—**C**alcinosis, **R**aynaud phenomenon, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias), localized scleroderma (morphea, linear), and scleroderma sine scleroderma (without sclerodactyly)
- **CLINICAL FEATURES**—Raynaud phenomenon may precede skin changes for years. Usually involves skin (starts from extremities extending proximally, progressing from edematous to fibrotic to atrophic stage). Common signs: dilated capillary loops, sclerodactyly, flexion contractures, *en coup de sabre deformity*, purse lips, telangiectasia, GI hypomotility (dry mouth, dysphagia, reflux, N&V, abdominal pain, constipation, overflow diarrhea, weight loss), lungs (pleural effusion, pulmonary fibrosis, pulmonary hypertension), kidneys (renal crisis), and heart (pericarditis)
- **DIAGNOSIS**—2013 ACR/EULAR Classification Criteria. A total score of ≥ 9 supports the diagnosis: skin thickening of fingers of both hands extending proximal to MCP joints (9) vs. skin thickening of fingers consisting of puffy fingers (2) or sclerodactyly distal to MCP joints but proximal to PIP (4) vs. fingertip lesions only with digital tip ulcers (2) or fingertip pitting scars (3), telangiectasia (2), abnormal nailfold capillaries (2), pulmonary arterial hypertension (2), interstitial lung disease (2), Raynaud (3),

SPECIFIC ENTITIES (CONT'D)

SsC-related autoantibodies: anticentromere, anti-topoisomerase I (anti-Scl-70), or anti-RNA polymerase III (3)

- **TREATMENTS**—skin changes (methotrexate, MMF, cyclophosphamide). Raynaud (calcium channel blockers). GERD (PPI BID). Renal crisis (ACE inhibitors-captopril). Interstitial pneumonitis (steroids, azathioprine, mycophenolate, cyclophosphamide). Pulmonary hypertension (endothelin antagonists [bosentan], phosphodiesterase inhibitors [sildenafil, tadalafil]). Autologous stem cell transplant may be indicated if early, rapidly progressive and at risk of organ failure

Herrick et al. *Ann Rheum Dis* 2017;76(7)

INFLAMMATORY MYOPATHIES

- **PATHOPHYSIOLOGY**—classified as polymyositis, dermatomyositis, inclusion body myositis (IBM), necrotizing autoimmune myopathy (NAM)
- **ASSOCIATIONS**—dermatomyositis is associated with malignancy (GI, lung, ovarian, breast, lymphoma) in 6–45% of patients, NAM is associated with statin exposure
- **CLINICAL FEATURES**—proximal, symmetric, progressive muscle weakness developing over weeks to months, +/- morning stiffness. Muscle pain uncommon. Extramuscular manifestations: **arthralgias**, **cardiac** (conduction abnormalities, cardiomyopathy), **respiratory** (muscle weakness, aspiration, interstitial lung disease), **skin** (Gottron papules [dorsal aspect of MCP and IP joints/elbows/knees], heliotrope rash (over upper eyelids with periorbital edema), V rash/shawl sign [erythematous rash over upper chest/back/shoulders], periungual telangiectasia, “mechanic’s hand” [with darkened horizontal lines across lateral and palmar aspects of fingers/hands]), and **constitutional symptoms**. Reflexes normal
- **DIAGNOSIS**—symmetric proximal weakness, elevation of muscle enzymes (CK), EMG and muscle biopsy findings consistent with inflammatory myositis. Need all 4 criteria for definite polymyositis, and 3 criteria plus skin findings for definite dermatomyositis. Anti-Jo1, anti-Mi2, anti-SRP, anti-MDA5, TIF1, HMGR. Important to exclude other causes of myopathies.
- **TREATMENTS**—prednisone, methotrexate, azathioprine, leflunomide, IVIG, rituximab

SPECIFIC ENTITIES (CONT'D)

DISTINGUISHING FEATURES BETWEEN STEROID MYOPATHY AND INFLAMMATORY MYOPATHIES

	Steroid myopathy	Inflammatory myopathies
History	Steroid use or other steroid-related symptoms	Other inflammatory myopathy symptoms
Physical	Neck flexor normal	Neck flexor weaker
Tests	CK normal or mild ↑	CK often ↑, anti-Jo1, anti-Mi2, HMGR Ab
EMG	Normal	Abnormal activity
Stop statin	Improves	Worsens

Osteoarthritis

DIFFERENTIAL DIAGNOSIS

PRIMARY OSTEOARTHRITIS

- **GENERALIZED**
- **LOCALIZED**—hands (nodal, erosive, inflammatory), feet (first MTP), knee, hip, spine

SECONDARY OSTEOARTHRITIS

- **MECHANICAL**—post-traumatic, post-surgical
- **NEUROPATHIC JOINTS**—diabetes, syphilis, spinal cord injury
- **INFLAMMATORY**—RA, crystal arthropathies, infectious
- **METABOLIC**—hemochromatosis, Wilson disease, acromegaly, Paget disease, Cushing syndrome, ochronosis
- **BLEEDING DYSCRASIAS**—hemophilic, warfarin use

OSTEOARTHRITIS MIMICS—inflammatory features and distribution should help to rule out inflammatory arthritis (seropositive, seronegative, crystal, infectious arthropathies). Diffuse idiopathic skeletal hyperostosis (DISH) is a bone forming condition characterized by ossification at skeletal sites of stress. Important to distinguish from periarticular structures (tendonitis, bursitis)

PATHOPHYSIOLOGY

ARTICULAR CARTILAGE—not just 'wear and tear' but involves increased activity of cartilage matrix formation and removal. As the repair effort becomes inadequate, metalloproteinases and collagenase cause degradation of cartilage

PATHOPHYSIOLOGY (CONT'D)

and subsequent degeneration of surrounding soft tissues

RISK FACTORS FOR PRIMARY OSTEOARTHRITIS—age, female, obesity, mechanical factors (previous joint injury, excessive varus/valgus), smoking, genetics

CLINICAL FEATURES

SUBTYPES OF PRIMARY OSTEOARTHRITIS

- **GENERALIZED**—affects DIP (Heberden nodes), PIP (Bouchard nodes) and first CMC joints, hips, knees, and spine. More common in women
- **ISOLATED NODAL**—affects DIP joints only. More common in women
- **EROSIVE**—affects DIP and PIP joints, with episodes of local inflammation, mucous cyst formation, and bony erosion resulting in joint deformity. Genetic predisposition. May mimic rheumatoid arthritis
- **DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (DISH, Forestier disease)**—affects spine mainly but peripheral joints may also be involved, with osteophytes connecting ≥ 4 vertebrae. X-rays are diagnostic. May mimic ankylosing spondylitis

INVESTIGATIONS

IMAGING—X-ray of affected joints (joint space narrowing, marginal osteophytes, subchondral sclerosis, and subchondral cysts)

DIAGNOSTIC ISSUES

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY OSTEOARTHRITIS—primary OA almost never involves the shoulders, elbows, ankles, MCP joints, or ulnar side of wrist. Consider secondary OA in young patients, unusual sites, widespread chondrocalcinosis, or constitutional symptoms

ACR CLASSIFICATION CRITERIA FOR HAND OSTEOARTHRITIS—hand pain, aching, or stiffness and three of the following: hard tissue enlargement > 2 selected joints (second and third DIP or PIP, first CMC), hard tissue enlargement of > 2 DIP joints, <3 swollen MCP joints, deformity of at least 1 selected joints. Sens 94%, spc 87%

ACR CLASSIFICATION CRITERIA FOR HIP OSTEOARTHRITIS—hip pain and at least two of the following: ESR <20 mm/h, radiographic femoral or acetabular osteophytes, radiographic joint space narrowing. Sens 89%, spc 91%

MANAGEMENT

CONSERVATIVE MEASURES—exercise, self-efficacy and self-management programs, weight loss, assistive devices (use cane to support unaffected side, 1st CMC orthotic, tibiofemoral bracing)

SYMPTOM CONTROL—NSAIDs (use lowest effective dose and add proton pump inhibitor for gastric protection if indicated. *Naproxen* 200–500 mg BID, *ibuprofen* 200–800 mg QID, *diclofenac gel* 5% apply to affected area QID), intra-articular glucocorticoids. Can consider *acetaminophen* 325–650 mg PO q4–6 h, tramadol, duloxetine. No medical treatment shown to slow progression

MANAGEMENT (CONT'D)

JOINT REPLACEMENT—indicated if uncontrollable pain, loss of function, failure of conservative therapies

2019 ACR/Arthritis Foundation Guideline OA Hand Hip Knee

SPECIFIC ENTITIES

POST-TRAUMATIC SECONDARY OA—usually isolated large joints. Knee OA may develop after meniscal tear, shoulder OA may develop with rotator cuff injury

HEMOCHROMATOSIS—classically affects second and third MCP and shoulders (see p. 482 for more details)

AVASCULAR NECROSIS/ASEPTIC NECROSIS

- **PATHOPHYSIOLOGY**—damage to vasculature from mechanical interruption, thrombosis/embolism, vessel wall injury, or venous occlusion, leading to medullary infarction. Affects the femoral head, tibial plateau, humeral head, scaphoid, and vertebrae more commonly
- **ASSOCIATIONS**—★**ASEPTIC**★ Alcohol, Steroids, Sepsis, Storage disease (Gaucher), Sickle cell disease, Emboli (fat, cholesterol), Post-radiation, Trauma, Idiopathic, Connective tissue disease (SLE, rheumatoid arthritis, vasculitis), Cancer, hyperCoagulable states
- **CLINICAL FEATURES**—joint pain. High index of suspicion, especially if steroid use
- **DIAGNOSIS**—plain radiographs (initially can appear normal), CT, bone scan. MRI is the most sensitive test
- **TREATMENTS**—stop offending agents. Avoid weight bearing. Pain control. Orthopedic consult for possible debridement, decompression, or joint replacement

Fibromyalgia**DIFFERENTIAL DIAGNOSIS OF DIFFUSE BODY PAIN****FIBROMYALGIA**

- **MYOPATHY**—metabolic (hypothyroidism), drug induced, myofascial pain syndrome
- **NEUROLOGIC**—multiple sclerosis, neuropathic pain
- **INFECTION**—viral infections, spirochetal infection (Lyme)

DIFFERENTIAL DIAGNOSIS OF DIFFUSE BODY PAIN (CONT'D)

- **RHEUMATOLOGIC**—polymyalgia rheumatica, polymyositis/dermatomyositis, rheumatoid arthritis, SLE, spondyloarthropathy
- **PSYCHIATRIC**—depression
- **OTHER**—medications, adrenal insufficiency, hypothyroidism

PATHOPHYSIOLOGY

- **INCREASED PAIN PERCEPTION ASSOCIATIONS**—irritable bowel/bladder syndrome, chronic headaches, mood disorders (depression, anxiety), sleep disorders

CLINICAL FEATURES

ACR 2010 DIAGNOSTIC CRITERIA—the diagnosis of fibromyalgia requires fulfillment of the following 3 criteria:

1. Widespread pain index (WPI) ≥ 7 and symptom severity scale score (SS) ≥ 5 , **or** WPI 3–6 and SS ≥ 9 ;
2. Symptoms present at a similar level for at least 3 months;
3. No other explanation

Note: WPI is based on the number of areas in which the patient has pain over the past week (0–19): left or right shoulder girdle, left or right hip (buttock, trochanter), left or right jaw, upper or lower back, left or right upper arm, left or right lower arm, left or right upper leg, left or right lower leg, neck, chest, abdomen

Note: SS scale score is based on the sum of the severity of 3 symptoms plus the extent of somatic symptoms in general (total score 0–12)

- **Fatigue, waking unrefreshed, cognitive symptoms:** for each of the 3 symptoms, indicate the level of severity over the past week using: no problem (0); slight or mild problems, generally mild or intermittent (1); moderate, considerable problems, often present or at a moderate level or both (2); severe, pervasive, continuous, life-disturbing problems (3)

CLINICAL FEATURES (CONT'D)

- Consider somatic symptoms in general, indicate whether the patient has no symptoms (0), few symptoms (1), a moderate number of symptoms (2), many symptoms (3)

INVESTIGATIONS**BASIC**

- **LABS** (usually normal)—CBC, lytes, urea, Cr, Ca, Mg, PO₄, CRP, TSH, CK

MANAGEMENT**REASSURANCE AND PATIENT EDUCATION PROGRAMS**

LIFESTYLE—physical therapy/activity, sleep hygiene

MEDICATIONS—amitriptyline, muscle relaxants (cyclobenzaprine), SSRI/SNRIs, pregabalin, gabapentin. Opioids are not effective and should be avoided

SPECIFIC ENTITIES**CHRONIC FATIGUE SYNDROME**

- **DIAGNOSTIC CRITERIA**—new-onset unexplained persistent or relapsing fatigue, exclude ongoing exertion, not alleviated by rest, substantial reduction in previous activities, and at least 4 of the following: self-reported impairment in short term memory or concentration, sore throat, tender cervical or axillary nodes, muscle pain, multi-joint pain without redness or swelling, headaches of a new pattern or severity, unrefreshing sleep, post-exertional malaise lasting >24 h
- **TREATMENTS**—cognitive behavior therapy and graded exercise

Vasculitis

Weyand et al. *NEJM* 2003;349(2)

Walsh et al. *NEJM* 2020;382(7)

DIFFERENTIAL DIAGNOSIS

PRIMARY VASCULITIDES—Takayasu aortitis, giant cell/temporal arteritis, polyarteritis nodosa (PAN), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA)

SECONDARY VASCULITIDES**DIFFERENTIAL DIAGNOSIS (CONT'D)****★ VASCULITIS ★**

- **VARIOUS DRUGS**
- **AUTOIMMUNE**—SLE, rheumatoid arthritis, Behçet disease, relapsing polychondritis
- **SERUM SICKNESS**—penicillin
- **CRYOGLOBULINEMIA**

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **ULCERATIVE COLITIS**
- **LOW COMPLEMENT**—hypocomplementemic urticarial vasculitis
- **INFECTIONS**—viral (HBV, HCV, HIV, CMV, EBV, parvovirus B19), rickettsial
- **TUMORS**—lymphoma, multiple myeloma
- **IGA NEPHROPATHY/HENOCH-SCHONLEIN PURPURA**
- **SMOKING-RELATED THROMBOANGIITIS OBLITERANS**—Buerger disease

VASCULITIS MIMICS

- **RHEUMATIC DISEASES**—SLE
- **INFECTIOUS**—bacteremia, necrotic arachnidism
- **INFILTRATIVE**—amyloidosis
- **CANCER**—lymphoma
- **CONGENITAL**—coarctation of the aorta, neurofibromatosis
- **EMBOLI**—endocarditis, mycotic aneurysm, cholesterol, atrial myxoma
- **ETC**—fibromuscular dysplasia, granulomatosis/polymorphic reticulosis, ergotism, radiation fibrosis, thrombocytopenia, malignant atrophic papulosis

PATHOPHYSIOLOGY

MECHANISM—inflammation of vessel wall → loss of vessel integrity results in bleeding, and compromise of the lumen leads to tissue ischemia and necrosis. The distribution of organ involvement depends on the distribution of antigen

CLASSIFICATION

- **LARGE VESSEL VASCULITIS**—Takayasu aortitis, giant cell/temporal arteritis
- **MEDIUM VESSEL VASCULITIS**—Kawasaki disease, polyarteritis nodosa
- **SMALL VESSELS VASCULITIS**—Immune complex-mediated (Goodpasture, cryoglobulinemic, IgA, hypocomplementemic urticarial); ANCA-associated (GPA, EGPA, MPA)
- **VARIABLE VESSEL VASCULITIS**—Behçet disease, Cogan syndrome

CLINICAL FEATURES**SYMPTOMS**

- **CONSTITUTIONAL**—fever, arthralgias, fatigue, anorexia

CLINICAL FEATURES (CONT'D)

- **ORGAN ISCHEMIA**—mesenteric ischemia, stroke, blindness, peripheral neuropathy
- **SKIN CHANGES**—palpable purpura (non-blanchable), livedo reticularis, necrotic lesions, infarcts of tips of digits

PALPABLE PURPURA

- **PATHOPHYSIOLOGY**—pathognomonic of small vessel vasculitis. Inflammation of the vessel allows extravasation of blood and fluid into the extravascular space, resulting in palpable edema. Since the blood is no longer intravascular, the lesion is purpuric (non-blanchable) rather than erythematous
- **CAUSES**—inflammatory (polyarteritis nodosa, GPA, Henoch-Schönlein purpura, SLE, cryoglobulinemia), infectious (sepsis, infective endocarditis, disseminated meningococemia), iatrogenic (drugs)
- **CLINICAL FEATURES**—bright to dark red purpuric papules/plaques
- **DIAGNOSIS**—skin biopsy shows leukocytoclastic vasculitis

WHEN TO SUSPECT VASCULITIS—multi-system or ischemic vascular disease, palpable purpura, glomerulonephritis, mononeuritis multiplex, myalgia, arthralgia, arthritis, abdominal/testicular pain, unexplained constitutional symptoms

INVESTIGATIONS**BASIC**

- **BLOOD TESTS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, albumin, ESR, CRP, ANA, urinalysis
- **IMAGING**—CXR

SPECIAL

- **INFLAMMATORY WORKUP**—RF, C3, C4, p-ANCA, c-ANCA, cryoglobulins, CK, serum protein electrophoresis
- **INFECTIOUS WORKUP**—serologies (HIV, HBV, HCV, EBV, CMV, *Treponema pallidum*, *B. burgdorferi*)
- **FURTHER IMAGING GUIDED BY SYMPTOMS**—MR head, CT chest/abd/pelvis, CT/MR/conventional angiogram
- **BIOPSY OF AFFECTED ORGAN**—most important. Guided by symptoms (e.g. temporal artery, skin, kidney, GI mucosa)

DIAGNOSTIC ISSUES

DIAGNOSIS BY ORGAN INVOLVEMENT

	Head (stroke, visual Δ)	Peripheral neuropathy	Lung (dyspnea, hemoptysis)	Kidneys (GN)	Abdomen (pain)	Skin (palpable purpura)	Others
Takayasu aortitis	+						Cardiovascular
Giant cell arteritis	+						ESR++, PMR
Polyarteritis nodosa		+			+	+	GI++
Microscopic polyangiitis			+	+	+		p-ANCA
Granulomatosis with polyangiitis (GPA)	\pm	+	+	+			Sinus, c-ANCA
Eosinophilic granulomatosis with polyangiitis (EGPA)			+	+		+	Asthma, eosinophilia
Henoch-Schönlein purpura					+	+	IgA
Behçet disease	+					+	Oral/GU/GI ulcers
Cryoglobulinemia		+		+		+	Cryoglobulin

SPECIFIC ENTITIES

TAKAYASU AORTITIS (PULSELESS DISEASE)

- **PATHOPHYSIOLOGY**—vasculitis of large arteries, typically aorta and its branches with vessel occlusion causing MI, TIA/stroke, visual disturbances, claudication
- **ASSOCIATIONS**—young women of Asian or Mexican descent
- **ACR CLASSIFICATION CRITERIA**—age at disease onset 10 mmHg between arms, bruit over subclavian arteries or aorta, arteriogram abnormality (narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental). Need 3 of 6 criteria (sens 91%, spc 98%)
- **TREATMENTS**—*prednisone* 1mg/kg/day with slow taper, vascular surgery, anti-platelet (ASA 81mg/day) if critical arterial stenosis. Frequent relapses. Methotrexate, tocilizumab (IL6R antagonist), infliximab (anti-TNF), azathioprine if refractory

POLYMYALGIA RHEUMATICA

- **ASSOCIATIONS**—temporal arteritis in 15%

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—age >50, morning stiffness > pain (in proximal musculature including hip and shoulder girdle), constitutional symptoms. May have oligoarticular joint swelling (knees, wrists, shoulders), \uparrow ESR. Diagnosis of exclusion
- **TREATMENTS**—*prednisone* 15–20 mg PO daily at stable dose until myalgia and stiffness resolved for 2–4 weeks, then reduce by 10% (no more than 1 mg/month) every 4 weeks until tapered off. Rapid dramatic response to prednisone. Use of prednisone > 15 mg decreases the diagnostic specificity. Relapse is frequent. Given prolonged steroid use, ensure appropriate bone protection with calcium 1200 mg/day, vitamin D 800 IU/day, +/- bisphosphonate based on FRAX with glucocorticoid correction. Should get a BMD within first 6 months of starting prednisone

GIANT CELL ARTERITIS/TEMPORAL ARTERITIS

- **ASSOCIATIONS**—older age, polymyalgia rheumatica in 30–50%
- **CLINICAL FEATURES**—vasculitis of the large and medium arteries. Temporal headache, amauro-

SPECIFIC ENTITIES (CONT'D)

sis fugax, diplopia, jaw claudication, painful scalp nodules, tender or palpably abnormal temporal artery. Extracranial GCA involves aorta in 10–15%

- **ACR CLASSIFICATION CRITERIA**—age >50, new-onset headache, temporal artery tenderness to palpation or decreased pulse, ESR >50 mm/h, abnormal temporal artery biopsy. Need 3 of 5 criteria (sens 94%, spc 91%)
- **DIAGNOSIS**—temporal artery biopsy is gold standard; consider contralateral biopsy if unilateral biopsy is negative and high suspicion. Color Doppler US, +/- CTA/MRA/PET imaging may be helpful. Biopsy should not delay initiation of treatment if high risk of GCA at risk of vision loss
- **TREATMENTS**—if no ocular symptoms, *prednisone* 40–60 mg PO daily x 1 month, taper to 7.5–15 mg daily over 6–9 months, may continue for several years (monitor symptoms, signs, and CRP). If ocular symptoms present, *methylprednisolone* 1 g IV daily x 3 days, then *prednisone* 80 mg PO daily and taper over time. Initiate therapy before biopsy if high index of suspicion. Consider tocilizumab or methotrexate if steroid-sparing therapy required. ASA 81 mg PO daily is recommended to reduce vascular complications. Given prolonged steroid use, ensure appropriate bone protection with calcium 1200 mg/day, vitamin D 800 IU/day, +/- bisphosphonate based on FRAX with glucocorticoid correction. BMD within first 6 months of starting prednisone

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE TEMPORAL ARTERITIS?

	LR+	LR-
History		
Jaw claudication	4.3	0.72
Diplopia	3.5	0.96
Any headache	1.7	0.67
Temporal headache	1.5	0.82
Unilateral visual loss	0.85	1.2
Fatigue	1.2	0.94
Fever	1.2	0.92
Physical		
Beaded temporal artery	4.6	0.93

SPECIFIC ENTITIES (CONT'D)

	LR+	LR-
Prominent temporal artery	4.3	0.67
Tender temporal artery	2.6	0.82
Absent temporal artery pulse	2.7	0.71
Any temporal artery	2	0.53
Scalp tenderness	1.7	0.73
Optic atrophy or ischemic optic neuropathy	1.6	0.8
Any fundoscopic abnormality	1.1	1.0
Synovitis	0.41	1.1
Male gender	0.83	—
White race	1.1	—
Laboratory investigations		
Anemia	1.5	0.79
ESR abnormal	1.1	0.2
ESR >50 mm/h	1.1	0.35
ESR >100 mm/h	1.9	0.8

Smetana et al. JAMA 2002;287(1)

UPDATE—Temporal arteritis score >70 (for patients ≥50 years; based on headache, jaw claudication, scalp tenderness, ESR, ischemic optic neuropathy, and age) predicts positive temporal artery biopsy

Simel et al. The Rational Clinical Examination McGraw-Hill; 2009

POLYARTERITIS NODOSA (PAN)

- **PATHOPHYSIOLOGY**—necrotizing vasculitis of medium and small arteries with no glomerulonephritis. Associated with HIV, CMV, parvovirus B19, HBV, HCV
- **CLINICAL FEATURES**—mononeuritis multiplex (particularly the peroneal and tibial branches of sciatic nerve), orchitis, skin (palpable purpura, livedo reticularis, subcutaneous nodules, distal gangrene), GI (mesenteric vasculitis), renal (vasculitis but NO glomerulonephritis)
- **ACR CLASSIFICATION CRITERIA**—weight loss >4 kg since illness, livedo reticularis, testicular pain or tenderness, myalgias, weakness or leg tenderness, mononeuropathy or polyneuropathy, diastolic blood pressure >90 mmHg, elevated urea >14 mmol/L [>39 mg/dL] or Cr >132 μmol/L [>1.45 mg/dL], HBsAg or HBsAb positive, arteriographic abnormality (aneurysms or occlusions of the visceral arteries, not due to arteriosclerosis, fibromuscular dysplasia, or other non-inflammatory causes), biopsy of small or

SPECIFIC ENTITIES (CONT'D)

medium-sized artery containing PMN. Need 3 of 10 criteria (sens 82%, spc 87%)

- **TREATMENTS**—*prednisone* 1mg/kg for 4 weeks with taper over 6-12 months, methotrexate, azathioprine (mild), cyclophosphamide (severe)

MICROSCOPIC POLYANGIITIS (MPA)

- **PATHOPHYSIOLOGY**—necrotizing vasculitis of the small vessels. Frequent glomerulonephritis and lung involvement
- **CLINICAL FEATURES**—renal (RPGN), pulmonary (hemoptysis, hemorrhage). GI, skin, and neurologic symptoms as in PAN. p-ANCA positive
- **TREATMENTS**—induction with IV corticosteroids PLUS cyclophosphamide or rituximab. Maintenance with methotrexate, azathioprine, rituximab

GRANULOMATOSIS WITH POLYANGIITIS (GPA)

- **PATHOPHYSIOLOGY**—systemic vasculitis of the medium and small arteries, venules, and arterioles. Also necrotizing granulomas involving upper and lower respiratory tracts and kidneys. Associated with sinusitis and c-ANCA (autoantibodies against proteinase-3)
- **CLINICAL FEATURES** ★**ELKS**★—**E**ars and nose, **L**ungs, **K**idneys, **S**kin involvement
- **ACR CLASSIFICATION CRITERIA**—nasal or oral inflammation/ulcers, abnormal CXR (nodules, fixed infiltrates, cavities), microhematuria (>5 RBC/HPF) or red cell casts in urine sediment, granulomatous inflammation on biopsy. Need 2/4 criteria (sens 88%, spc 92%)
- **TREATMENTS**—induction with IV corticosteroids PLUS cyclophosphamide or rituximab. Maintenance with methotrexate, azathioprine, rituximab. Trimethoprim-sulfamethoxazole for PJP prophylaxis and to prevent recurrent sinus infections.

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA)

- **PATHOPHYSIOLOGY**—systemic vasculitis of the medium and small arteries, typically involving the lung and skin. Also vascular and extravascular granulomatosis with necrosis. Associated with asthma and p-ANCA (autoantibodies against myeloperoxidase), eosinophilia, and ↑ IgE and ESR
- **ASSOCIATIONS**—leukotriene type I receptor antagonists

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—pneumonic infiltrate, skin rash, myocarditis, peripheral neuropathy, and nephropathy
- **ACR CLASSIFICATION CRITERIA**—asthma, eosinophilia >10%, mono- or polyneuropathy, pulmonary infiltrates (non-fixed), paranasal sinus abnormality, extravascular eosinophils. Need 4/6 criteria (sens 85%, spc 99.7%)
- **TREATMENTS**—steroids alone if mild, induction with IV corticosteroids PLUS cyclophosphamide if severe. Mepolizumab or rituximab in refractory cases

HENOCH-SCHÖNLEIN PURPURA

- **PATHOPHYSIOLOGY**—systemic vasculitis of small vessels characterized by IgA-containing immune complex deposition in tissues
- **ACR CLASSIFICATION CRITERIA**—palpable purpura, age <20 at disease onset, intestinal angina, granulocytes in walls of arterioles or venules on biopsy. Need 2/4 criteria (sens 87%, spc 88%)
- **TREATMENTS**—usually resolves spontaneously. Consider steroids (*prednisone* 1 mg/kg PO daily, taper by 5–10 mg/week) for symptom control. Consider cyclophosphamide plus high-dose steroids if crescentic glomerulonephritis

BEHÇET DISEASE

- **PATHOPHYSIOLOGY**—systemic vasculitis of the large, medium, and small arteries, typically involving the oral mucosa, eyes, skin, and CNS
- **CLINICAL FEATURES**—occurs more commonly along the Silk Route of Asia and Europe. Typically involves painful aphthous ulcers (gingival, tongue, buccal), eyes (pan-uveitis, hypopyon), skin (erythema nodosum, pseudofolliculitis, acneiform nodules), painful genital ulcers, joints (non-deforming monoarthritis, sometimes oligo- or polyarthritis), venous thrombosis (vena cava, portal, hepatic veins, extremities), CNS (aseptic meningitis, meningoencephalitis, focal neurological deficits)
- **DIAGNOSTIC CRITERIA**—oral aphthous ulcers recurring $\geq 3\times$ over 1 year, plus 2 of the following: recurrent genital aphthous ulcers, eyes features, skin features, and positive pathergy testing at 24–48 h
- **TREATMENTS**—*prednisone* 15 mg PO daily for 1 week (taper over 3 weeks), *colchicine* 0.6 mg PO BID, apremilast (phosphodiesterase 4 inhib-

SPECIFIC ENTITIES (CONT'D)

itor), azathioprine and others (lesion dependent)

IgG4-RELATED DISEASE

- **PATHOPHYSIOLOGY**—immune-mediated multiorgan condition associated with fibroinflammatory lesions

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—retroperitoneal fibrosis; autoimmune pancreatitis; sclerosing cholangitis; salivary or lacrimal gland enlargement; orbital pseudotumor or proptosis
- **TREATMENTS**—corticosteroids, rituximab if refractory

Approach to Serologies**INFLAMMATORY MARKERS****ERYTHROCYTE SEDIMENTATION RATE (ESR)** (non-specific)

- **DISORDERS**—elevated in vasculitis such as temporal arteritis, PMR and almost all inflammatory disorders (rheumatologic, infectious, malignancy), anemia, renal disease, female sex, obesity, and old age
- **UTILITY**—associated with disease activity in temporal arteritis and PMR. Normal value corrected for age and is usually less than $[\text{age in years} + 10 \text{ (if female)}] / 2$

C-REACTIVE PROTEIN (CRP) (non-specific)

- **DISORDERS**—elevated in vasculitis such as temporal arteritis and PMR and almost all inflammatory disorders (rheumatologic, infectious, malignancy), obesity, diabetes, CAD, and smoking
- **UTILITY**—associated with disease activity in temporal arteritis and PMR

RHEUMATOID ARTHRITIS

RHEUMATOID FACTOR—polyclonal IgM against Fc portion of IgG (non-specific)

- **DISORDERS**—significantly elevated in RA (sens 80%), Sjögren syndrome, mixed cryoglobulinemia, subacute bacterial endocarditis. Mildly elevated in other rheumatologic diseases (SLE, MCTD, polymyositis, sarcoidosis), pulmonary and hepatic diseases, infections, and malignancy. May be positive in the normal elderly
- **UTILITY**—seronegative RA does not have extraarticular findings. Does not correlate with disease activity

ANTICYCLIC CITRULLINATED PEPTIDES (anti-CCP) (very specific)

- **UTILITY**—very useful for diagnosis of RA (sens 70%, spc 95%)

LUPUS

ANTINUCLEAR ANTIBODIES (ANA) (non-specific but sensitive screening test for SLE and other autoimmune rheumatic diseases)

- **DISORDERS**—SLE (sens >99%), mixed connective tissue disease (sens >95%), Sjögren syndrome (sens 75%), inflammatory myopathies (sens >75%), scleroderma (sens >60–90%), rheumatoid arthritis (sens 15–35%), and normal elderly
- **STAINING PATTERNS**
- **NUCLEAR**
 - **HOMOGENEOUS/DIFFUSE**—SLE (e.g. associated with anti-dsDNA, histones)
 - **SPECKLED**—various autoimmune diseases including SLE, neonatal lupus, DM, scleroderma, Sjögren, overlap, and MCTD (e.g. anti-SS-A/Ro, SS-B, Mi-2, TIF1 γ , Sm, RNP, RNA polymerase III)
 - **CENTROMERE**—limited cutaneous scleroderma (e.g. anti-centromere)
 - **NUCLEOLAR**—scleroderma and scleroderma-autoimmune inflammatory myositis overlap (e.g. anti-PM-Scl and other specific autoantibodies for SSC)
 - **DNA TOPO I-LIKE**—highly specific for scleroderma, in particular diffuse cutaneous scleroderma (e.g. anti-Scl-70)
- **CYTOPLASMIC**
 - **HOMOGENEOUS**—anti-synthetase syndrome and SLE (e.g. anti-ribosomal P)
 - **SPECKLED**—anti-synthetase syndrome (e.g. anti-Jo-1)
- **MITOTIC**—infrequent patterns with low predictive value for autoimmune disease
- **UTILITY**—negative ANA can help to exclude SLE, but ANA testing is not useful in known SLE patients

LUPUS (CONT'D)

ANTIBODIES TO EXTRACTABLE NUCLEAR ANTIGENS (ENA) (ENA panel tests for autoantibodies reacting to cell components, use after positive ANA)

ANTI-DOUBLE-STRANDED DNA (most specific test for SLE)

- **DISORDERS**—elevated in SLE (sens 20–30%, spc >95%) and chronic active hepatitis. Usually not elevated in drug-induced lupus
- **UTILITY**—associated with lupus nephritis and disease activity in SLE (most useful for following disease)

ANTI-SMITH (very specific)

- **DISORDERS**—SLE. Usually not elevated in drug induced lupus
- **UTILITY**—SLE (sens 30%, spc >95%). Associated with lupus nephritis

ANTI-U1 RNP

- **DISORDERS**—mixed connective tissue disease, SLE
- **UTILITY**—associated with milder SLE

ANTI-HISTONE

- **DISORDERS**—drug-induced lupus (sens >90%, very spc), SLE (sens >50%)

C3, C4

- **DISORDERS**—decreased in SLE, cryoglobulinemic vasculitis, Henoch-Schönlein purpura
- **UTILITY**—associated with lupus nephritis and disease activity in SLE and cryoglobulinemic vasculitis

SCLERODERMA

ANTI-SCL-70 (TOPOISOMERASE I) (very specific)

- **DISORDERS**—scleroderma (sens 20–30%, very spc)
- **UTILITY**—associated with disease activity

ANTICENTROMERE

- **DISORDERS**—CREST (sens 90%), idiopathic Raynaud (sens 25%)

SJÖGREN SYNDROME

ANTI-RO (SS-A)

- **DISORDERS**—Sjögren syndrome (sens 75%), SLE (sens 25%)
- **UTILITY**—associated with sicca in other connective tissue disorders, extraglandular disease in Sjögren syndrome, heart block in neonates with anti-Ro positive mothers, cutaneous lupus rash, photosensitivity, and thrombocytopenia in SLE

SJÖGREN SYNDROME (CONT'D)

ANTI-LA (SS-B)

- **DISORDERS**—Sjögren syndrome (sens 40%), SLE (sens 10%)
- **UTILITY**—associated with anti-Ro and benign course in SLE if no other autoantibody present except ANA

INFLAMMATORY MYOPATHIES

ANTI-JO-1—antibodies against t-RNA histidyl synthetase

- **DISORDERS**—polymyositis (sens 30%)
- **UTILITY**—associated with deforming arthritis, mechanic's hands, Raynaud phenomenon, and pulmonary fibrosis in dermatomyositis and polymyositis

ANTI-MI-2

- **DISORDERS**—dermatomyositis (sens 5%)
- **UTILITY**—associated with V-sign, shawl sign, cuticular overgrowth, good response to therapy, and good prognosis

ANTI-SRP—antibodies against anti-signal recognition protein

- **DISORDERS**—necrotizing autoimmune myositis

ANTI-HMG-CoA REDUCTASE

- **DISORDERS**—necrotizing autoimmune myositis
- **UTILITY**—up to 80% have prior exposure to statin

ANTI-TIF1 GAMMA—p155/140

- **DISORDERS**—dermatomyositis
- **UTILITY**—strong association with cancer

ANTI-MDAS—cytoplasmic RNA helicase

- **DISORDERS**—dermatomyositis and polymyositis, clinically amyopathic DM
- **UTILITY**—associated with rapidly progressive ILD

VASCULITIS

PR-3 ANCA—autoantibodies against proteinase-3. Associated with cANCA.

- **DISORDERS**—granulomatosis with polyangiitis, (spc 98% for generalized active GPA)

MPO ANCA—autoantibodies against myeloperoxidase (MPO) (non-specific)

- **DISORDERS**—eosinophilic granulomatosis with polyangiitis (sens 65%), idiopathic crescentic glomerulonephritis (sens 65%), microscopic polyangiitis (sens 45%), polyarteritis nodosa (sens 15%), granulomatosis with polyangiitis (sens 10%)

Joint Examination

	Inspection (SEADS^a)	ROM (active and passive)	Palpation (SWAT^b)	Special tests
Shoulder	Winging of scapulae	Abduction (180°) Adduction (50°) Flexion (180°) Extension (60°) Internal rotation (90°) External rotation (90°)	Clavicle, AC joint, coracoid process, acromion, spine of scapula, greater and lesser tuberosity of humerus, biceps tendon	Initial abduction against resistance (supraspinatus) External rotation against resistance (infraspinatus and teres minor) Internal rotation against resistance (subscapularis) Relocation and anterior release tests (shoulder instability) Biceps load I and II (labrum tear) Biceps tendonitis
Hand and wrist	Boutonnière, swan neck, subluxation @ MCP and wrist, ulnar deviation @ MCP, radial deviation @ carpus, rheumatoid nodules, Heberden and Bouchard nodes	Thumb flexion, extension, abduction, and adduction Finger flexion/extension Opposition Wrists flexion/extension	Wrist Carpal joints MCP joints PIP joints DIP joints	Also examine C-spine and upper limb (neurological testing) Tinel test, Phalen test (carpal tunnel syndrome) Finkelstein test (de Quervain tenosynovitis) Hand grip strength and function (write) Neurological testing of hand

	Inspection (SEADS^a)	ROM (active and passive)	Palpation (SWAT^b)	Special tests
Hip	Lumbar lordosis	Abduction (50°)	ASIS	FABER test (groin pain = hip joint, buttock pain = SI joint)
	Gait ^c	Adduction (20°)	Iliac crest	Thomas test (hip flexion contracture)
		Internal rotation (35°)	SI joint	Trendelenburg test (weakness of gluteus medius on standing side)
		External rotation (45°)	Greater trochanter	Leg length discrepancy (true and false)
Knee	Varus	Flexion (120°)	Ischial tuberosity	Anterior drawer test, Lachman test, pivot shift (anterior cruciate ligament)
		Extension (20–30°)	Patella, tibial tuberosity	
	Valgus	Flexion (135°)	Head of tibia/fibula	Posterior drawer test (posterior cruciate ligament)
	Genu recurvatum	Extension (10°)	Joint line tenderness	
	Baker cyst	Eversion (10°)	Femoral condyles	Collateral ligaments
	Gait ^c	Inversion (10°)	Bursas (suprapatellar, subpatellar, infrapatellar, anserine)	McMurray test, medial-lateral grind test (meniscal)
Bulge test, balloon test, patella tap				
Ankle and foot	Varus	Dorsiflexion (20°)	Achilles tendon	Anterior drawer test
	Valgus	Plantarflexion (50°)	Malleolus	Lateral/medial stability
	Achilles tendon	Subtalar joint—	Anterior talofibular ligament	Subtalar complex stability
	Nails, bunion	inversion and	Deltoid ligament	Achilles tendon rupture
	Hallux valgus	eversion (5°)	Calcaneus	
	Metatarsus varus	Forefoot joints	Base of MTP	
	Pes planus	Joints of toes	Calcaneus	
Shoes		Navicular		

^aSEADS—Symmetry/swelling, Erythema, Atrophy, Deformity, and Surgeries/scars

^bSWAT—Swelling/synovitis, Warmth, Anatomic landmarks, Tenderness

^cGait—heel strike, foot flat (mid-stance), heel off (lift off), toes off (swing)



Brain Tumors

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY AND MOLECULAR FEATURES

- **NEUROEPITHELIAL**
 - **GLIOMAS**
 - **OLIGODENDROGLIOMA** (4%)—isocitrate dehydrogenase (IDH)-mutant, 1p19q codeletion; WHO Grade II or III (favorable prognosis)
 - **ASTROCYTOMA** (30%)—IDH-mutant, ATRX loss or TP53 mutation; WHO Grade II or III (intermediate prognosis)
 - **GLIOBLASTOMA** (20%)—IDH-wild type; WHO Grade IV (poor prognosis)
 - **EPENDYMOMA** (2%)—propensity for ventricles or spinal cord; WHO Grade II
 - **CHOROID PLEXUS TUMORS** (WHO Grade II or III)
 - **NEURONAL AND MIXED NEURONAL-GLIAL TUMORS** (WHO Grade I or II)
 - **PINEAL PARENCHYMAL TUMORS**
 - **EMBRYONAL TUMORS** (1.7%)—medulloblastoma (WHO Grade IV), pineoblastoma, neuroblastoma, ependymoblastoma
- **CRANIAL/SPINAL NERVES**—schwannoma, neurofibroma, malignant peripheral nerve sheath tumor (malignant schwannoma, 8%)
- **MENINGES**
 - **BENIGN MENINGIOMA** (30%)—WHO Grade I
 - **ATYPICAL MENINGIOMA**—WHO Grade II
 - **ANAPLASTIC MENINGIOMA**—WHO Grade III
 - **MALIGNANT NEOPLASMS**—hemangiopericytoma, chondrosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, meningeal sarcomatosis
 - **PRIMARY MELANOCYTIC LESIONS**—diffuse melanosis, melanocytoma, malignant melanoma
- **LYMPHOMA** (3%)—malignant lymphomas, plasmacytoma, granulocytic sarcoma

PATHOPHYSIOLOGY (CONT'D)

- **GERM CELL**—germinoma, embryonal carcinoma, choriocarcinoma, teratoma
- **CYSTS AND TUMOR LIKE**—Rathke cleft cyst, epidermoid cyst, dermoid cyst, colloid cyst
- **SELLAR REGION**—pituitary adenoma (9–13%), pituitary carcinoma, craniopharyngioma (2–5%)
- **LOCAL EXTENSION FROM REGIONAL TUMORS**—paraganglioma, chordoma, chondrosarcoma
- **METASTATIC TUMORS**

RISK FACTORS

- **FAMILY HISTORY**
- **ENVIRONMENTAL**—radiation (meningioma, glioma), vinyl chloride (glioma)
- **DISEASES**—HIV (CNS lymphoma), familial adenomatous polyposis (medulloblastoma), Li-Fraumeni syndrome (astrocytomas), Turcot syndrome (medulloblastoma, glioblastoma), neurofibromatosis (astrocytomas, nerve sheath tumors)

GLIOBLASTOMA DEVELOPMENT—in elderly patients, more likely *de novo* (primary GBM). In younger patients, more likely evolved from low-grade glioma (secondary GBM) with stepwise mutation

MANAGEMENT IN GLIOBLASTOMA—epigenetic silencing with methylation of MGMT (*O6-methylguanine*-methyltransferase) DNA-repair gene is both prognostic and predictive of better outcomes. Inactivation of MGMT prevents it from repairing the damage caused by alkylating agents, thus contributing to increased effectiveness of treatment

MASS EFFECT—tumors → vasogenic edema → direct compression of neurons causing demyelination and necrosis and specific neurological symptoms based on anatomical location. Also increases intracranial pressure causing headache, nausea and vomiting, papilledema, cranial nerve

PATHOPHYSIOLOGY (CONT'D)

palsy, and herniation syndromes. Hydrocephalus may also occur with obstruction of third or fourth ventricle due to posterior fossa tumors

Related Topics

CNS Lymphoma (p. 197)

Seizures (p. 335)

Headaches (p. 339)

CLINICAL FEATURES

SYMPTOMS—headache (70%), seizure (50%, more with low-grade tumors), focal neurological deficits (motor, sensory, more with high-grade tumors), cognitive dysfunction, visual spatial dysfunction, aphasia, N&V, altered level of consciousness

SIGNS—cranial nerve examination, with particular attention to fundoscopy and visual fields (driving), cognitive assessment with MMSE or Montreal Cognitive Assessment (MoCA), speech, motor, sensory, gait, cerebellum, pronator drift, Romberg sign

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—MRI head with gadolinium, CT head with contrast enhancement
- **BIOPSY**—open biopsy, stereotactic biopsy

SPECIAL

- **MR SPECTROSCOPY**—*N*-acetylaspartate, choline, lactate
- **FUNCTIONAL MR**—blood flow

PROGNOSTIC ISSUES

PROGNOSIS FOR LOW-GRADE GLIOMAS—median survival 7–8 years, 5-year survival 50–94%; median time to recurrence 4.5 years, median survival from recurrence 12 months

PROGNOSIS FOR GLIOBLASTOMA—median survival 14 weeks with observation only, 20 weeks with resection, 36 weeks with radiation added, and 40–60 weeks with chemotherapy added

PROGNOSTIC FACTORS FOR ANAPLASTIC ASTROCYTOMA AND GLIOBLASTOMA—older age, poor Karnofsky performance status, degree of excision, neurologic deficits

PROGNOSTIC ISSUES (CONT'D)**MEDIAN SURVIVALS FOR OLIGODENDROGLIOMA**

Oligodendroglioma	1p19q deletion	No 1p19q deletion
Low grade	15 years	5 years
High grade	5–10 years	2 years

MANAGEMENT

SYMPTOM CONTROL—seizure control (preferred options include levetiracetam or lamotrigine with other options including topiramate, lacosamide, clobazam, valproic acid, perampanel), steroids may be used short term for cerebral edema with symptoms such as headaches, neurological deficits. Palliative care referral

TUMOR CONTROL

- **GLIOMAS**
 - **GLIOBLASTOMA (GRADE IV)**—maximal surgical debulking, concurrent chemoradiation with temozolomide \times 6 weeks, followed by 4-week break and then adjuvant temozolomide d1–5 q28d \times 6
 - **ASTROCYTOMA AND OLIGODENDROGLIOMA**
 - **GRADE II**—maximal surgical resection. Radiation and chemotherapy may be delayed until progression or symptoms
 - **GRADE III**—maximal surgical resection plus chemotherapy (PCV or temozolomide) and radiation
 - **SALVAGE CHEMOTHERAPY FOR GLIOMAS**—nitrosoureas, bevacizumab, etoposide, carboplatin, procarbazine
 - **INVESTIGATIONAL THERAPIES FOR GLIOMAS**—IDH-targeted therapies, other molecular targeted agents, biologic therapies, immunotherapy, vaccine based or local gene therapies
- **EPENDYMOMA**—resection \pm radiation. Palliative chemotherapy may be provided with recurrence
- **PRIMARY NEUROECTODERMAL TUMORS** (medulloblastoma, supratentorial, pineoblastoma)—resection plus craniospinal radiation for low risk tumors may be curative. Add adjuvant chemotherapy (cisplatin, etoposide, cyclophosphamide or lomustine and vincristine) for high-risk tumors
- **MENINGIOMA**—observation if asymptomatic and no mass effect. Otherwise, resection or radiation if surgery not possible

MANAGEMENT (CONT'D)

DRIVING—the key factors that affect driving include seizures, visual fields, motor deficits, and cognition

TREATMENT ISSUES**SIDE EFFECTS OF BRAIN IRRADIATION**

- **RADIONECROSIS**—contrast-enhancing focal lesion may be difficult to differentiate from recurrent brain tumor. Supportive measures
- **RADIATION-INDUCED LEUKOENCEPHALOPATHY**—occurs months to years later. Symptoms may include gait ataxia, urinary incontinence, and dementia
- **RADIATION MYELOPATHY**—associated with accumulative radiation dose to the spinal cord, peaking at 1 and 2 years. Symptoms may include Lhermitte sign, paresthesia (pain and temperature) with progressive loss of cord function over 6 months. Supportive measures only

SPECIFIC ENTITIES**HERNIATION SYNDROMES**

- **TRANSTENTORIAL**—symmetric downward displacement of the hemispheres, causing impaction of the diencephalon and midbrain into the tentorial notch → rostrocaudal deterioration with decorticate evolving to decerebrate posturing
- **UNCAL**—temporal lobe and uncus shift medially into the tentorial notch, causing compression of third nerve (pupillary dilation, eye deviation ‘down and out’) and contralateral cerebral peduncle (ipsilateral hemiparesis, false localizing sign)

SPECIFIC ENTITIES (CONT'D)

- **TONSILLAR**—cerebellar tonsils downward into the foramen magnum compresses the medulla and upper spinal cord, resulting in rapid failure of vital functions

BRAIN METASTASES

- **PATHOPHYSIOLOGY**—occurs in 20–40% of patients, most commonly from lung, breast, melanoma, renal cell, and gastrointestinal cancers. About 10 × more frequent than primary brain tumors. Found in cerebral hemispheres, cerebellum, and brainstem 80%, 15% and 5% of the time
- **TREATMENT**—surgery plus radiation offers survival advantage over radiation alone, although <50% of brain metastases can be resected. Radiation reduces recurrence but does not improve survival. Novel systemic therapies emerging. Individualized treatment with multidisciplinary team recommended. Palliative care referral should be considered

LEPTOMENINGEAL CARCINOMATOSIS

- **PATHOPHYSIOLOGY**—occurs in 5% of patients, most commonly from leukemias, non-Hodgkin lymphoma, and solid tumors (lung, breast, and melanoma)
- **DIAGNOSIS**—CSF analysis for cytologic confirmation (multiple taps often necessary). MRI spine may also be helpful
- **TREATMENT**—median survival 4–6 weeks without treatment and may improve to 3–6 months with intrathecal therapy (methotrexate, cytarabine, thiotepe). Necrotizing leukoencephalopathy may develop months after in those who survive, particularly after combined methotrexate and radiation administration. Palliative care referral should be considered

Acute Stroke Syndromes**2018 Canadian Stroke Best Practices Guidelines****DIFFERENTIAL DIAGNOSIS****ISCHEMIC STROKE**

- **THROMBOTIC/INTRINSIC VESSEL DISEASE**—atherosclerosis, vasculitis, vasospasm, dissection, compression, fibromuscular, hypercoagulable state
- **EMBOLIC/REMOTE ORIGIN**—cardiogenic, artery, septic, air, fat, paradoxical (from VTE)
- **GLOBAL ISCHEMIA**—MI, VT

DIFFERENTIAL DIAGNOSIS (CONT'D)**HEMORRHAGIC STROKE**

- **INTRACEREBRAL VESSEL RUPTURE**—hypertension, cerebral amyloid angiopathy, vascular malformation, neoplasm, trauma, bleeding diatheses, venous sinus thrombosis, vasculitis, illicit drug use
- **SUBARACHNOID VESSEL RUPTURE**—aneurysm rupture, vascular malformation, bleeding

DIFFERENTIAL DIAGNOSIS (CONT'D)

diatheses, trauma, amyloid angiopathy, illicit drug use (cocaine)

STROKE MIMICS (usually global rather than focal neurological symptoms) ★**DIMS**★

- **DRUG INTOXICATION/WITHDRAWAL**
- **INFECTIONS**—herpes simplex encephalitis
- **INSANITY**—conversion disorder or functional neurologic disorder
- **METABOLIC**—hypoglycemia, renal failure, hepatic failure, hypoxia/hypercarbia, endocrine disorders (thyrotoxicosis, myxedema, adrenal insufficiency)
- **MIGRAINES**
- **SYNCOPE**
- **SEIZURES**—Todd paralysis
- **STRUCTURAL**—trauma, tumors, subdural hemorrhage

PATHOPHYSIOLOGY**FIVE QUESTIONS**

1. Is the patient stable? Circulation, airway, breathing
2. Is this a stroke vs. a stroke mimic?
3. Where is the stroke? Symptoms/signs, CT head
4. What kind of stroke? Ischemic, hemorrhagic
5. Is acute stroke treatment indicated? Thrombolytics, endovascular

PATHOPHYSIOLOGIC STROKE CLASSIFICATION

- **THROMBOTIC STROKE**
 1. **LARGE VESSEL STROKE**—most commonly due to atherothrombosis. Found at bifurcation of common carotid artery, siphon portion of common carotid artery, middle cerebral artery stem, intracranial vertebral arteries proximal to middle basilar artery, origin of vertebral arteries
 2. **SMALL VESSEL STROKE** (lacunar/penetrating vessels)—most commonly due to lipohyalinotic occlusion related to hypertension and occasionally atheroma at the origin of

PATHOPHYSIOLOGY (CONT'D)

vessels. Found at penetrating branches of the anterior, middle, and posterior cerebral and basilar arteries

- **CARDIOAORTIC EMBOLIC STROKE**
 1. **CARDIAC SOURCES DEFINITE** (anticoagulant or antithrombotic therapy generally used)—LV thrombus, LA thrombus, rheumatic valve disease, artificial valve (mechanical, bioprosthetic), AF
 2. **CARDIAC SOURCES DEFINITE** (anticoagulation hazardous)—bacterial endocarditis, atrial myxoma
 3. **CARDIAC SOURCES POSSIBLE**—mitral annular calcification, left ventricular dysfunction, status post-MI, LA spontaneous echo contrast, PFO, ASD, mitral valve strands
 4. **UNKNOWN SOURCE EMBOLIC STROKE**
 5. **OTHERS**—dissection, moyamoya, primary thrombosis, cerebral mass

RISK FACTORS FOR STROKE

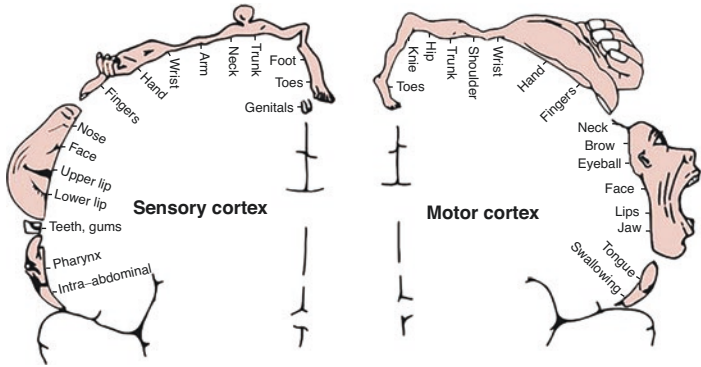
- **MAJOR MODIFIABLE**—hypertension, diabetes, atrial fibrillation, dyslipidemia, smoking, physical inactivity
- **NON-MODIFIABLE**—age, race, ethnicity, male sex, family history, genetic predisposition
- **OTHERS**—obstructive sleep apnea, kidney disease, heavy alcohol intake, diet, cardiac disease, hypercoagulable state, radiotherapy

COMPLICATIONS OF STROKE—about 25% of patients can worsen during the first 24–48 h after stroke

- **NEUROLOGIC**—cerebral edema, seizures, hemorrhagic transformation of infarction with or without hematoma, neurological deficits (dysphagia, falls, compressive neuropathies)
- **NON-NEUROLOGIC**—myocardial infarction, arrhythmia, aspiration, pneumonia, UTI, DVT, pulmonary embolism, malnutrition, pressure sores, orthopedic complications, contractures, sleep disordered breathing, depression

PATHOPHYSIOLOGY (CONT'D)

MAP OF MOTOR/SENSORY CORTEX



From Khurana R, Teal P. (2009) Carotid Artery Stenosis Prevalence and Medical Therapy. In: Saw J. (eds) *Carotid Artery Stenting: The Basics*. Contemporary Cardiology. Humana Press, Totowa, NJ. https://doi.org/10.1007/978-1-60327-314-5_1, with permission Springer Nature

CLINICAL FEATURES

TRANSIENT ISCHEMIC ATTACK—defined as an ischemic episode causing transient focal neurologic symptoms without evidence of infarct (on MRI) nor persistent symptoms following event. Risk of stroke in patients with TIA is 5% within 2 days and 10% within 90 days

RISK STRATIFICATION AFTER TIA OR MINOR NONDISABLING STROKE

• **VERY HIGH RISK**

- **TIMELINE**—symptom onset within 48 hours
- **SYMPTOMS**—unilateral weakness or sensory symptoms, speech disturbance, vision, ataxia, dysphagia, dysarthria, binocular diplopia
- **MANAGEMENT**—**immediate assessment** by healthcare professional with stroke expertise and urgent CT/CTA or MRI/MRA, ECG, and laboratory investigations

• **HIGH RISK**

- **TIMELINE**—symptom onset between 48 hours and 2 weeks
- **SYMPTOMS**—unilateral weakness or speech disturbance
- **MANAGEMENT**—assessment by healthcare professional with stroke expertise as soon as possible, ideally **within 24 hours**

CLINICAL FEATURES (CONT'D)

• **MODERATE RISK**

- **TIMELINE**—symptom onset between 48 hours and 2 weeks
- **SYMPTOMS**—unilateral sensory symptoms, vision disturbance, or ataxia
- **MANAGEMENT**—assessment by healthcare professional with stroke expertise as soon as possible, ideally **within 2 weeks**

• **LOWER RISK**

- **TIMELINE**—symptom onset of more than 2 weeks
- **MANAGEMENT**—assessment by healthcare professional with stroke expertise **within 1 month**

CLINICAL STROKE CLASSIFICATION

- **ANTERIOR CEREBRAL ARTERY** (embolic > thrombotic)—motor and sensory deficit (leg > arm, face), frontal release signs (grasp, snout, root, and suckling reflexes), abulia, paratonic rigidity, gait apraxia, personality Δ
- **MIDDLE CEREBRAL ARTERY** (left dominant hemisphere, embolic > thrombotic)—aphasia, right hemiparesis, and sensory deficit (face, arm > leg), may be complete hemiplegia if internal capsule involved, right spatial neglect, right homonymous hemianopia, impaired right conjugate gaze

CLINICAL FEATURES (CONT'D)

- **MIDDLE CEREBRAL ARTERY** (right non-dominant hemispheric, embolic > thrombotic)—anosognosia, left motor and sensory deficit (face, arm > leg), left spatial neglect, left homonymous hemianopia, impaired left conjugate gaze
- **DEEP (SUBCORTICAL/LACUNAR) HEMISPHERE OR BRAINSTEM** (small artery infarct)—hemiparesis (pure motor stroke); sensory loss (pure sensory stroke); hemisensory and hemiparesis (sensorimotor syndrome); dysarthria and clumsy hand syndrome; ataxic hemiparesis. No abnormalities of cognition, language, or vision
- **POSTERIOR CEREBRAL ARTERY** (embolic > thrombotic)—homonymous hemianopia with macular sparing, alexia without agraphia (dominant hemisphere), visual hallucinations, visual perseverations (calcarine cortex), choreoathetosis, spontaneous pain (thalamus), third nerve palsy, paresis of vertical eye movement, sensory loss, motor deficit (cerebral peduncle, midbrain)
- **VERTEBROBASILAR ARTERY** (brainstem, embolic = thrombotic)—motor or sensory loss in ALL 4 limbs; crossed signs (ipsilateral cranial nerve palsy with contralateral motor/sensory deficit), dysconjugate gaze, nystagmus, ataxia, dysarthria, dysphagia
- **CEREBELLUM**—ipsilateral limb ataxia, gait ataxia
- **INTERNAL CAROTID ARTERY** (thrombotic > embolic)—progressive or stuttering onset of MCA syndrome, occasionally ACA syndrome as well

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT HAVING A STROKE? PRE-TEST LIKELIHOOD—probability of a stroke among patients with neurologically relevant symptoms is 10%

	LR+	LR-
PRE-HOSPITAL ASSESSMENT		
Presence of any one of acute facial paresis, arm drift, or abnormal speech	5.5	0.39
	LR+	PROB. STROKE
IN-HOSPITAL CLINICAL ASSESSMENT		
Focal neurological deficit, persistent neurological deficit, acute onset during prior week, no history of head trauma		
0 factor	0.14	1.5%
1–3 factors	–	≥10%
4 factors	40	80%

CLINICAL FEATURES (CONT'D)

NIH STROKE SCALE (NIHSS)—universally used in the evaluation of acute stroke

1. **Level of consciousness** (0 = alert, 1 = not alert, 2 = obtunded, 3 = unresponsive)
2. **Level of consciousness questions** (0 = answers both correctly, 1 = answers one correctly, 2 = answers neither correctly)
3. **Level of consciousness commands** (0 = performs both tasks correctly, 1 = performs one task correctly, 2 = performs neither task)
4. **Gaze** (0 = normal, 1 = partial gaze palsy, 2 = total gaze palsy)
5. **Visual fields** (0 = no visual loss, 1 = partial hemianopsia, 2 = complete hemianopsia, 3 = bilateral hemianopsia)
6. **Facial palsy** (0 = normal, 1 = minor paralysis, 2 = partial paralysis, 3 = complete paralysis)
7. **Motor arms (right/left)** (0 = no drift, 1 = drift before 5 s, 2 = falls before 10 s, 3 = no effort against gravity, 4 = no movement)
8. **Motor legs (right/left)** (0 = no drift, 1 = drift before 5 s, 2 = falls before 5 s, 3 = no effort against gravity, 4 = no movement)
9. **Ataxia** (0 = absent, 1 = one limb, 2 = two limbs)
10. **Sensory** (0 = normal, 1 = mild loss, 2 = severe loss)
11. **Language** (0 = normal, 1 = mild aphasia, 2 = severe aphasia, 3 = mute or global aphasia)
12. **Dysarthria** (0 = normal, 1 = mild, 2 = severe)
13. **Extinction/inattention** (0 = normal, 1 = mild, 2 = severe)

INTERPRETATION—minor stroke (0–4 points), moderate stroke (5–15 points), moderate-severe stroke (15–20 points), severe stroke (21–42 points) Refer to https://www.stroke.nih.gov/documents/NIH_Stroke_Scale_508C.pdf for online version of NIH Stroke Scale

APPROACH—onset of symptoms → prehospital assessment → in-hospital assessment → if likely stroke, assess with NIH stroke score, perform neuroimaging and laboratory tests to exclude stroke mimics → begin stroke treatment. “The accurate determination of stroke subtype requires neuroimaging to distinguish ischemic from hemorrhagic stroke. Early mortality increases among those with any one of impaired consciousness, hemiplegia, and conjugate gaze palsy (LR+ 1.8, LR 0.36).”

Goldstein et al. JAMA 2005;293(19)

CLINICAL FEATURES (CONT'D)

Related Topics
 CT Head (p. 362)
 Dysphagia (p. 128)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A CLINICALLY IMPORTANT CAROTID BRUIT?

	Sens	Spc	LR+
Ability of carotid bruits to indicate carotid stenosis in symptomatic patients			
TIA patients with >50% stenosis	29%	88%	2.4
Anterior circulation TIA patients with 75–99% stenosis	76%	76%	3.2
Anterior circulation TIA patients with 70–99% stenosis	62%	61%	1.6

Ability of carotid bruit to predict carotid stenosis in asymptomatic patients

Bruit predicting carotid stenosis (70–99%)	–	–	6.0
--	---	---	-----

APPROACH—“Although the presence of a carotid bruit in a patient with carotid-territory [TIA/stroke] increases the probability that the underlying stenosis is high grade (and therefore amenable to endarterectomy), the accuracy of this physical finding is low. Accordingly, carotid bruit cannot be used to rule in or rule out surgically amenable carotid artery stenosis in symptomatic patients.”

“Asymptomatic preoperative bruits are not predictive of increased risk of perioperative stroke. However, they may be harbingers of transient postoperative cognitive and behavioral abnormalities.”

Sauvé et al. *JAMA* 1993;270(23)
 Simel et al. *The Rational Clinical Examination*. McGraw-Hill; 2009

CLINICAL CLUES TO DIAGNOSIS

- **THROMBOTIC**—stuttering progression with periods of improvement. Lacunes develop over hours or at most a few days; large artery isch-

CLINICAL FEATURES (CONT'D)

- emia may evolve over longer periods. May have neck bruit or prior TIAs
- **EMBOLIC**—sudden onset with deficit maximal at onset. Clinical findings may improve quickly. Can be precipitated by getting up at night to urinate, or sudden coughing or sneezing
- **ICH**—gradual progression over minutes to hours. May be precipitated by sex or physical activities
- **SAH**—abrupt onset, thunderclap, severe headache, loss of consciousness, neck stiffness, vomiting, focal brain dysfunction less common. May be precipitated by sex or other physical activity

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A HEMORRHAGIC STROKE?

In patients for whom clinical diagnosis of stroke has *already* been made (see Goldstein et al. *JAMA* 2005;293[19]) differentiation of ischemic vs. hemorrhagic subtypes guides treatment

	LR+	LR–
RISK FACTORS		
Coronary artery disease	0.44	1.1
Atrial fibrillation	0.44	1.1
Peripheral arterial disease	0.41	1.1
Prior TIA	0.34	1.2
SYMPTOMS		
Seizures with neuro deficit	4.7	0.93
Vomiting	3.0	0.73
Headache	2.9	0.66
Loss of consciousness	2.6	0.65
PHYSICAL SIGNS		
Coma	6.2	–
Neck stiffness	5.0	0.83
DBP >110 mmHg	4.3	0.59
Cervical bruit	0.12	1.1
LABORATORY FINDINGS		
Xanthochromia in CSF	15	0.31
Atrial fibrillation on EKG	0.19	1.2
CLINICAL IMPRESSION AND STROKE SCORES		
Clinician's impression hemorrhage is most likely Dx	6.2	0.28
Siriraj Stroke Score >1 (hemorrhage)	5.7	–
Siriraj Stroke Score <–1 (infarction)	0.3	–
Besson score ≥1 (hemorrhage)	1.4	–
Besson score <1 (infarction)	0.2	–

CLINICAL FEATURES (CONT'D)

APPROACH—among stroke patients, the presence of several clinical findings such as headaches, vomiting, severe hypertension, neck stiffness, and coma increase the probability of hemorrhagic stroke. However, because these findings only have low to moderate diagnostic accuracy, neuroimaging is recommended for definitive diagnosis. Xanthochromia has high diagnostic performance but requires an invasive procedure

Runchey et al. JAMA 2010;303(22)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, troponin, CK, PTT, INR, AST, ALT, ALP, bilirubin, total cholesterol, TGL, LDL, HDL, homocysteine, ESR
- **IMAGING**—CT head without contrast, MRI head (more sensitive than CT head in detecting acute ischemic stroke), angiogram (CT, MR, contrast), carotid Dopplers, echocardiogram (TEE > TTE)

SPECIAL

- **ECG**—ST depression, QT prolongation, inverted T, prominent U waves
- **HOLTER MONITOR**—evaluation for occult atrial fibrillation
- **EEG**—if seizures
- **TOXICOLOGY SCREEN**

DIAGNOSTIC AND PROGNOSTIC ISSUES

DOMINANT HEMISPHERE—the left hemisphere is dominant (language functions) in 95% of right-handed and 70% of left-handed individuals

CT HEAD—gold standard, but relatively insensitive in detecting acute and small cortical or subcortical infarctions, especially in the posterior fossa. Critical for excluding hemorrhagic disease. Early signs (within 6 h) of MCA infarction include **hyperdense middle cerebral artery sign** (thrombus or embolus in first portion of MCA), **loss of gray-white differentiation in the cortical ribbon** (especially at the lateral margins of the insula), or lentiform nucleus and **sulcal effacement**. Hypodense lesions may not appear until after 24 h. They become more hypodense over time

MORTALITY RATE—30-day mortality post-ischemic stroke is 10–17%

PROGNOSTIC MARKERS—age, degree of neurological deficit (NIH stroke scale), extent of stroke on CT, fever

MANAGEMENT

ACUTE THROMBOTIC STROKE—ABC, O₂, IV. **Avoid rapid or excessive BP lowering** because of risk of ischemia in acute setting (if receiving thrombolytic therapy, BP should be kept <185/110 mmHg before alteplase and <180/105 mmHg afterwards × 24 h to reduce risk of hemorrhagic transformation; if not receiving thrombolytic therapy, BP should not be routinely treated unless SBP >220 mmHg or DBP >120 mmHg, where BP should be reduced by 15% [and not more than 25%] over 24 h). **Thrombolytics** (if within 4.5 h of onset of ischemic stroke, see below; *alteplase* 0.9 mg/kg IV, maximum 90 mg).

Endovascular thrombectomy (large artery occlusion within 6 h of onset or selected cases up to 24 h). **Anticoagulation is not indicated** unless embolic stroke with obvious cardiac source (e.g. atrial fibrillation). **ASA** 81–325 mg PO daily (if thrombolytics given, may start ASA after first 24 h. For long-term secondary prophylaxis, consider clopidogrel or dipyridamole if cannot tolerate ASA). **Hemicraniectomy** or posterior fossa decompression may be considered in large MCA or cerebellar strokes with evidence of edema and mass effect

ACUTE HEMORRHAGIC STROKE—ABC, O₂, IV, blood pressure reduction (target SBP 140 [possibly ranging from 140–180 mmHg]), reverse anticoagulation, consider neurosurgical consultation for evacuation

ACUTE SUBARACHNOID HEMORRHAGE—ABC, O₂, IV, blood pressure reduction (possible target SBP <160 mmHg), reverse anticoagulation, consider nimodipine. **Neurology or neurosurgery consult**

GENERAL STROKE CARE—early mobilization/rehabilitation with multi-disciplinary team management (e.g. swallowing assessment prior to initiating diet, physiotherapy, occupational therapy). Monitor complications and treat modifiable risk factors

TREATMENT ISSUES**THROMBOLYSIS**

- **INCLUSION**—clinical diagnosis of ischemic stroke, age 18 years or older, onset of symptoms within 4.5 h, measurable neurological deficit
- **EXCLUSION**
 - **ABSOLUTE**—any source of active hemorrhage **or** any condition that could increase the risk of major hemorrhage after alteplase **or** any hemorrhage on brain imaging

TREATMENT ISSUES (CONT'D)

- **RELATIVE—historical** (prior history of ICH, stroke/head trauma <3 months, major surgery/trauma <14 days, GI/GU bleed <21 days, arterial puncture in non-compressible site <7 days), **clinical** (rapidly improving stroke symptoms, minor/isolated symptoms, seizure at onset of stroke with residual impairment secondary to postictal phenomenon, suspicion of SAH, persistent hypertension $\geq 185/110$, taking a direct non-vitamin K oral anticoagulant), **labs** (platelet $<100 \times 10^9/L$, glucose <2.7 mM [50 mg/dL], \uparrow PTT, INR >1.7), **CT head** (hemorrhage, major early infarct signs), radiographically (stroke involving $>1/3$ of cerebral hemisphere)

TREATMENT ISSUES (CONT'D)

- **OUTCOME**—among patients receiving thrombolysis within 3 h of onset, favorable outcomes in 31–50% of treated patients compared to 20–38% of nontreated patients at 3 months and 1 year. Patients benefit more if treated early (<90 min) but benefit extends out to 6 h. Major risk is symptomatic brain hemorrhage (3–5%). However, mortality rate is similar between the two groups at 3 months and 1 year. Thrombolysis administered between 3 and 4.5 h after symptom onset associated with favorable outcome in 52.4% compared to 45.2% in non-treated patients, with an increased risk of intracranial hemorrhage, but no effect on mortality

RELATIVE RISK REDUCTION FOR ISCHEMIC STROKE/TIA

Condition	Primary prophylaxis	Secondary prophylaxis
Hypertension	Anti-HTN 20%	Anti-HTN 28%
Hyperlipidemia	Statins	Statins
Atrial fibrillation	ASA 20–30% Coumadin 60%	ASA 20–30% Coumadin 60%
Post-MI	ASA 31%	ASA
Post-stroke	Not needed if no previous stroke	ASA 30% Clopidogrel 43% ASA/dipyridamole 43%

The percentages in this table represent relative risk reduction

CRITERIA FOR CAROTID ENDARTERECTOMY

Carotid stenosis	Symptomatic	Asymptomatic
$\geq 70\%$	Yes (NNT 6.3)	Yes if stenosis $\geq 60\%$ and life expectancy over 5 years (NNT 33)
50–69%	Yes (NNT 22) Patient factors such as age, sex, and comorbidities should be taken into account	
$<50\%$	No	No

Medical management (ASA) for those not eligible for carotid endarterectomy
NNT number needed to treat

SPECIFIC ENTITIES**DISTINGUISHING FEATURES BETWEEN UPPER MOTOR NEURON AND LOWER MOTOR NEURON LESIONS**

	Upper motor neuron	Lower motor neuron
Inspect	Atrophy after long term	Atrophy and fasciculations
Tone	Spasticity (velocity dependent)	Flaccidity
Strength	Upper limbs flexors > extensors, pronation > supination Lower limbs extensors > flexors	Nerve root/peripheral nerve distribution
Reflex	Increased with clonus Babinski present (upgoing toe)	Decreased Babinski absent
Pronator drift	Present	Absent

SPECIFIC ENTITIES (CONT'D)**APHASIA (LANGUAGE IMPAIRMENT)**

• TESTING PHRASES

- **COMPREHENSION WITHOUT REPLY**—"Touch your chin, then your nose, then your ear"
- **COMPREHENSION WITH ANSWERS**—"Do you put your shoes on before your socks?"
- **FLUENCY**—"Describe your daily activities"
- **NAMING**—"Name this object" (e.g. pen)
- **REPETITION**—"No ifs, ands, or buts"

SPECIFIC ENTITIES (CONT'D)**DYSARTHRIA (SPEECH IMPAIRMENT)**

- **DYSARTHRIA**—speech disorder resulting from disturbances in muscular control that affects respiration, articulation, phonation, resonance, or prosody
- **DYSPHONIA**—voice disturbance in parameters of vocal quality, pitch, or intensity

DISTINGUISHING FEATURES BETWEEN DIFFERENT TYPES OF APHASIA

	Wernicke	Broca	Global	Anomic	Conduction	Transcortical motor	Transcortical sensory
Fluency	Normal	–	–	Normal	Normal	–	Normal
Comprehension	–	Normal	–	Normal	Normal	Normal	–
Naming	–	–	–	–	–	–	–
Repetition	–	–	–	Normal	–	Normal	Normal
Reading	–	–	–	Normal	–	+/-	–
Writing	Normal	–	–	Normal	–	+/-	–
Other associated signs		Right hemiparesis / hemisensory loss	Right hemiparesis /hemisensory loss				

Types of dysarthria

Spastic (bilateral upper motor neuron)

Hyperkinetic (extrapyramidal [Huntington])

Hypokinetic (extrapyramidal [Parkinson])

Ataxic (cerebellar lesion)

Flaccid (LMN [myasthenia gravis])

Quality

Harsh, strained voice, reduced dexterity

Low pitch voice

Harsh, strained voice

Low pitch voice

Voice stoppages

Rapid rate, monopitch, low volume

Explosive, scanning speech

Breathy, nasal, low volume

Wheezing

SPECIFIC ENTITIES (CONT'D)

PRIMITIVE REFLEXES

- **GRASP REFLEX**—deep pressure over palmar surface results in grasp response
- **SUCK REFLEX**—insertion of an object into mouth results in sucking motion

SPECIFIC ENTITIES (CONT'D)

- **ROOT REFLEX**—gentle stroking of cheek results in mouth turning toward that side
- **SNOUT REFLEX**—gentle pressure over the nasal philtrum results in puckering of lips
- **GLABELLAR TAP REFLEX**—repeated tapping forehead produces persistent blinking

Cranial Nerve Examination

CN	Nucleus location	Skull exit	Abnormalities
I	Olfactory tract	Cribriform plate	Sensory—smell (coffee, vanilla, peppermint)
II	Thalamus	Optic canal	Sensory—visual acuity and color, visual fields, blind spot, fundoscopy Reflex—pupillary reflex (afferent)
III	Midbrain	Superior orbital fissure ^b	Motor—ptosis and eye deviated downward and outward. Poor medial elevation and accommodation ^d Reflex—pupillary reflex (efferent) Parasympathetic—pupillary dilation ^d
IV	Midbrain	Superior orbital fissure ^b	Motor—patient tilts head to contralateral side, vertical diplopia worst looking to one side and down
V	Principal—Pons Spinal—pons to spinal cord Mesencephalic—midbrain Motor—Pons	V1—superior orbital fissure ^b V2—foramen rotundum V3—foramen ovale	Sensory—light touch, pain and temperature over V1, V2 and V3 ^e Reflex—corneal reflex (afferent) and jaw jerk (afferent and efferent) Motor—wasting of temporal and masseter muscles, weakness of jaw movement
VI	Pons	Superior orbital fissure ^b	Motor—crossed eyes, impaired lateral gaze
VII ^a	Motor, solitary, superior salivatory—Pons to midbrain	Motor—internal acoustic meatus ^c and stylomastoid foramen Taste—stylomastoid foramen	Sensory—numbness around the ear canal and altered taste (anterior 2/3 of tongue) Motor—difficulty raising eye brows, closing eyes, frowning, blowing out cheeks and showing teeth. Altered speech (“Pa Pa Pa”) and hyperacusis Reflex—corneal reflex (efferent) Parasympathetic – lacrimation and saliva production ^f
VIII	Vestibular, cochlear— medulla	Internal acoustic meatus ^c	Sensory—whispering, Rinne test, Weber test. Dix-Hallpike maneuver (if vertigo). Check for nystagmus
IX	Nucleus ambiguus, inferior salivatory, solitarius—medulla	Jugular foramen	Sensory—sensation of palate, taste (posterior 1/3 of tongue) Motor—uvula and palate movement. Speech (“Ka Ka Ka”), coughing, swallowing Reflex—gag reflex
X	Nucleus ambiguus, dorsal motor vagal, solitary—medulla	Jugular foramen	Sensory—sensation of palate Motor—uvula and palate movement. Speech (“Ka Ka Ka,” hoarseness), coughing, swallowing Reflex—gag reflex

Cranial Nerve Examination (Cont'd)

CN	Nucleus location	Skull exit	Abnormalities
XI	Spinal accessory— cervical cord	Jugular foramen	Motor—weakness with shrugging shoulders and rotating head against resistance
XII ^a	Medulla	Hypoglossal foramen	Motor—tongue wasting and fasciculations, tongue deviation (toward affected side). Altered speech (“La La La”)

^a**UPPER MOTOR NEURON INNERVATION**—all cranial nerves receive bilateral innervation from the cortex, except for VII (lower facial muscles) and XII (tongue), which receive innervation from the contralateral pyramidal tract only. Therefore, a left MCA stroke can cause right lower facial droop and tongue deviation to the right. See Bell palsy (p. 334) for differentiating UMN vs. LMN VII palsy

^b**CAVERNOUS SINUS LESIONS** (tumor, aneurysm, and thrombosis)—may lead to III, IV, V1 and VI palsies

^c**CEREBELLOPONTINE ANGLE LESIONS** (acoustic neuroma, glomus tumor)—may lead to V1–3, VII, and VIII palsies

^d**OCULOMOTOR (III) NERVE LESIONS**—central lesions include vascular lesions and tumor of brainstem. Peripheral lesions include aneurysm, tumor, meningitis, nasopharyngeal carcinoma, orbital lesions, and ischemic lesions (diabetes, hypertension). “Pupil-sparing” suggests ischemic lesions (as opposed to compressive aneurysmal lesions) as they tend to involve the central portion of the nerve, sparing the parasympathetic fibers. Spontaneous resolution of symptoms typically occurs over 3–6 months. Intact accommodation reflex but absent light reflex suggests midbrain tectal lesion (Argyll Robertson pupil in neurosyphilis)

^e**TRIGEMINAL (V) NERVE LESIONS**—sensory function can be helpful in localization. If all three divisions (V1–V3) get affected, the lesion is likely at the ganglion or sensory root level (trigeminal neuroma, meningioma). If only a single division is affected, the lesion is likely at the post-ganglion level (e.g. V1 abnormality alone suggests cavernous sinus lesion). Loss of pain/temperature sensation but not light touch suggests brainstem or upper cord lesion (syngolbulbia, PICA infarction). Loss of light touch but not pain/temperature suggests pathology of pontine nuclei (tumor, vascular lesion)

^f**FACIAL (VII) NERVE LESIONS**—for details on localization, please refer to p.365

SPECIFIC ENTITIES

VISUAL FIELD DEFECTS

- **MONOCULAR VISUAL LOSS**—lesion is located before optic chiasm (optic nerve, eye pathology)
- **BITEMPORAL HEMIANOPIA**—lesion is at the optic chiasm. The pituitary gland lies below the optic chiasm. A pituitary adenoma may compress the optic chiasm inferiorly, causing superior bitemporal quadrantanopsia and eventually complete bitemporal hemianopsia
- **HOMONYMOUS HEMIANOPIA**—lesion is located post optic chiasm, contralateral
- **FORMAL VISUAL FIELD TESTING**—Goldman perimeter, Humphrey

SPECIFIC ENTITIES (CONT'D)

OCULAR FINDINGS IN HYPERTENSION AND DIABETES

- **HYPERTENSION**—see p. 70
- **DIABETES**—see p. 365

Related Topics

Diplopia (p. 331)
Dysarthria (p. 328)
Facial Droop (p. 332)
Ptosis (p. 353)

SPECIFIC ENTITIES (CONT'D)**DISTINGUISHING FEATURES BETWEEN PAPILLEDEMA, OPTIC ATROPHY, AND OPTIC NEURITIS**

	Papilledema	Optic atrophy	Optic neuritis
Etiology	↑ ICP Tumors Malignant hypertension	Neuritis Glaucoma Congenital	Multiple sclerosis Inflammatory Infectious
Symptoms	Headaches N&V, ↓ level of consciousness Focal deficits	↓ vision ↓ color	↓ vision ↓ color Eye pain
Optic disc	Swollen optic disc Disc margins obscured	Gray–white optic disc	Swollen optic disc
Other signs	Flame hemorrhages Cotton wool spots ↑ blind spot	↓ acuity ↓ color vision ↓ pupil reflex	↓ acuity ↓ color vision ↓ pupil reflex ↑ blind spot

MEDULLARY SYNDROMES

	Medial (Dejerine syndrome)	Lateral (Wallenberg syndrome)
Artery supply	Vertebral and anterior spinal arteries	Vertebral artery or posterior inferior cerebellar artery
Structures (ipsilateral)	Hypoglossal nucleus & CN XII— tongue weakness	Trigeminal nucleus & tract—↓ facial sens Vestibular nuclei—nystagmus, vertigo, nausea, ataxia Nucleus ambiguus—dysphagia, hoarseness Nucleus solitaries—altered taste Sympathetic—Horner
Motor (contralateral)	Pyramidal tract—UMN weakness	None
Sensory (contralateral)	Medial lemniscus—vibration, proprioception	Spinothalamic tract—↓ pain and temperature
Cerebellum (ipsilateral)	Normal	Inferior cerebellar peduncle—ataxia

Diplopia**DIFFERENTIAL DIAGNOSIS**

BINOCULAR DIPLOPIA (resolves with one eye closed, suggestive of ocular misalignment)

- **CRANIAL NERVES**—III, IV, VI palsy, internuclear ophthalmoplegia

- **RECTUS MUSCLES**—myasthenia gravis, trauma

MONOCULAR DIPLOPIA (persists with one eye closed, suggestive of intrinsic eye disease)

- **CORNEA**—deformity, keratoconus

- **LENS**—cataract, displaced lens

- **RETINA**—macular scarring

PATHOPHYSIOLOGY**EXTRAOCULAR EYE MOVEMENTS**

Muscle	Nerve	Movement
Superior rectus	III	Elevation and intorsion
Inferior rectus	III	Depression and extorsion
Lateral rectus	VI	Abduction
Medial rectus	III	Adduction
Superior oblique	IV	Depression and intorsion
Inferior oblique	III	Elevation and extorsion

CLINICAL FEATURES

HISTORY—determine whether diplopia resolves with one eye closed, which direction diplopia is worse, whether separation of images occurs vertically, horizontally, or obliquely, whether any head position makes diplopia better, and whether diplopia is worse at distance (typically lateral rectus palsy) or near (typically medial rectus palsy). Characterize duration, progression, limitation of function and any pain. Past medical history (head injury, stroke, infections, aneurysm, myasthenia gravis) and medications

PHYSICAL—inspect for eye position, corneal abrasion, cataract, ptosis (CN III palsy, myasthenia gravis), eyelid retraction (thyroid ophthalmopathy), and extraocular eye movements (each eye individually, then both eyes together). Palpate for bony tenderness. Auscultate over eye for bruit of carotid cavernous fistula. Also check visual acuity, visual fields, pupil size, pupillary reflex, exophthalmos, and examine the other cranial nerves (particularly II, V, VII)

INVESTIGATIONS**BASIC**

- **IMAGING**—CT head, MR skull/orbit

INVESTIGATIONS (CONT'D)**SPECIAL**

- **ICE PACK TEST**—place ice pack on ptotic eyelid for 1–2 minutes to improve neuromuscular transmission and assess for improvement if myasthenia gravis

MANAGEMENT

TREAT UNDERLYING CAUSE—extraocular muscle surgery, prisms

SPECIFIC ENTITIES**INTERNUCLEAR OPHTHALMOPLEGIA (INO)**

- **PATHOPHYSIOLOGY**—lesion in the medial longitudinal fasciculus (MLF), which connects the ipsilateral VI nucleus with the contralateral III nucleus
- **CAUSES**—multiple sclerosis (bilateral), brainstem infarction (unilateral), infections, malignancy, metabolic
- **CLINICAL FEATURES**—horizontal eye movement with weak adduction of the ipsilateral eye and abduction nystagmus of the contralateral eye

Bell PalsyGilden *NEJM* 2004;351(13)**CAUSES OF FACIAL DROOP**

CENTRAL (upper motor neuron)—stroke

PERIPHERAL (lower motor neuron)

- **PONS**—infarction, glioma, multiple sclerosis
- **CEREBELLOPONTINE ANGLE**—acoustic or facial neuroma, meningioma, cholesteatoma, lymphoma, aneurysm, sarcoidosis
- **INTERNAL AUDITORY CANAL PROXIMAL TO OR INVOLVING GENICULATE GANGLION**—Bell palsy, Ramsay Hunt syndrome (VZV), acoustic or facial neuroma
- **DISTAL TO INTERNAL AUDITORY CANAL AND GENICULATE GANGLION**—Bell palsy, temporal bone fracture, cholesteatoma, glomus tumor, middle-ear infection
- **STYLOMASTOID FORAMEN**—head injury, parotid tumor

PATHOPHYSIOLOGY

INNERVATION—the upper facial muscles are innervated by both cerebral hemispheres, while the lower facial muscles are only innervated by the contralateral cerebral hemisphere. Thus, an upper motor neuron lesion would spare the

PATHOPHYSIOLOGY (CONT'D)

upper face, while a lower motor neuron lesion would lead to ipsilateral upper and lower facial weakness

CLINICAL FEATURES**DISTINGUISHING FEATURES BETWEEN UPPER AND LOWER MOTOR NEURON FACIAL NERVE LESIONS**

	Central (stroke)	Peripheral (Bell palsy)
Lesion	Contralateral cortex or corticobulbar fibers	Ipsilateral facial nerve nucleus or facial nerve
Upper facial muscles	Furrows present	No furrows
	Can close eyes	Cannot close eyes
Lower facial muscles	Unable to show teeth	Unable to show teeth
Salivation, taste, and lacrimation	Normal	Varies depending on lesion location ^a

CLINICAL FEATURES (CONT'D)

	Central (stroke)	Peripheral (Bell palsy)
Other findings	Hemiplegia (same side as palsy)	Hyperacusis

*Lacrimation, salivation, and taste all affected if lesion in internal auditory canal proximal to or involving geniculate ganglion. Lacrimation intact but salivation and taste both affected if lesion distal to geniculate ganglion. Lacrimation, salivation, and taste all intact if lesion in cortex, pons, cerebello-pontine angle, or at stylomastoid foreman

INVESTIGATIONS**BASIC**

- **LABS**—CBC, fasting glucose

SPECIAL

- **IMAGING**—MRI head (in atypical cases)
- **CENTRAL CAUSES WORKUP**—Lyme serology, VDRL, HIV serology, lumbar puncture
- **ELECTRONEUROGRAPHY**—if persistent facial paralysis after 1 week of treatment

DIAGNOSTIC AND PROGNOSTIC ISSUES FOR BELL PALS

INVESTIGATIONS—consider if other cranial nerve deficits develop, no recovery in 3–6 weeks, facial twitch or spasm precedes Bell palsy (suggestive of tumor)

DIAGNOSTIC AND PROGNOSTIC ISSUES FOR BELL PALS

PROGNOSIS—71% of untreated patients recover spontaneously

MANAGEMENT OF BELL PALS

TREAT UNDERLYING CAUSE—*prednisone* 1 mg/kg PO \times 7 days (given within 3 days of onset). For severe facial weakness, consider *valacyclovir* 1 g PO TID \times 7 days. Surgical decompression (only if documented 90% nerve degeneration by electroneurography)

SPECIFIC ENTITIES

RECURRENT OR BILATERAL FACIAL PALS—Guillain-Barré syndrome, myasthenia gravis, lesions at skull base (lymphoma, sarcoidosis, Lyme disease)

RAMSAY HUNT SYNDROME—reactivation of herpes zoster virus in geniculate ganglion. Polycranial neuropathy affecting CN V, IX, X. Facial palsy, ear pain, and vesicles in external auditory meatus may be present. Taste often affected, \pm vertigo. Consider antiviral therapy

Multiple Sclerosis**DIFFERENTIAL DIAGNOSIS**

INFLAMMATORY DISEASES—neuromyelitis optica spectrum disorders (Devic disease), acute disseminated encephalomyelitis, SLE, PAN, Sjögren, Behçet disease, granulomatous angiitis, paraneoplastic encephalomyelopathies

INFECTIONS—Lyme neuroborreliosis, neurosyphilis, HIV, HTLV-1, PML (JC virus)

GRANULOMATOUS DISEASES—sarcoidosis, granulomatosis with polyangiitis, lymphomatoid granulomatosis

DISEASES OF MYELIN—adult metachromatic leukodystrophy, adrenomyeloleukodystrophy

OTHERS—vitamin B12 deficiency, Arnold-Chiari malformation, spinocerebellar disorders

PATHOPHYSIOLOGY

MULTIPLE SCLEROSIS—autoimmune demyelination of the central nervous system

CLINICAL COURSE

- **RELAPSING-REMITTING**—85% at presentation, half will have more progressive disease over time. Average about 1 attack every 2 years
- **PRIMARY PROGRESSIVE**—15% at presentation
- **SECONDARY-PROGRESSIVE**—occurring after a relapsing-remitting period
- **PROGRESSIVE-RELAPSING**—relapsing course, but with overall progression following each relapse

EXACERBATIONS—new neurological deficit or reappearance/worsening of old deficit that lasts

PATHOPHYSIOLOGY (CONT'D)

longer than 24 h and is not due to fever or other systemic process

PSEUDO-EXACERBATIONS—transient fluctuations in neurological function due to concomitant illness (e.g. UTI), heat, or exertion that typically resolve with removal of precipitant

CLINICAL FEATURES

CRANIAL NERVES—optic neuritis (afferent pupillary defect), diplopia (internuclear ophthalmoplegia, especially if bilateral), trigeminal neuralgia, other cranial nerves

SENSORY (most common)—paresthesia, dysesthesia, hyperesthesia. Pain syndromes include trigeminal neuralgia, Lhermitte sign (lightning bolt radiating down neck with flexion), dysesthetic pain, back pain, visceral pain, and painful tonic spasms. May be migratory (contralateral, ascending). Other sensory changes include useless hand syndrome (loss of discriminatory function and proprioception), “cold water trickling” feeling along limb, and pseudoathetosis (loss of sensory feedback from arm causing involuntary writhing movements of fingers and wrist when eyes closed)

TONE—spasms spells (maybe painful), spontaneous clonus

MOTOR—weakness, spasticity, and hyperreflexia. Upper motor neuron weakness in lower extremities characteristic of multiple sclerosis

AUTONOMIC—bladder, bowel, and erectile dysfunction

CEREBELLAR—loss of balance, action tremor, slurred speech, and incoordination

COGNITIVE—inattention, slowed information processing, memory loss, and difficulties with abstract concepts and complex reasoning

FATIGUE, DEPRESSION

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, Ca, Mg, PO₄, CK, quantitative Ig, ANA, ENA
- **IMAGING**—MRI head/spine (sens 90%)
- **LUMBAR PUNCTURE**—with CSF IgG index and oligoclonal bands (mild lymphocytosis <50/mm³, mild ↑ protein with ≥2 oligoclonal bands)

SPECIAL

- **EVOKED POTENTIAL STUDIES**

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIAGNOSTIC CRITERIA—typical MS-related demyelinating syndrome with objective evidence of CNS involvement and fulfilling **dissemination in space criteria** (clinical attacks localizing to 2 different CNS locations or symptomatic/asymptomatic T2 MRI lesions in at least 2 of the 4 regions [periventricular, cortical/juxtacortical, infratentorial, spinal cord]) and **dissemination in time criteria** (CSF oligoclonal bands, or second clinical attack, or simultaneous gadolinium enhancing and non-enhancing lesions on MRI, or interval development of new T2 lesion on MRI) with no better explanation other than MS

2017 Position Paper Revisions McDonald Criteria Diagnosis MS

PROGNOSIS—most patients initially in relapsing–remitting course experience relapses with complete or partial recovery once to twice a year. At 10 years, 50% enter secondary progressive phase and 90% by 25 years. Primary progressive disease affects 15% of patients, more commonly men. Eventually, 1/3 of patients would develop disabling paraparesis, 1/4 incontinent or catheterized, and 15% confined to wheelchair; 50% of patients unable to work at 5 years; 10% may remain minimally disabled at 10 years

POOR PROGNOSTIC FACTORS IN RELAPSING–REMITTING MULTIPLE SCLEROSIS—>2 exacerbations/year, motor/cerebellar exacerbations, older age at onset (greater than 40 years), residual motor/cerebellar deficits 6 months following attack, moderate disability within 5 years, number of lesions on MRI

GOOD PROGNOSTIC FACTORS IN RELAPSING–REMITTING MULTIPLE SCLEROSIS—initial presentation optic neuritis, purely sensory disorder, lower number of lesions on MRI

MANAGEMENT

EXACERBATIONS—*methylprednisolone* 500–1000 mg IV daily × 3–7 days or *prednisone* 1250 mg PO daily × 3–7 days ± short taper. Plasma exchange

IMMUNOTHERAPY—no consensus guidelines. Treatment choice based on relative risks/benefits as well as patient/clinician preference. For newly diagnosed disease, consider Avonex® (interferon β-1a), Betaseron® (interferon β-1b), Copaxone® (glatiramer acetate), Rebif® (interferon β-1a),

MANAGEMENT (CONT'D)

Tecfidera® (dimethyl fumarate), or Aubagio® (teriflunomide). For highly active relapsing-remitting MS with inadequate response to interferon β or glatiramer acetate, consider Gilenya® (fingolimod), Mayzent® (siponimod), Tysabri® (natalizumab), Lemtrada® (alemtuzumab), Ocrevus® (ocrelizumab)

- **RELAPSING-REMITTING**—early treatment shown to have favorable outcomes
- **PRIMARY AND SECONDARY PROGRESSIVE**—evidence does not support benefit from interferon β in primary progressive disease, and limited in secondary progressive disease

Reich et al. *NEJM* 2018;378(2)

MANAGEMENT (CONT'D)

SYMPTOM CONTROL—**fatigue** (*amantadine* 100 mg PO BID; *modafinil* 100 mg PO TID), **spasticity** (physiotherapy, baclofen, tizanidine, benzodiazepines), **hyperreflexic bladder** (fluid restriction, timed voiding, oxybutynin, propantheline, imipramine, intermittent catheterization)

Related Topics

Cranial Nerve Lesions (p. 329)

Orthostatic Hypotension (p. 53)

Dementia

See DEMENTIA (p. 419)

Delirium

See DELIRIUM (p. 422)

Seizures

French et al. *NEJM* 2008;359(2)

2017 ILAE Position Paper Classification Seizure Types

DIFFERENTIAL DIAGNOSIS

PROVOKED SEIZURES—due to a temporary lowered seizure threshold; recurrence risk generally small and anti-seizure medication usually not required long-term; focus on correcting provoking etiology

- **DRUGS**—sedative withdrawal (ETOH, benzodiazepine), sympathomimetics (cocaine, amphetamine), others (clozapine, cephalosporins, fluoroquinolones, bupropion, tramadol, meperidine, theophylline, isoniazid, high-dose penicillin, imipenem)
- **INFECTIONS**—fever, abscess, meningitis, encephalitis
- **METABOLIC**—hypoglycemia, hyperglycemia, hyponatremia, hypocalcemia, hypomagnesemia, uremia, hyperthyroidism, acute intermittent porphyria
- **STRUCTURAL**—concussion/traumatic brain injury, subdural hematoma, acute stroke, subarachnoid hemorrhage, central venous thrombosis, hypoxic ischemic injury
- **OTHER**—eclampsia, posterior reversible encephalopathy syndrome,

DIFFERENTIAL DIAGNOSIS (CONT'D)

UNPROVOKED SEIZURES AND EPILEPSY—anti-seizure medication treatment usually required. Inflammatory and structural etiologies are considered unprovoked when seizures occur outside the initial acute phase of injury, usually 1 week

- **STRUCTURAL**—stroke, trauma, infection, hypoxic ischemic encephalopathy, malformations of cortical development, mesial temporal lobe sclerosis, hypothalamic hamartoma, Rasmussen syndrome
- **GENETIC**—monogenic (e.g., Dravet), polygenic/multifactorial (e.g., juvenile myoclonic epilepsy)
- **INFECTIOUS**—meningitis, encephalitis, neurocysticercosis, tuberculosis, HIV, cerebral malaria, subacute sclerosing panencephalitis, cerebral toxoplasmosis, congenital infections (e.g., CMV)
- **METABOLIC**—porphyria, uremia, aminoacidopathies, or pyridoxine-dependent seizures

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **IMMUNE**—NMDA, LGI1, AMPA, GABA, GAD, Hu, Ma2
- **IDIOPATHIC (UNKNOWN)**

SEIZURE MIMICS

- **SYNCOPE**—vasovagal, cardiogenic, neurogenic
- **PSYCHOGENIC NON-EPILEPTIC SEIZURES (PSEUDO-SEIZURES)**—stressful psychological conflicts, major emotional trauma
- **OTHER**—TIA, migraine, benign positional vertigo, hypoglycemia, sleep disorders (sleep apnea, narcolepsy/cataplexy, night terrors, nightmares, nocturnal myoclonus), periodic paralysis, breath-holding spells

PATHOPHYSIOLOGY**DEFINITIONS**

- **SEIZURE**—"a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" (ILAE 2005)
- **EPILEPSY**—enduring predisposition to seizures defined by (1) two or more unprovoked seizures separated by 24 h; (2) one unprovoked seizure and probability of second seizure of at least 60% over the next 10 years (i.e., often in context of prior brain insult, abnormal brain imaging, epileptiform discharges on EEG, nocturnal event, or abnormal neurologic exam); or (3) diagnosis of an epilepsy syndrome

CLASSIFICATION

- **FOCAL ONSET SEIZURE**—originating in one cortical hemisphere and further subclassified by awareness. Further optional subclassification can be made based on the first prominent symptom; motor (automatisms, atonic, clonic, tonic, hyperkinetic, epileptic spasms) or non-

PATHOPHYSIOLOGY (CONT'D)

motor (autonomic, behavioral arrest, cognitive, emotional, sensory)

- **FOCAL AWARE SEIZURE**—indicates retained sense of self and the environment during the seizure. Correlates with old terminology of "simple partial seizure"
- **FOCAL IMPAIRED AWARENESS SEIZURE**—impairment in awareness at some point during the seizure. Correlates with old terminology of "complex partial seizure"
- **GENERALIZED ONSET SEIZURE**—engaging cortex bilaterally. Loss of consciousness
- **UNKNOWN ONSET SEIZURE**—obscured or missed seizure onset
- **STATUS EPILEPTICUS**—5 min of continuous seizure activity, or ≥ 2 discrete seizures without complete recovery of consciousness in between events

COMPLICATIONS OF SEIZURES—seizure related injuries (see Medical Fitness to Drive, p. 492), aspiration pneumonia, neurogenic pulmonary edema, hypoxic brain injury, cardiac injury, rhabdomyolysis (acute renal failure, hyperkalemia), lactic acidosis, sudden unexpected death in epilepsy (SUDEP), lifestyle (driving, work safety), psychosocial (stigma)

CLINICAL FEATURES

HISTORY—when was first seizure, prodrome, aura, ictal symptoms, postictal period, diurnal variation, history suggestive of missed seizure (e.g. waking up with sore muscles, blood in the mouth, or urinary incontinence), precipitants (e.g. sleep deprivation, skipped meals, stress, menses, alcohol, missed medications, medication withdrawal), maximum seizure-free period, seizure types, related injuries, driving and employment

DISTINGUISHING FEATURES BETWEEN SEIZURES AND SYNCOPE

	Generalized seizures	Vasovagal syncope
Past history	Seizures, head injury, stroke, tumor	No strong history
Pre-event	Awake or sleep No warning Aura	Usually upright Usually warning Lightheaded
Event	Vocalization at onset Tonic-clonic convulsions Cyanotic/gray Incontinence frequent Tongue biting (side)	No vocalization Occasional myoclonic movements, hypotonia Pale Incontinence occasionally Tongue biting rare (tip)

	Generalized seizures	Vasovagal syncope
	Frequent injuries (fall on face, #, dislocations)	Less commonly injured
	Longer ↓ level of consciousness	Short ↓ level of consciousness
Post-event	Confused, tired, sleepy, post-ictal Todd paralysis	Alert
	Muscle ache	Diaphoretic

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, Ca, Mg, PO₄, AST, ALT, ALP, bilirubin, albumin, CK, troponin, TSH, INR, PTT, prolactin (acute increase 10–20 min after generalized tonic clonic seizures, low sens)
- **IMAGING**—CT head, MRI head
- **EEG ± SLEEP DEPRIVATION**—for unprovoked or recurrent seizures (best done within 24 h of seizure onset). Consider also sleep deprived EEG to increase the yield of detecting epileptiform activity/focal abnormality

SPECIAL

- **CXR**—if suspect aspiration
- **LUMBAR PUNCTURE**—if suspect meningitis/encephalitis

DIAGNOSTIC ISSUES

AURA—focal seizure with subjective sensory or psychic phenomenon

JACKSONIAN MARCH—focal motor seizure of primary motor cortex will produce clonic activity in contralateral side of the body. Rhythmic activity spreads to adjacent areas (e.g. fingers to wrists to arms)

TODD PARALYSIS—hemiparesis or hemiplegia following a seizure, suggests focal onset

ELECTROENCEPHALOGRAM (EEG)

- **DIAGNOSTIC**—useful for epilepsy (sens 40–50%, high spc), metabolic and toxic encephalopathies, herpes encephalitis, subacute sclerosing panencephalitis, and prion diseases such as Creutzfeldt–Jakob disease
- **PROGNOSTIC**—useful for anoxic brain injury (burst suppression, alpha coma, and electrocerebral silence suggests very poor prognosis)

MANAGEMENT

STATUS EPILEPTICUS—**ABC**, O₂, IV, **stat investigations** (ABG, CBC, lytes, Cr, glucose, Mg, Ca, PO₄, toxic screen, antiepileptic drug level), *glucose* if hypoglycemia (*thiamine* 100 mg IV, 50% *dextrose* 50 mL IV), **first line** (*lorazepam* 2 mg q1–3 min IV push, consider rectal diazepam if no

MANAGEMENT (CONT'D)

IV access), **second line** (*phenytoin* 20 mg/kg IV [no faster than 50 mg/min, start continuous monitor], or *valproic acid* 20–40 mg/kg IV [max dose 3000 mg], or *levetiracetam* 60 mg/kg IV [max dose 4500 mg]), **third line** (*midazolam* 0.05–0.3 mg/kg over 20–30 s, repeat PRN), **fourth line** (anesthetic doses of *propofol* 50–100 mg IV bolus, need to intubate). Note: phenytoin and benzodiazepines are incompatible in IV tubing and will precipitate if infused in same line. Use separate IV sites. See p. 481 for treatment of rhabdomyolysis

ACUTE SEIZURE CONTROL—**benzodiazepines** (*lorazepam* 1 mg IV/SL PRN, up to a total dose of 0.1 mg/kg, *midazolam* 5–10 mg [or 0.2 mg/kg; max 10 mg] IM or intranasal once, *diazepam* 10–20 mg [or 0.2 mg/kg; max 20 mg] PR once). **Antiepileptic** (*fosphenytoin* 20 mg/kg IV, *phenytoin* 300 mg IV over 10 min, levetiracetam, carbamazepine, valproate). If **alcohol withdrawal** (add *thiamine* 100 mg IV/PO daily, *multivitamin* 1 tab IV/PO daily)

LONG-TERM MANAGEMENT—*valproic acid* 200–500 mg or 10–15 mg/kg PO daily, increase dose by 250–500 mg/week, typical daily dose is 750–2000 mg; *lamotrigine* 25 mg PO daily, increase dose by 25 mg/week, typical daily dose is 100–400 mg; *topiramate* 25–50 mg PO daily, increase by 25–50 mg/week, typical daily dose is 200–400 mg; *levetiracetam* 250–500 mg PO BID, increase dose by 250–500 mg/week, typical daily dose is 1000–3000 mg; *carbamazepine* 200 mg PO daily, increase by 200 mg every 3 days, typical daily dose is 400–800 mg divided BID; *phenytoin* 3–5 mg/kg PO daily (loading dose may be given for quicker effect), typical daily dose is 200–400 mg; *gabapentin* 300 mg daily-BID, increase dose by 300–600 mg/week, typical daily dose is 1800–3600 mg; *pregabalin* 75–150 mg PO daily, increase dose by 75–150 mg/week, typical daily dose is 150–300 mg

PSYCHOSOCIAL ASPECTS—loss of independence, employment, insurance, self-esteem, and ability to drive

MANAGEMENT (CONT'D)

DRIVING ISSUES—recommendations vary from region to region. Canadian Medical Association publishes the *CMA's Driver's Guide* to help evaluate medical fitness to drive. Check with driving authority for specific restrictions and legal requirements. A single unprovoked seizure often has shorter driving restriction of 3 months or no driving restriction. If >1 unprovoked seizure, consider 6–12 months of seizure-free interval before reinstating driver's license (varies with jurisdiction). Some places may also restrict driving for 6 months after antiepileptic dose adjustments. More stringent rules may exist for commercial drivers

TREATMENT ISSUES

FIRST TIME SEIZURE—if no structural lesion, no physical findings, and normal EEG, usually do not need to start antiseizure medications. Risk of recurrence after first seizure is 30–60%. Risk after second seizure is 80–90%

ANTIEPILEPTIC CHOICES

- **BROAD-SPECTRUM ANTIEPILEPTIC DRUGS**—include valproic acid, lamotrigine, topiramate, levetiracetam, brivaracetam, felbamate, perampnel, rufinamide and zonisamide
- **NARROW-SPECTRUM ANTIEPILEPTIC DRUGS**—include carbamazepine, lacosamide, phenytoin, gabapentin, pregabalin, oxcarbazepine, eslicarbazepine, cenobamate, phenobarbital, stiripentol, vigabatrin and tiagabine. These medications are effective against focal seizures with or without secondarily generalized features, but have limited activity against primary generalized seizure disorders (e.g. carbamazepine may even worsen juvenile myoclonic epilepsy)

	P	C	V	B	L	G	T	E
Tonic-clonic	+	+	1	+	+	±		
Absence			+					1
Status	+			+				
Partial	+	1	+	+		±	+	
Myoclonic			+	+				

Key: P phenytoin, C carbamazepine, V valproate, B phenobarbital, L lamotrigine, G gabapentin, T levetiracetam or topiramate, E ethosuximide, 1 drug of choice, + possible use, ± adjunct use

TREATMENT ISSUES (CONT'D)**ADDITIONAL CONSIDERATIONS**

- **GENERALLY WELL-TOLERATED IN ELDERLY PATIENTS**—levetiracetam, lamotrigine, gabapentin
- **ASSOCIATED WITH HIGH RISK OF RASH**—phenytoin, carbamazepine, lamotrigine
- **ASSOCIATED WITH WEIGHT GAIN**—valproate, gabapentin, carbamazepine
- **ASSOCIATED WITH OSTEOPOROSIS**—phenytoin, carbamazepine, phenobarbital, valproate
- **ASSOCIATED WITH HYPONATREMIA**—carbamazepine, oxcarbazepine
- **MOOD-STABILIZING PROPERTIES**—valproate, lamotrigine, carbamazepine
- **WORSENS PSYCHIATRIC SYMPTOMS**—levetiracetam, perampnel, topiramate
- **CAUTION WITH CARDIAC DISEASE**—lacosamide
- **GENERALLY SAFER WITH RENAL IMPAIRMENT**—levetiracetam, lacosamide (needs dose-adjustment)
- **GENERALLY SAFER WITH LIVER IMPAIRMENT**—levetiracetam, lamotrigine
- **GENERALLY SAFER WITH PREGNANCY**—levetiracetam, lamotrigine, carbamazepine
- **INTERACTION WITH HORMONAL CONTRACEPTION**—lamotrigine, topiramate, carbamazepine, phenytoin, phenobarbital

EPILEPSY SURGERY—consider in focal epilepsy patients who are medically refractory (ongoing seizures despite 2 appropriately chosen and dosed anti-seizure medications). Rates of seizure-freedom after surgery depend on etiology; 65–75% with mesial temporal sclerosis, 60–100% brain tumors, 65–85% cavernous malformations, 60% malformations of cortical development

STOPPING ANTIEPILEPTICS—consider stopping anticonvulsants after a seizure-free period of 2–5 years. Relapse is 26–63% within 1–2 years after withdrawal. Risk factors for recurrence include abnormal EEG before or during withdrawal, abnormal neurologic findings, frequent seizures before remission, and developmental delay. Be sure to consult local driving regulations with regards to restrictions while undertaking an antiepileptic drug taper

DRUG- OR TOXIN-INDUCED SEIZURES—top five drug-induced etiologies include isoniazid, theophylline, oral hypoglycemic agents, carbon monoxide, and bupropion. Supportive management for theophylline-induced, carbon

TREATMENT ISSUES (CONT'D)

monoxide-induced, and bupropion-induced seizures. Treat isoniazide-induced seizures with pyridoxine; hypoglycemic seizures with glucose ± octreotide and glucagon; and carbon monoxide-associated seizures with oxygen (hyperbaric oxygen controversial)

TREATMENT ISSUES (CONT'D)**Related Topics**

Brain Tumors (p. 319)

Seizures in Pregnancy (p. 463)

Toxicology (p. 120)

Syncope

See SYNCOPE (p. 52)

Migraine HeadachesCharles *NEJM* 2017;377(6)Ashina *NEJM* 2020;383(19)**DIFFERENTIAL DIAGNOSIS OF HEADACHES**

PRIMARY—migraine, tension, trigeminal autonomic cephalalgias (cluster), others (primary cough headache, hypnic headache)

INFECTIONS—meningitis, encephalitis, CNS abscess, systemic infection

STRUCTURAL—**hemorrhage** (subarachnoid, epidural, subdural, intracerebral), **thrombosis** (ischemic stroke, cerebral vein), **tumor, trauma**

OTHERS—sinusitis, temporal arteritis, cervicogenic headache, acute angle closure glaucoma, idiopathic intracranial hypertension, low CSF pressure headache, trigeminal neuralgia, pituitary apoplexy, medication overuse headache, substance use, substance withdrawal

CLINICAL FEATURES**RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH HEADACHE HAVE A MIGRAINE OR NEED NEUROIMAGING?**

★**POUND**★ **CRITERIA**—Pulsating, duration of 4–72 h, Unilateral, Nausea, Disabling (LR+ 24 if 4 criteria, LR+ 3.5 if 3 criteria, LR+ 0.41 if ≤2 criteria)

	LR+	LR-
Chronic headache features suggestive of serious intracranial abnormality requiring neuroimaging		
Cluster-type headache	11	0.95
Abnormal findings on neurologic examination	5.3	0.71
Undefined headache	3.8	0.66
Headache with aura	3.2	0.51
Headache aggravated by exertion or a Valsalva-like maneuver	2.3	0.7
Headache with vomiting	1.8	0.47

CLINICAL FEATURES (CONT'D)

APPROACH—"The presence of 4 simple historical features can accurately diagnose migraine." Headaches may be classified as new headache, acute thunderclap headache, or chronic headache. Neuroimaging may be done for new headaches at the discretion of physician. All acute thunderclap headaches should be investigated with neuroimaging and lumbar puncture. Chronic headaches with high risk features above should be investigated with neuroimaging. "No clinical features were useful in ruling out significant pathologic conditions."

Detsky et al. *JAMA* 2006;296(10)

ALARM SYMPTOMS (suggesting secondary causes)—★**SNOOP2**★

- **SYSTEMIC SYMPTOMS OR ILLNESS**—constitutional symptoms (fever, weight loss, malaise, myalgias, scalp tenderness, jaw claudication), malignancy, HIV, pregnancy
- **NEUROLOGICAL SYMPTOMS OR SIGNS**—confusion, decreased level of alertness, meningismus, papilledema, seizures, focal neurologic deficits
- **ONSET OF "THUNDERCLAP HEADACHE"**—maximal intensity within first 60 s
- **OLDER AGE**—new onset after age 50
- **POSTURAL CHANGE**—increased head pain supine (suggesting high ICP), increased head pain standing (suggesting low ICP), precipitated by Valsalva maneuver or exertion
- **PROGRESSIVE WORSENING**—rapidly over days to months, or worsening of a previously stable/typical headache

HISTORY—temporal factors such as onset and duration of each episode as well as frequency are particularly important in making the diagnosis.

CLINICAL FEATURES (CONT'D)

Characterize headaches (location, nature, intensity, radiation, alleviation, and aggravation), precipitants (stress, food, physical activity), and any associated neurological symptoms. Consider past medical history, current medications (especially headache medications). Consider temporal arteritis (jaw claudication, visual changes, scalp tenderness) in the elderly, history of PMR

PHYSICAL—vitals. Neurological examination including visual fields and fundoscopy. Remember to check temporal arteries in the elderly

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, ESR (temporal arteritis), INR, PTT
- **IMAGING**—CT head, MRI head

SPECIAL

- **LUMBAR PUNCTURE**

DIAGNOSTIC ISSUES**INTERNATIONAL HEADACHE SOCIETY MIGRAINE CRITERIA (ICHD-III)**

1. At least 5 attacks
2. Episodic attacks lasting 4–72 h (untreated or unsuccessfully treated)
3. Any 2 of unilateral pain, pulsating, moderate or severe intensity, pain aggravated by or causing avoidance of routine physical activity
4. Any 1 of nausea, vomiting, photophobia, phonophobia
5. Exclude secondary causes

MANAGEMENT OF MIGRAINE HEADACHES

SYMPTOM CONTROL—**regularity in life activities** (sleep, eat, exercise), **first-line agents** (*acetaminophen* 650 mg PO q4h, *ibuprofen* 400–800 mg PO q6h), **second-line agents** (*dihydroergotamine* 0.5–1 mg IV, *ketorolac* 30 mg IV, *sumatriptan* 50 mg PO or 6 mg SC, *naratriptan*, *rizatriptan*, *eletriptan*, *zolmitriptan*), **antiemetics/dopamine antagonists** (*metoclopramide* 10 mg IV, *prochlorperazine* 10 mg IV + 500 mL NS). Consider adding *dexamethasone* 10–25 mg IV or IM × 1 with standard acute migraine therapy for patients in ER or clinic to reduce rate of early headache recurrence

PROPHYLAXIS—indicated if patient has ≥ 3 attacks per month, severe prolonged attacks, or when poor response to abortive medications. Choices include **tricyclic antidepressants**

MANAGEMENT OF MIGRAINE HEADACHES (CONT'D)

(*amitriptyline* 25–150 mg PO nightly nortriptyline), **β -blockers** (atenolol, propranolol, metoprolol, and nadolol), **anticonvulsants** (valproic acid, topiramate, gabapentin), **calcium channel blockers** (verapamil, flunarizine), **botulinum toxin**, **calcitonin gene-related peptide (CGRP) receptor antagonists**

SPECIFIC ENTITIES

CHRONIC DAILY HEADACHES—any headaches >15 days per month for >3 months. Risk factors include obesity, history of frequent headache (>1 per week), caffeine consumption, and overuse of acute headache medications (analgesics, ergots, triptans). Common forms of chronic daily headaches include transformed migraine (migraine symptoms with chronic daily features), medication overuse headache (use of headache medications >15 days per month), and chronic tension-type headache. Less common forms include hemicrania continua, chronic cluster headache, idiopathic intracranial hypertension, spontaneous intracranial hypotension

TENSION HEADACHES—chronic daily, mild-to-moderately severe, bilateral (band like), usually stress related. Treatments include stress reduction, tricyclic antidepressants for prophylaxis, and pain control PRN

CLUSTER HEADACHES—chronic daily headaches with up to 8×1 -h attacks each day lasting 4–8 weeks per episode, with 1–3 episodes per year. Extremely severe, mostly periorbital or temporal. Associated with autonomic symptoms (tearing, rhinorrhea), Horner syndrome (Horton headache), and motor restlessness

HYPNIC HEADACHES—chronic daily (only happens during sleep), moderately severe, bilateral. Treatment includes caffeine or indomethacin

HEMICRANIA CONTINUA—constant exacerbations of severe headaches (“ice-pick” pain), unilateral, cranial autonomic symptoms. By definition, responsive to indomethacin

PAROXYSMAL HEMICRANIA—similar to cluster headaches except that attacks are more frequent ($>5 \times$ and up to $24 \times$ per day) and are shorter (8–25 min). By definition, responsive to indomethacin

IDIOPATHIC INTRACRANIAL HYPERTENSION (PSEUDOTUMOR CEREBRI)

- **PATHOPHYSIOLOGY**—idiopathic \uparrow in intracranial pressure predominantly in obese women of

SPECIFIC ENTITIES (CONT'D)

- child-bearing age → headache worse upon awakening and with change of position, associated with transient visual changes, papilledema and sometimes sixth nerve palsy
- **DIAGNOSIS**—MRI/MRV (to exclude other causes such as cerebral vein thrombosis), lumbar puncture with ↑ opening pressure (>200 mmH₂O in non-obese, >250 mmH₂O in obese patients, otherwise normal CSF chemistry)

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—weight loss, NSAIDs for pain, furosemide, *acetazolamide* 500 mg PO BID initially (max 4000 mg total daily dose). Medical management should be combined with surgical management if visual loss; lumboperitoneal shunting, optic nerve sheath fenestration, serial neuro-ophthalmologist follow-up

Meningitis

See MENINGITIS (p. 257)

Dizziness and VertigoKattah et al. *Stroke* 2009;40(11)**DIFFERENTIAL DIAGNOSIS****VERTIGO**

- **CENTRAL**—vertebrobasilar insufficiency, vertiginous migraine (9%), multiple sclerosis, cerebellopontine angle tumor, cerebellar hemorrhage, subclavian steal
- **PERIPHERAL**—benign positional vertigo (30%), acute labyrinthitis/vestibular neuritis (3%), acute recurrent peripheral vestibulopathy, Ménière disease (6%), cholesteatoma, drugs (aminoglycoside, phenytoin), acoustic neuroma, herpes zoster oticus, deep sea diving

SYNCOPE/PRE-SYNCOPE/ORTHOSTATIC HYPOTENSION—see SYNCOPE (p. 52)

IMBALANCE—spastic gait (infarction), apraxic gait (normal pressure hydrocephalus, frontal lobe dementia, Alzheimer), ataxia gait (cerebellar disorder), shuffling gait (Parkinson disease), sensory ataxia gait (decreased proprioception), Trendelenburg gait (proximal muscle weakness), steppage gait (impaired dorsiflexion)

VAGUE DIZZINESS/LIGHT-HEADEDNESS—panic attacks, hyperventilation, multisensory dizziness

CLINICAL FEATURES

HISTORY—distinguish between vertigo (illusion of movement), light-headedness, pre-syncope, and imbalance. Characterize duration of each episode and frequency (most important), direction of spin, precipitants, aggravations (standing or other positions), alleviations, any associated neurologic symptoms (particularly hearing changes, visual

CLINICAL FEATURES (CONT'D)

changes, facial sensory change, bulbar symptoms, headache), N&V, falls, past medical history (stroke, malignancy), medications (aminoglycosides)

PHYSICAL—postural vitals. Complete neurological examination, particularly focusing on nystagmus, hearing, dysmetria, and gait. Examine for BPPV with Dix-Hallpike maneuver (predicts responsiveness to canalith repositioning). HINTS (Head Impulse, Nystagmus, Test of Skew) exam where any one of the 3 (normal horizontal head impulse test, direction-changing nystagmus, or skew deviation) suggests a central rather than peripheral etiology (100% sens, 96% spec)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A SERIOUS FORM OF VERTIGO?

	PPV	NPV	LR+	LR-
History				
Positive head-hanging maneuver plus either vertigo or vomiting predict peripheral vertigo	85%	68%	7.6	0.6
Absence of vertigo or age >69 or presence of neurological deficit predict serious causes of dizziness	40%	88%	1.5	0.3

CLINICAL FEATURES (CONT'D)

APPROACH—"In patients with suspected vertigo, ask whether they have dizziness when changing body position (rolling over in bed, looking up at the ceiling, or bending over to tie shoelaces) and perform a headhanging maneuver to check for positional nystagmus. In combination with other data (including a brief neurological examination) in an emergency department setting, the presence of positional nystagmus can be useful in identifying serious causes of dizziness."

Froehling et al. *JAMA* 1994;271(5)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, Cr, glucose, TSH
- **IMAGING**—CT head, MRI head

SPECIAL

- **ELECTRONYSTAGMOGRAPHY WITH CALORIC TESTING**
- **SYNCOPE WORKUP**—ECG, 24 h Holter
- **AUDIOMETRY**

DIAGNOSTIC ISSUES**DISTINGUISHING BETWEEN CENTRAL AND PERIPHERAL VERTIGO**

	Central	Peripheral
Onset	More gradual	More sudden
Nystagmus	Purely horizontal, vertical, rotational	Usually horizontal and rotational
	Not inhibited by fixation onto object	Inhibited by fixation of eyes onto object
	Persists for a longer period	Shorter duration
N&V	Varies	More severe
Others	Severe imbalance	Tullio phenomenon (nystagmus and vertigo caused by loud noises at a particular frequency)
	Other non-auditory cranial nerve symptoms usually present	Tinnitus, hearing loss

MRI HEAD—used to rule out acoustic neuroma, posterior fossa tumors, stroke, or demyelinating disease. Indications include unexplained asymmetric sensorineural hearing loss with retrocochlear features, sudden and unexplained

DIAGNOSTIC ISSUES (CONT'D)

complete unilateral vestibular loss, or other brainstem signs or symptoms

Related Topic

Syncope (p. 52)

MANAGEMENT

SYMPTOM CONTROL—**benzodiazepines** (*diazepam* 2–10 mg IV), **antihistamines** (*meclizine* 25 mg PO q8–12 h, *dimenhydrinate* 25–50 mg PO q4h, *diphenhydramine* 25–50 mg PO q4h), **antiemetics** (*ondansetron* 4–8mg PO/IV q8h, *prochlorperazine* 5–10mg PO/IV q8h, *promethazine* 25 mg PO q4–6 h), **histamine analogue** (*betahistine* 8–16 mg PO TID for Ménière disease)

SPECIFIC ENTITIES**BENIGN PAROXYSMAL POSITIONAL VERTIGO**

- **PATHOPHYSIOLOGY**—calcium debris in semicircular canals (canalithiasis)
- **CLINICAL FEATURES**—vertigo (typically <1 min/episode, multiple episodes per day) usually precipitated by change in position, nystagmus, and sometimes N&V. No hearing loss or focal deficits
- **DIAGNOSIS**—Dix-Hallpike maneuver (examiner stands at head of bed; patient is supported and quickly lowered into supine position with head ~30° below level of examining table and rotated ~30° to side; examiner observes for induced nystagmus, reproduced symptoms; repeat with rotation in opposite direction)
- **TREATMENTS**—may improve with canalith repositioning maneuvers (e.g. Epley maneuver). Usually self-limited and resolves over months

MIGRAINOUS VERTIGO

- **CLINICAL FEATURES**—vertigo (typically minutes to hours, sporadically), photophobia, sonophobia, headache

BRAIN-STEM/LABYRINTH TIA

- **PATHOPHYSIOLOGY**—embolic/thrombotic phenomenon
- **CLINICAL FEATURES**—vertigo (minutes to hours, sporadically), usually other neurological deficits such as facial sensory loss, diplopia, dysarthria, dysphagia, weakness, or numbness
- **DIAGNOSIS**—CT head, MRI head

SPECIFIC ENTITIES (CONT'D)**MÉNIÈRE'S DISEASE**

- **PATHOPHYSIOLOGY**—endolymphatic hydrops → distension of the labyrinthine system, compressing the perilymphatic spaces
- **CLINICAL FEATURES**—vertigo (typically hours, sporadically), N&V, sensorineural hearing loss, tinnitus and aural fullness
- **DIAGNOSIS**—2 spontaneous episodes of vertigo (>20 min each), audiometric confirmation of sensorineural hearing loss, tinnitus/aural fullness

Hearing Impairment**DIFFERENTIAL DIAGNOSIS**

SENSORINEURAL (inner ear to cortex)—**CVA**, **presbycusis**, **multiple sclerosis**, **Ménière disease**, **trauma** (noise exposure, barotrauma, penetrating trauma), **tumor** (acoustic neuroma, meningioma), **infectious** (viral cochleitis, meningitis, syphilis), **congenital** (viral infections, malformations, hereditary hearing loss), **iatrogenic** (5-FU, bleomycin, nitrogen mustard, erythromycin, vancomycin, tetracycline, aminoglycoside, ASA, otologic surgery), **autoimmune**, **thyrotoxicosis**

CONDUCTIVE

- **MIDDLE EAR**—**trauma** (tympanic membrane perforation, temporal bone trauma), **tumor** (cholesteatoma, otosclerosis, glomus tumors), **infectious** (otitis media), **congenital** (congenital atresia, ossicular chain malformation)
- **OUTER EAR**—**trauma** (canal), **tumor** (squamous cell cancer, exostosis, osteoma), **infectious** (external otitis), **congenital** (congenital microtia, atresia), **others** (cerumen, psoriasis)

MIXED—conductive and sensorineural hearing loss

CLINICAL FEATURES

RINNE TEST—256 Hz tuning fork on mastoid process, when vibration no longer heard, placed in line with external meatus. If can still hear (air conduction > bone conduction), either normal or sensorineural loss on that side (equally affected bone and air conduction). If cannot hear any more (bone conduction > air conduction), conductive hearing loss on that side. Note: positive Rinne test refers to *normal* air conduction > bone conduction (paradoxical terminology)

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—diet and lifestyle (low salt, limit alcohol and caffeine), betahistine, diuretics, steroids, hearing aid use, intracochlear gentamicin injection, labyrinthectomy

ACUTE LABYRINTHITIS/VESTIBULAR NEURONITIS

- **PATHOPHYSIOLOGY**—labyrinthitis/vestibular neuronitis secondary to viral infection
- **CLINICAL FEATURES**—vertigo (typically days, sporadically) that may be precipitated by change in position (labyrinthitis) or spontaneous (vestibular neuronitis), severe N&V

CLINICAL FEATURES (CONT'D)

WEBER TEST—256 Hz tuning fork on bridge of forehead. Normal = equal on both sides. If hear louder on one side, either that side has conductive loss or opposite side has sensorineural loss

	Weber	Rinne
Conductive loss		
Good ear	Quieter	AC > BC
Bad ear	Louder	BC > AC
Sensorineural loss		
Good ear	Louder	AC > BC
Bad ear	Quieter	AC > BC

AC air conduction, BC bone conduction

INVESTIGATIONS**BASIC**

- **FORMAL AUDIOLOGICAL ASSESSMENT**—formal audiogram, tympanogram, site of lesion testing

SPECIAL

- **IMAGING**—MRI/CT of posterior fossa/internal auditory canal
- **REVERSIBLE CAUSES WORKUP**—TSH, VDRL

MANAGEMENT

SYMPTOM CONTROL—**speak in front of patient** so they can read lips (do not speak too loudly as this changes lip movement). If they do not understand, restructure sentence. Do not just repeat. **Write. Hearing amplifier** (stethoscope, electronic)

TREAT UNDERLYING CAUSE—**audiology** and/or **ENT** consult

Ataxia

DIFFERENTIAL DIAGNOSIS

CEREBELLAR ATAXIA

- **HEMISPHERES/POSTERIOR LOBE SYNDROME** (intention tremor, dysmetria, dysdiadochokinesia, slurred speech)
- **SUPERIOR VERMIS/ANTERIOR LOBE SYNDROME** (truncal and gait ataxia)—alcoholism and thiamine deficiency

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **FLOCCULONODULAR LOBE SYNDROME** (dysequilibrium, vertigo, and nystagmus)—brain tumors (medulloblastoma)
- **SENSORY ATAXIA** (proprioceptive changes)—tabes dorsalis, peripheral neuropathy
- **VESTIBULAR ATAXIA** (may be associated with vertigo)
- **THALAMIC ATAXIA** (pyramidal tract signs)

CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN CEREBELLAR DISORDER AND TABES DORSALIS (see p. 262)

	Cerebellar ataxia	Tabes dorsalis
History	Speech Δ Incoordination Gait difficulties	Sensory Δ Bowel/bladder Δ Impotence, pain
Inspection	Normal cognition Ataxic speech	Dementia if neurosyphilis
H&N	Nystagmus Scanning speech Explosive speech	Argyll Robertson pupils Optic atrophy
Motor	Hypotonia Dysmetria, dysdiadochokinesia, heel-shin test Pendular reflexes	Normal tone Heel-shin test Absent reflexes (Westphal sign) Extensor plantar
Sensory	Normal	\downarrow vibration and proprioception
Gait	Truncal ataxia Wide-based gait	Slap foot gait Wide-based gait
Romberg	Positive with eyes closed and open	Positive with eyes closed only

CLINICAL FEATURES (CONT'D)

HISTORY—characterize ataxia (truncal or limb, timing, progressive), speech changes, vision changes, incoordination, falls, headaches, nausea and vomiting, weight loss, past medical history (alcohol use, stroke, multiple sclerosis, malignancy, Wilson disease), medications, family history

PHYSICAL—nystagmus, ataxic speech (“British constitution,” explosive in volume, scanning), hypotonia, dysdiadochokinesia, finger-to-nose test (dysmetria), heel-shin test, pendular reflex,

CLINICAL FEATURES (CONT'D)

wide based stance, ataxic gait (wide based and staggering), rebound (outstretched arms swing easily when pushed), pronator drift (upward), truncal ataxia (Romberg test shows unsteadiness with eyes both open and closed)

INVESTIGATIONS

IMAGING—CT/MR head

MANAGEMENT

TREAT UNDERLYING CAUSE

Subacute Combined Degeneration

See VITAMIN B12 DEFICIENCY (p. 453)

Parkinson Disease

CLASSIFICATION OF MOVEMENT DISORDERS

HYPOKINETIC

- **BRADYKINESIA**
- **RIGIDITY**
- **POSTURAL INSTABILITY**
- **PARKINSONIAN SYNDROMES**—constellation of rest tremor, rigidity, bradykinesia, and loss of postural reflexes

HYPERKINETIC

- **ATAXIA**—incoordination of voluntary movements
- **DYSTONIA/ATHETOSIS**—sustained muscle contraction, causing twisting and repetitive movements/posture
- **TREMOR**—oscillations produced by alternating contractions of reciprocally innervated muscles, e.g. physiological, essential, intention, rest
- **MYOCLONUS**—sudden shock-like muscle contractions, e.g. focal, multifocal, generalized
- **CHOREA/BALLISM**—arrhythmic, rapid, jerky, purposeless movements. Ballismus is large amplitude, proximal chorea, e.g. Huntington chorea
- **PSEUDOATHETOSIS**—chorea-type movements secondary to sensory loss
- **PAINFUL LEGS AND MOVING TOES**—continuous, stereotyped, flexion–extension, or adduction–abduction movements of toe
- **PERIODIC LEG MOVEMENT OF SLEEP**—nocturnal myoclonus, with repetitive stereotyped extension of big toe
- **RESTLESS LEG SYNDROME**—abnormal sensation in legs, especially at night
- **ALIEN LIMB**—complex non-volitional movements (reaching, grasping)
- **TICS**—rapid, non-rhythmic movement or sound on background of normal activity
- **STEREOTYPY**—tardive dyskinesia
- **AKATHISIA**—motor activity from voluntary effort to relieve uncomfortable sensation, mainly in daytime
- **PHANTOM DYSKINESIA**—amputees
- **HEMIFACIAL SPASM**—unilateral contraction of facial muscles involving eyelids, cheek, and corner of mouth
- **STARTLE DISEASE OR HYPERKPLEXIA, STIFF-PERSON SYNDROME**—continuous isometric contractions of somatic muscles

PATHOPHYSIOLOGY

PARKINSONISM ★TRAP★—Tremor, Rigidity, Akinesia/bradykinesia, and Postural instability. Parkinsonism defined as bradykinesia plus either tremor or rigidity

PATHOPHYSIOLOGY (CONT'D)

Parkinson disease is primary or idiopathic parkinsonism. Secondary or acquired parkinsonism may be due to head trauma, cerebrovascular disease, drugs (neuroleptics, dopamine receptor antagonists), or hydrocephalus

PARKINSONISM PLUS SYNDROMES—progressive supranuclear palsy, multiple system atrophy, Lewy body dementia, cortico-basal ganglionic degeneration

CLINICAL FEATURES

PHYSICAL EXAMINATION FOR PARKINSON DISEASE—resting tremor (4–6 Hz), rigidity, bradykinesia, micrographia, dementia, stare (reduced blink rate), mask face (hypomimia), glabellar tap, sialorrhea, dysarthria, difficulty getting up from chair, postural instability, difficult with heel-to-toe walking, festination, freezing gait, shuffling gait, and *en bloc* turn. Associated with disordered sleep (difficulty turning in bed), constipation, pain, and depression

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE PARKINSON DISEASE?

	LR+	LR–
History		
Tremor	1.4–11	0.24–0.60
Rigidity	1.3–4.5	0.12–0.93
Difficulty rising from chair	1.9–5.2	0.39–0.58
Loss of balance	1.6–6.6	0.29–0.35
Shuffling gait	3.3–15	0.32–0.50
Difficulty opening jars	6.1	0.26
Difficulty turning in bed	13	0.56
Micrographia	2.8–5.9	0.30–0.44
Physical		
Tremor	1.5	0.47
Rigidity and bradykinesia	4.5	0.12
Rigidity	2.8	0.38
Asymmetry	1.8	0.61
Bradykinesia	0.4–0.9	1.67–3.7
Heel-to-toe difficulties	2.9	0.32
Glabellar tap	4.5	0.13

TESTING—**glabellar tap** (percussion of forehead for ~20 times. Normally blinking stops after 5–10 times. Persistent blinking suggests positive Myerson sign), **bradykinesia maneuvers** (tapping finger, twiddling-like motor, pinching and circling, tapping with heel)

CLINICAL FEATURES (CONT'D)

APPROACH—a combination of tremor, rigidity, bradykinesia, loss of balance, shuffling gait, micrographia, difficulty with turning in bed, opening jars, and rising from a chair should raise suspicion of Parkinson disease. On examination, the diagnostic value of the classic combination of tremor, rigidity, bradykinesia is limited. Useful signs include the glabellar tap, difficulty walking heel-to-toe and rigidity

Rao et al. *JAMA* 2003;289(3)
Simel et al. *The Rational Clinical Examination*. McGraw-Hill; 2009

DISTINGUISHING FEATURES BETWEEN VARIOUS TREMORS

	Parkinson	Essential	Cerebellar
Tremor	Resting	Postural (action)	Intention (action)
Frequency (Hz)	4–6	8–12	3–5
Head direction	Up-down (“yes”)	Side-to-side (“no”)	None
Legs involved	Yes	Rare	Yes
Effect of alcohol	No change	Improved	No change

CHARACTERIZING MOVEMENT DISORDERS

- **SPEED**—slow (dystonia, athetosis, dystonic tics), moderate (chorea, tremor, asterixis), quick (myoclonus, myoclonic tics)
- **SUPPRESSIBILITY**—volitional in tics, sensory tricks in dystonia, activity in rest tremor
- **AGGRAVATING FACTORS**—stress, anxiety. Improves with rest and sleep
- **PRECIPITATING FACTORS**—alcohol, caffeine, stress, fatigue, cold, quick movements, prolonged exercises

INVESTIGATIONS**SPECIAL**

- **IMAGING**—CT/MR head, particularly if atypical features. Diagnosis of Parkinson disease remains clinical

MANAGEMENT**TREAT UNDERLYING CAUSE**

- **DECARBOXYLASE INHIBITOR/DOPAMINE PRECURSOR**—*carbidopa/levodopa* (Sinemet®) 25/100–25/250 mg PO TID. Risk of dyskinesia. Combined use with entacapone can lead to more sustained levodopa levels. See Lewitt *NEJM* 2008;359:23 for details

MANAGEMENT (CONT'D)

- **DOPAMINE AGONISTS**—*bromocriptine* 5–10 mg PO BID, *pramipexole*, *ropinirole*, *pergolide*. Can delay need to initiate levodopa but ineffective in patients unresponsive to levodopa. Risk of impulse control disorders
- **COMT AND MAO-B INHIBITORS**—*entacapone* 200 mg with each dose of levodopa, *rasagiline* 0.5–1 mg PO daily
- **ANTICHOLINERGICS**—*benztropine* 0.5–2 mg PO BID
- **AMANTADINE**—*amantadine* 200–300 mg PO daily
- **APPROACH**—Carbidopa/levodopa should be first-line therapy for most patients because of its effectiveness. COMT/MAO-B inhibitors or dopamine agonists may be used in combination with Sinemet® or as first-line agent alone for young patients. Anticholinergics have limited activity but can help with tremor and dyskinesia. Amantadine may be useful for mild disease and dyskinesia
- **DYSKINESIA**—a classic complication of Carbidopa/levodopa. Consider lowering dose of levodopa, changing its timing/frequency, and replacing part of the levodopa dose with a dopamine agonist. Amantadine may be added to counteract dyskinesia

SYMPTOM MANAGEMENT

- **GENERAL**—education, support, exercise, speech therapy
- **NAUSEA**—domperidone is safe as it does not cross the blood–brain barrier. Avoid antidopaminergic medications such as metoclopramide and phenothiazines (prochlorperazine, chlorpromazine)
- **PSYCHOSIS AND HALLUCINATIONS**—consider stopping anti-Parkinsonian drugs in sequence. May need to start atypical neuroleptic antipsychotics such as quetiapine or clozapine. Avoid older neuroleptic antipsychotics such as haloperidol
- **DEPRESSION**—antidepressants such as TCAs and SSRIs may be used with caution

INVESTIGATIONS FOR HYPERKINETIC MOVEMENT DISORDERS**BASIC**

- **LABS**—CBC, lytes, Cr, glucose, AST, ALT, ALP, bilirubin, LDH, CK, INR, PTT, urinalysis
- **IMAGING**—CT head, MRI head

INVESTIGATIONS FOR HYPERKINETIC MOVEMENT DISORDERS (CONT'D)**SPECIAL**

- **FURTHER NEUROLOGIC WORKUP**—genetic testing (Huntington, spinocerebellar ataxia, Friedreich) EMG/NCS, muscle/nerve biopsy, lumbar puncture, acanthocytes
- **INFLAMMATORY WORKUP**—ESR, CRP, ANA, ENA, RF, ANCA, C3, C4, lupus anticoagulant, antiphospholipid antibody, antistreptolysin O
- **MALIGNANCY WORKUP**—quantitative immunoglobulin, serum protein electrophoresis
- **ENDOCRINE WORKUP**—TSH, calcium, pregnancy test
- **METABOLIC WORKUP**—vitamin B12, copper, 24 h urinary copper, ceruloplasmin, RBC folate, lactate pyruvate

SPECIFIC ENTITIES**GAIT ASSESSMENT**

- **GENERAL INSPECTION**—inspect pelvis, knees, ankles, and feet for asymmetry, deformity. Ask the patient to walk normally, then heel-to-toe, walk on heels, walk on toes, and squat (testing strength, coordination)
- **FOOT MOVEMENTS**—heel strike, foot flat (mid-stance), heel off (lift off), toes off (swing)
- **GAIT MOVEMENTS**—comment on pace length, width, coordination, and stability (see table below for specific pathologies)
- **NEUROLOGICAL EXAMINATION**—lower limb motor and sensory examination. Also include Romberg test

Type	Pathology
Spastic gait	Upper motor neuron lesion (stroke)
Scissor gait	Bilateral upper motor neuron disease
Apraxic/magnetic gait	Frontal lobe (NPH, stroke)

SPECIFIC ENTITIES (CONT'D)

Type	Pathology
Shuffling gait	Extrapyramidal lesion (Parkinson)
Broad based gait	Cerebellar—vermis
Ataxic gait	Cerebellar—anterior (alcohol)
Unsteady, sensory ataxia gait	Posterior column (tabes dorsalis, B12 deficiency, Friedreich ataxia)
Trendelenburg gait (waddling)	Hip adductor muscle weakness (gluteus medius)
Steppage gait	Foot drop (peroneal nerve palsy)

PSYCHOGENIC (FUNCTIONAL) MOVEMENT DISORDER

- **HISTORY**—abrupt onset, static course, spontaneous remissions (inconsistency over time), obvious psychiatric disturbance, multiple somatizations, healthcare worker, pending litigation or compensation, secondary gain
- **PHYSICAL**—inconsistent character of movement (amplitude, frequency, distribution, selective disability), paroxysmal, movements increase with attention or decrease with distraction, ability to trigger or relieve the abnormal movements with unusual or non-physiological interventions, false weakness, false sensory complaints, self-inflicted injuries, deliberate slowness of movements, functional disability out of proportion to exam findings
- **THERAPEUTICS**—unresponsiveness, response to placebo, remission with psychotherapy

Related Topics

Dementia (p. 419)
Orthostatic Hypotension (p. 53)

Radiculopathy

Carette et al. *NEJM* 2005;353(4)

PATHOPHYSIOLOGY

FORAMINAL ENCRoACHMENT OF THE SPINAL NERVE—usually due to a combination of decreased disc height and degenerative changes of the uncovertebral joints anteriorly and zygapophyseal joints posteriorly

COMMONLY AFFECTED NERVE ROOTS

- **CERVICAL REGION**—C7 (70%) and C6 (20%) are the most commonly affected nerve roots

PATHOPHYSIOLOGY (CONT'D)

- **LUMBOSACRAL REGION**—L5 and S1 (>90% combined) are the most commonly affected nerve roots

Related Topics

Back Pain (p. 302)
Peripheral Neuropathy (p. 355)
Spinal Cord Compression (p. 243)

CLINICAL FEATURES

HISTORY—characterize neck or back pain. Paresthesia, radiation of pain, and weakness over specific nerve root distribution, any associated neurological symptoms. Ask about risk factors for radiculopathy (e.g. spinal injury or trauma) as well as peripheral neuropathy (e.g. diabetes mellitus, nerve entrapment, repetitive strain, prolonged kneeling, or recent musculoskeletal trauma). Ask about reproduction of symptoms with axial compression, Valsalva maneuver, or positional change. Ask about red flags (fever, chills, unexplained weight loss, unremitting night pain, previous cancer, immunosuppression, and IDU) that may suggest tumor or infections

SPURLING SIGN—reproduction of symptoms with extension and lateral rotation of neck toward affected side followed by compressive force to the top of the head suggests cervical radiculopathy (LR+ 3.6). Caution, as there is risk of spinal injury in patients with rheumatoid arthritis, cervical malformations, or metastatic disease

INVESTIGATIONS

IMAGING—spine X-ray (low sens), CT spine, MR spine (especially if suspect radiculopathy/

INVESTIGATIONS (CONT'D)

myelopathy, red flags, progressive neurologic deficits, no improvement for 4–6 weeks), myelography (rarely used now)

EMG AND NERVE CONDUCTION STUDY

TREATMENT OF CERVICAL RADICULOPATHY

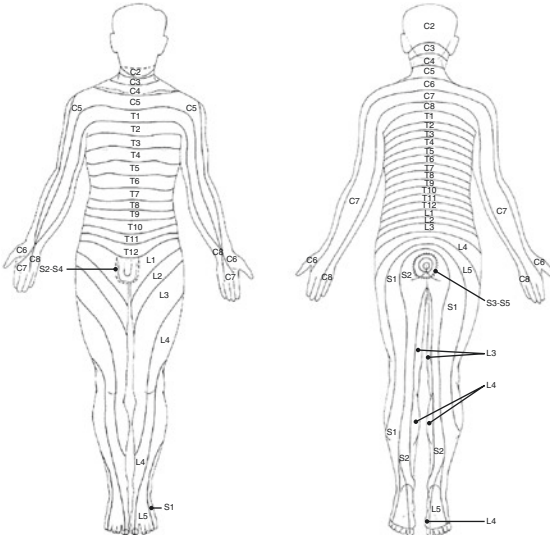
NON-SURGICAL—acetaminophen, NSAIDs, opioids, corticosteroid injections, cervical traction, exercise

SURGICAL—indicated if myelopathy or a combination of definite cervical root compression by CT/MRI, radiculopathy symptoms/signs, and persistent pain despite non-surgical treatment of 6–12 weeks or progressive motor weakness

SPECIFIC ENTITIES

CERVICAL MYELOPATHY—diffuse hand numbness and clumsiness (often attributed to peripheral neuropathy), imbalance, sphincter disturbances (late finding, urinary urgency/frequency initially, then retention or incontinence). Physical findings include hypertonia, hyperreflexia/clonus, positive Babinski, Hoffmann (flexion and adduction of the thumb when the examiner flexes the terminal phalanx of the long finger), and Lhermitte sign

DERMATOMES



From Mendoza J.E. (2011) Dermatome. In: Kreutzer JS, DeLuca J, Caplan B. (eds) *Encyclopedia of Clinical Neuropsychology*. Springer, New York, NY. https://doi.org/10.1007/978-0-387-79948-3_725, with permission Springer Nature

MYOTOMES

Root	Muscles
C3,4,5	Diaphragm
C5	Deltoid (shoulder abduction)
C6	Biceps and brachioradialis (elbow flexion), radial wrist extensors (wrist extension)
C7	Triceps (elbow extension), ulnar wrist extensors (wrist extension), wrist flexors, finger extensors
C8	Intrinsic muscles of hand (finger flexion/extension)
T1	Intrinsic muscles of hand (finger abduction/adduction)
T2–12	Chest wall and abdominal muscles
L2	Iliopsoas (hip flexion)
L3	Quadriceps (knee extension), adductor longus (hip adduction)
L4	Quadriceps (knee extension), tibialis anterior (dorsiflexion and inversion)
L5	Extensor hallucis longus (big toe extension), tibialis posterior (plantarflexion and eversion), gluteus medius (hip abduction)
S1	Gluteus maximus (hip extension), gastrocnemius, soleus, peroneus longus (plantar flexors, eversion)
S2,3,4	Bowel, bladder, sexual organs, anal other pelvic muscles

Note: may have some overlap between myotomes and peripheral nerve roots

BRACHIAL PLEXUS

Nerve	Root/origin	Muscle function
Dorsal scapular	C45 Root level	Rhomboids (retracts scapula)
Long thoracic	C567 Root level	Serratus anterior (scapula abduction)
Suprascapular	C56 Upper trunk	Supraspinatus (arm abduction) Infraspinatus (arm external rotation)
Lateral anterior thoracic	C67 Upper, middle trunk	Pectoralis major (arm adduction, internal rotation)
Medial anterior thoracic	C8 Lower trunk	Pectoralis major (arm adduction, int. rotation) Pectoralis minor (protracts scapula)
Subscapular	C56 Posterior cord	Subscapularis (arm adduction) Teres major (arm extension, ext. rotation)
Thoracodorsal	C78 Posterior cord	Latissimus dorsi (arm extension, adduction, internal rotation)
Axillary	C5 Posterior cord	Deltoid (arm abduction) Teres minor (arm external rotation)
Musculo-cutaneous	C56 Lateral cord	Biceps (forearm flexion) Brachioradialis (supination)
Median	C567T1 Anterior cord	See tables below
Radial	C678 Posterior cord	See tables below
Ulnar	C8T1 Lateral cord	See tables below

MUSCLE–NERVE FUNCTION CORRELATION

Muscle	Innervation	Function
Tibialis anterior	Deep peroneal n. (L4S1)	Inversion, dorsiflexion
Tibialis posterior	Tibial n. (L45)	Inversion , planter flexion
Peroneus longus	Superficial peroneal n.(L5S1)	Eversion , planter flexion
Peroneus brevis	Superficial peroneal n.(L5S1)	Eversion , planter flexion

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS**C6 VS. MEDIAN NERVE LESION**

	C6	Median nerve (C6-T1)
Sensory	Palmar and dorsal surfaces of 1st-2nd fingers (including anatomical snuff box), lateral surface of arm/forearm	Palmar surface of 1st, 2nd, and 3rd fingers and lateral portion of 4th finger
Motor	Biceps (musculocutaneous nerve), brachioradialis (musculocutaneous nerve), supinator (radial nerve)	★ LOAF ★ Lateral lumbricals (1st and 2nd), O pponens pollicis (opposition), A bductor pollicis brevis (abduction of thumb), F lexor pollicis brevis (flexion of thumb/fingers)
Reflex	Biceps, brachioradialis	None
Other	Reproduction of symptoms with axial compression or positional change	Inspect for Benediction sign (index ± middle finger held in extension; associated with median nerve injury at or above the elbow), percuss for Tinel sign (over carpal tunnel), palpate for Durkan test (direct compression over carpal tunnel), flex at wrist for Phalen sign, and perform Ochsner clasp test (index finger fails to flex)

C7 VS. RADIAL NERVE LESION

	C7	Radial nerve (C5–T1)
Sensory	Palmar surface of 3rd finger	Dorsal surface of 1st, 2nd, and 3rd fingers and lateral portion of 4th finger (including anatomical snuff box)
Motor	Pronator teres (median nerve), adduction of shoulder by latissimus dorsi (thoracodorsal nerve) and pectoralis major (lateral and medial pectoral nerves)	★ BEST ★ B rachioradialis (radial nerve), E xtensor pollicis longus (posterior interosseous nerve), E xtensor indicis (posterior interosseous nerve), S upinator (posterior interosseous nerve), T riceps (radial nerve)

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT'D)

	C7	Radial nerve (C5–T1)
Reflex	Note: triceps reflex does not reliably differentiate between C7 vs. radial nerve lesion	Brachioradialis
Other	Reproduction of symptoms with axial compression or positional change	Inspect for wrist drop and examine mid-humerus for trauma or injury
C8 VS. ULNAR NERVE LESION		
	C8	Ulnar nerve (C8T1)
Sensory	Medial aspect of forearm , palmar and dorsal surface of 4th and 5th fingers	Note: sensation to palmar and dorsal surfaces of 4th and 5th fingers does not reliably differentiate between C8 vs. ulnar nerve lesion (affected in both)
Motor	Extensor indicis (posterior interosseous nerve), extensor pollicis longus (posterior interosseous nerve), flexor pollicis longus (anterior interosseous nerve), LOAF muscles (median nerve)	Adductor pollicis , first dorsal interosseous muscle
		Note: motor activity of lumbricals (3rd, 4th), interossei 5th finger opposition, abduction and flexion, as well as thumb adduction do not reliably differentiate between C8 vs. ulnar nerve lesion (affected in both)
Reflex	Flexion of fingers of lateral two lumbricals	None
Other	Reproduction of symptoms with axial compression or positional change	Inspect for claw hand, percuss for Tinel sign (in groove between medial epicondyle and the olecranon), and perform Froment test (patient pinches sheet of paper between thumb and index finger; pulling paper away reveals weakness of adductor pollicis and compensatory flexion of IP joint of the thumb)

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT'D)**L4 VS. FEMORAL NERVE LESION**

	L4	Femoral nerve (L234) Anterior thigh and medial lower leg
Sensory	Note: sensation from lateral leg to medial malleolus does not reliably differentiate between L4 vs. femoral nerve lesion (affected in both)	
Motor	Hip adductors (obturator nerve), ankle dorsiflexion with tibialis anterior (deep peroneal nerve)	Note: hip flexion and knee extension does not reliably differentiate between L4 vs. femoral nerve lesion (affected in both)
Reflex	Hip adductor jerk	Note: knee jerk reflex does not reliably differentiate between L4 vs. femoral nerve lesion (affected in both)
Other	Straight leg raise and femoral nerve stretch test (for nerve root impingement)	Inspect for hematoma (for nerve entrapment)

L5 VS. PERONEAL NERVE LESION

	L5	Common peroneal nerve (L45S1)
Sensory	Note: some sources claim that L5 uniquely provides sensation to lateral aspect of foot and little toe, but this is probably supplied by the sural nerve/lateral dorsal cutaneous nerve (S1). Does not reliably differentiate between L5 vs. common peroneal nerve lesion	Note: sensation to lateral leg and dorsal foot (including web space between big toe and 2nd toe) does not reliably differentiate between L5 vs. common peroneal nerve lesion (affected in both)
Motor	Ankle inversion with posterior tibialis (tibial nerve), hip abduction from gluteus medius and minimus (superior gluteal nerve), hip extension with gluteus maximus (inferior gluteal nerve), and knee flexion with hamstrings (sciatic nerve)	Note: dorsiflexion (deep peroneal nerve), eversion (superficial peroneal nerve), and great toe dorsiflexion (deep peroneal nerve) do not reliably differentiate between L5 vs. common peroneal nerve lesion (affected in both)
Other	Straight leg raise	Tinel sign (percussion over fibular head)

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT'D)**L5 VS. SCIATIC NERVE LESION**

	L5	Sciatic nerve (L4–S3) Lateral aspect of foot (little toe)
Sensory	Note: sensation to lateral leg and dorsal foot does not reliably differentiate between L5 vs. sciatic nerve lesion	
Motor	Hip abduction from gluteus medius and minimus (superior gluteal nerve), hip extension with gluteus maximus (inferior gluteal nerve)	Ankle plantar flexion with gastrocnemius and soleus (tibial nerve) Note: ankle eversion and knee flexion do not reliably differentiate between L5 vs. sciatic nerve lesion (affected in both)
Reflex	None	Ankle jerk
Other	Straight leg raise	Palpation of sciatic nerve

For the nerve root/peripheral nerve lesions tables above,

BOLD = highlights important differences between nerve root and peripheral nerve lesions

REFLEXES—complete peripheral nerve lesions will lead to complete areflexia, while complete nerve root lesions will only lead to partial reduction of reflexes

SPECIFIC CONSIDERATIONS

DISTINGUISHING FEATURES BETWEEN MEDIAN NERVE LESION, ULNAR NERVE LESION, AND T1 RADICULOPATHY—these lesions can be differentiated by testing two muscles: abductor pollicis brevis is supplied by the median nerve (i.e. supinate hand, point thumb toward ceiling, test power by pushing thumb down), while first dorsal interosseous is supplied by the ulnar nerve (i.e. test power of index finger abduction)

SPECIFIC CONSIDERATIONS (CONT'D)

	Abductor pollicis brevis	1st dorsal interosseous
Lesion		
T1 radiculopathy	Weak	Weak
Median nerve	Weak	Spared
Ulnar nerve	Spared	Weak

NOTE: may also test little finger abduction (abductor minimi digiti) to assess ulnar nerve integrity

Myasthenia Gravis**DIFFERENTIAL DIAGNOSIS OF PTOSIS**

MECHANICAL—aponeurotic ptosis (spontaneous dehiscence of the levator aponeurosis), eyelid infections, eyelid tumors

NEUROMUSCULAR—third nerve palsy (usually unilateral), Horner syndrome (usually unilateral), myasthenia gravis (bilateral or unilateral), botulism (usually bilateral), Lambert-Eaton syndrome, myotonic dystrophy (usually bilateral), oculopharyngeal muscular dystrophy, chronic progressive external ophthalmoplegia

PATHOPHYSIOLOGY

ANTIBODY AGAINST POST-SYNAPTIC ACETYLCHOLINE RECEPTOR—leads to decreased neurotransmission and muscle weakness (ocular, bulbar, and skeletal)

ASSOCIATIONS—thymic diseases (hyperplasia, thymoma, carcinoma) can be found in 75% of patients with myasthenia gravis. Other associations include hyperthyroidism, small cell lung cancer, Hodgkin lymphoma, SLE, and rheumatoid arthritis. Key differential diagnoses include depression, ALS, and Lambert-Eaton syndrome

CLINICAL FEATURES

HISTORY—ptosis (classically fluctuating and asymmetric in myasthenia gravis), diplopia, bulbar weakness (slurred speech, hoarseness, difficulty chewing and swallowing), limb weakness, shortness of breath, symptoms better with rest and worse with prolonged use, past medical history (malignancy, trauma), medications

PHYSICAL—vitals, pulmonary examination, measure palpebral fissure at rest and after sustained upward gaze for 30 s, extraocular eye movements, orbicularis oculi weakness (cannot bury eye lashes). Peek sign is positive when palpebral fissure can be seen after patient tries to gently close the eye lids), voice changes, assess for weakness of neck flexor, deltoids, hip flexors, finger/wrist extensors, and foot dorsiflexors with repeated challenges. Sensory examination should be normal and reflexes should demonstrate fatigability

SPECIAL TESTS FOR MYASTHENIA GRAVIS

GRAVIS—**ice test** (improvement of ptosis with palpebral fissure increase of 2 mm after applying ice over eyelid for 2 min), **sleep test** (improvement of ptosis with palpebral fissure increase of 2 mm after resting in dark room for 30 min), **curtain sign**, **lid twitch sign**, **cover-uncover test** (examiner covers one eye as patient fixates on a distant object. Observe for deviation of the uncovered eye during lateral and then upward gazing. With extraocular weakness, the uncovered eye will drift)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE MYASTHENIA GRAVIS?

	LR+	LR-
History		
Food in mouth after swallowing	13	0.70
Speech becoming unintelligible during prolonged speaking	4.5	0.61
Physical		
Peek sign	30	0.88
Ice test	24	0.16
Sleep test	53	0.01
Special tests		
Edrophonium test	15	0.11

CLINICAL FEATURES (CONT'D)

APPROACH—"The presence of speech becoming unintelligible during prolonged periods and peek sign may be useful in confirming the diagnosis of myasthenia gravis, though their absence does not rule it out. The ice test, sleep test, and response to anticholinesterase agents (especially the edrophonium test) are useful in confirming the diagnosis and reduce the likelihood when results are negative. A positive test result should prompt acetylcholine receptor antibody testing and specialist referral for electrophysiologic tests and should help confirm the diagnosis in patients who have negative results for the acetylcholine receptor antibody panel."

Scherer et al. *JAMA* 2005;293(15)

DISTINGUISHING FEATURES BETWEEN HORNER SYNDROME AND THIRD NERVE PALSY

	Horner syndrome	Third nerve palsy
Ptosis	Partial. Never complete	Partial or complete
Pupil size	Constricted	Dilated
Pupil asymmetry	Worse in darkness	Worse in light
Pupil reflex	Normal	Sluggish or absent
Others	Anhydrosis	Affected eye downward and outward
	Enophthalmos	
	Absent cilio-spinal reflex	
	Heterochromia (congenital)	

INVESTIGATIONS**BASIC**

- **LABS**—TSH, ANA, RF
- **IMAGING**—CT chest (thymoma, malignancy), CT/MR head (if third nerve palsy)

INVESTIGATIONS (CONT'D)**SPECIAL**

- **EDROPHONIUM (TENSILON) TEST**—injection of acetylcholinesterase inhibitor, improvement may be detected in 30 s and lasts <5 min
- **ANTIBODIES**—anti-acetylcholine receptor antibody (sens 80–90%, very high spc), muscle-specific receptor tyrosine kinase antibody
- **SINGLE FIBER EMG WITH/WITHOUT REPETITIVE STIMULATION**

MANAGEMENT OF MYASTHENIA GRAVIS

MYASTHENIA GRAVIS—*pyridostigmine* 30 mg PO q3–6 h. Thymectomy (if thymoma, or when all the following are present: AChR positive, under age 60, generalized myasthenia, disease onset less than 5 years). Other treatments include corticosteroids, azathioprine, cyclosporine, mycophenolate, plasmapheresis, IVIG

MYASTHENIA CRISIS—ICU admission, treat any precipitating infection, discontinue any anticholinesterase agents, correct electrolyte abnormality (careful with magnesium replacement as can precipitate crisis), monitor respiratory status, and intubate if FVC <15 to 20 mL/kg or MIP <–25 to –30 cmH₂O, plasmapheresis

SPECIFIC ENTITIES**LAMBERT-EATON SYNDROME (LES)**

- **PATHOPHYSIOLOGY**—antibody against pre-synaptic voltage-gated calcium channels. Small cell lung cancer is found in 50–70% of patients with Lambert-Eaton syndrome
- **CLINICAL FEATURES**—proximal muscle weakness (hip girdle and shoulder. Less likely bulbar, but ptosis still possible. Hyporeflexia that improves with repeated effort (facilitation), autonomic symptoms (dry mouth, impotence). Symptoms worse in morning and improve during day/exercise
- **DIAGNOSIS**—nerve conduction studies with repetitive nerve stimulation. CXR to look for malignancy
- **TREATMENTS**—treat underlying malignancy, plasma exchange, IVIG

Related Topics

Horner Syndrome (p. 354)
Thymoma (p. 210)

Peripheral Neuropathy**DIFFERENTIAL DIAGNOSIS**

MONONEUROPATHY—compression, infiltration, mononeuritis

MONONEURITIS MULTIPLEX—vasculitis, diabetes

POLYNEUROPATHY

- **AXONAL INJURY**
 - **NEOPLASTIC**—carcinoma, lymphoma, MGUS-IgA, IgG, IgM
 - **INFECTIOUS**—sepsis, HIV, Lyme
 - **INFLAMMATORY**—Sjögren, sarcoidosis, SLE, paraneoplastic
 - **METABOLIC**—diabetes, uremia, thyroid
 - **VITAMIN DEFICIENCY**—malabsorption, B12,
 - **DRUGS**—cisplatin, taxanes, vincristine, isoniazid, nucleoside analogue
- **DEMYELINATING**—Guillain-Barré, neoplastic (carcinoma, lymphoma, MGUS-IgM), drugs (taxanes), chronic inflammatory demyelinating polyradiculoneuropathy

CLINICAL FEATURES

HISTORY—sensory loss, pain, dysesthesias, burning, gait abnormalities, weakness, past medical history (diabetes, medications, malignancy, infections), family history. Assess time course, distribution (length-dependent, “stocking and glove”, migration and progression)

PHYSICAL—muscle wasting, muscle strength, sensation to pin prick, light touch, vibration, temperature, proprioception, reflexes

DIFFERENTIATING SITE OF MEDIAN NERVE INJURY—if lesion at carpal tunnel, LOAF muscles affected. If lesion at or above the elbow, there may be lateral forearm wasting and the index finger held in extension (Benediction sign)

DIFFERENTIATING SITE OF ULNAR NERVE INJURY—low lesion (below the wrist) characterized by marked hand clawing (because of unopposed flexor digitorum profundus flexion of DIPs). High lesions have subtle clawing, termed ulnar paradox

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, Cr, glucose, ESR, serum protein electrophoresis, vitamin B12, ANA, TSH, urinalysis

SPECIAL

- **EMG AND NERVE CONDUCTION STUDY**
- **NERVE/MUSCLE BIOPSY**
- **LUMBAR PUNCTURE**
- **INFECTIOUS WORKUP**—Lyme serology, HIV, RPR, HBV/HCV serology

MANAGEMENT

TREAT UNDERLYING CAUSE—diabetic (glucose control), **lymphoma/myeloma** (chemotherapy)

SYMPTOM MANAGEMENT—**tricyclic antidepressants** (*desipramine* 10–50 mg nightly), **gabapentin** (300 mg PO daily × 1 day, then 300 mg PO BID × 1 day, then 300 mg PO TID, max 1800 mg/day), **pregabalin**, **anticonvulsants** (topiramate, carbamazepine), **duloxetine** 60 mg PO daily

SPECIFIC ENTITIES

CARPAL TUNNEL SYNDROME

- **PATHOPHYSIOLOGY**—median nerve entrapment syndrome
- **ASSOCIATIONS**—repetitive use, acromegaly, amyloidosis, hypothyroidism, rheumatoid arthritis, diabetes mellitus, pregnancy, and mucopolysaccharidosis. Bilateral disease or early involvement of non-dominant hand suggests a systemic condition
- **DIAGNOSIS**—nerve conduction studies (sens 49–84%, spc 95–99%) should be done if inadequate response to conservative therapy (changes in the workplace, night-time neutral splints), thenar atrophy, or if the diagnosis is unclear
- **TREATMENTS**—activity modifications, wrist splinting, NSAIDs, corticosteroid injections (success 49–81%, recurrence 50–86%), carpal tunnel release (success 75–99%)

SPECIFIC ENTITIES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE CARPAL TUNNEL SYNDROME?

KATZ HAND DIAGRAM—**classic** (tingling of at least two of digits 1–3. The classic pattern permits symptoms in the 4th and 5th digits, wrist pain, and radiation of pain to wrist, but not symptoms on the palm/dorsum of the hand), **probable** (same symptom pattern as classic, except palmar symptoms are allowed unless confined solely to the ulnar aspect), **possible**, **unlikely**

	LR+	LR-
History		
Classic/probable Katz diagram	2.4	0.5
Age >40	1.3	0.5
Nocturnal paresthesia	1.2	0.7
Bilateral symptoms	1.4	0.7
Physical		
Hypalgesia (↓ pain sensation) in the median nerve territory	3.1	0.7
Abnormal vibration	1.6	0.8
Weak thumb abduction strength	1.8	0.5
Thenar atrophy	1.6	1.0
Square wrist sign	2.7	0.5
Closed fist sign	7.3	0.4
Flick sign	1.4	0.1
Tinel sign	1.5	0.8
Phalen sign	1.3	0.7

APPROACH—Katz hand symptom diagrams, hypalgesia, and thumb abduction strength testing are helpful in establishing diagnosis of carpal tunnel syndrome

D'Arcy et al. JAMA 2000;283(23)

UPDATE—Flick sign, Tinel sign, and Phalen sign are not helpful in making the diagnosis of CTS. In addition, clinical provocation maneuvers do not significantly alter the likelihood of CTS

Simel et al. The Rational Clinical Examination. McGraw-Hill; 2009

SPECIFIC ENTITIES (CONT'D)

AUTONOMIC NEUROPATHY

- **CAUSES**—autonomic failure may be secondary to peripheral neuropathy associated with diabetes, cancer (paraneoplastic), amyloidosis, cachexia, HIV, Guillain-Barré syndrome, Lambert-Eaton syndrome, other inflammatory/infectious conditions, or due to primary disorders such as Parkinson disease, Shy-Drager syndrome (multiple system atrophy with autonomic failure), Lewy body dementia, and multiple sclerosis

	Sympathetic dysfunction	Parasympathetic dysfunction
Vitals	Orthostatic hypotension	Tachycardia
Skin	Warm and moist	Cool and dry
H&N	Horner	Dry eyes + mouth Dilated pupil
Heart	No respiratory variation	
GI/GU		Constipation Distended bladder Impotence
MSK, gait	Postural instability	

Related Topics
 Diabetic Neuropathy (p. 365)
 Radiculopathy (p. 347)

GUILLAIN-BARRÉ SYNDROME (GBS)

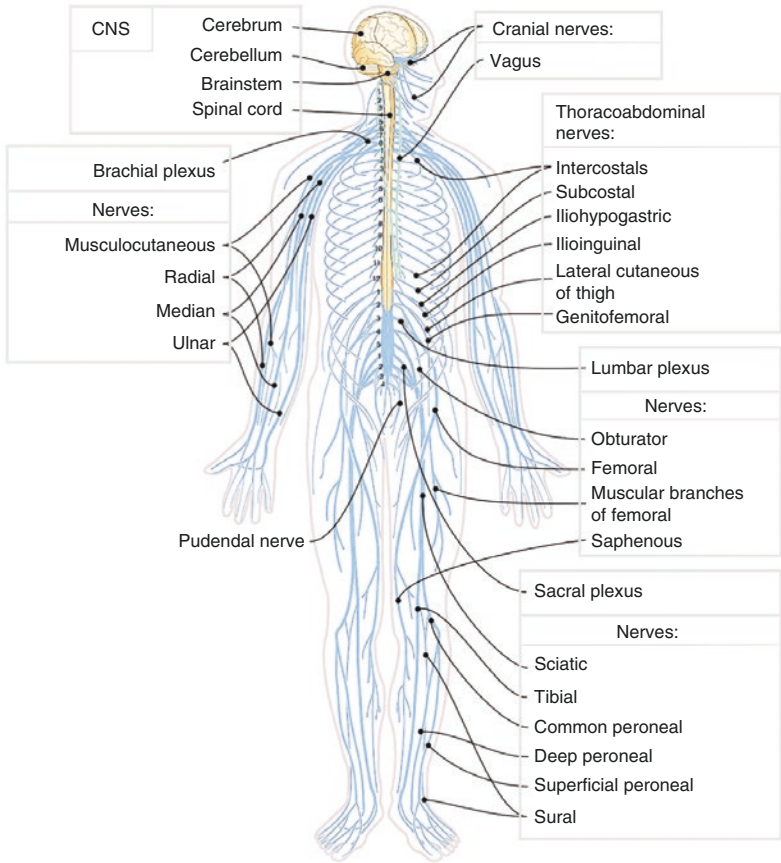
- **PATHOPHYSIOLOGY**—precipitants (*Campylobacter jejuni* [ask about bloody diarrhea], CMV infection, upper respiratory tract infections,

SPECIFIC ENTITIES (CONT'D)

- possibly flu shots)→ acute inflammatory demyelinating polyradiculoneuropathy 2–4 weeks later→ reach nadir of symptoms 2–4 weeks (25% require mechanical ventilation)→ recovery weeks to months
- **CLINICAL FEATURES**—fine paresthesias in toes and fingertips→ weakness in lower/upper extremities (often ascending)→ potential autonomic dysfunction (50%), cranial nerves, respiratory muscle involvement. **Areflexia** is a key feature (but may be preserved early on), but presence of hyperreflexia strongly suggests alternative diagnosis (e.g. transverse myelitis). Low/mid-back pain common
- **SUBTYPES**—four subtypes include demyelinating (acute inflammatory demyelinating polyradiculoneuropathy), axonal motor (acute motor axonal neuropathy), axonal motor and sensory (acute motor and sensory axonal neuropathy), and Miller-Fischer syndrome (ophthalmoplegia, ataxia, areflexia)
- **DIAGNOSIS**—EMG (demyelinating neuropathy), lumbar puncture (albuminocytologic dissociation = normal CSF WBC but ↑ CSF protein), PFT (↓ FVC, MIP, MEP)
- **TREATMENTS**—*IVIg* 2 g/kg IV divided over 5 days, plasma exchange. ICU admission with respiratory support if FVC <20 mL/kg, maximum inspiratory pressure <30 cmH₂O, maximum expiratory pressure <40 cmH₂O, rapid progression <7 days, cranial or autonomic involvement

MONONEURITIS MULTIPLEX—simultaneous/sequential involvement of multiple named nerves (e.g. median, ulnar, radial, peroneal nerves). Multiple nerve infarcts due to a systemic vasculitis

PERIPHERAL NERVES



Courtesy of Wikipedia CC BY-SA 4.0

https://commons.wikimedia.org/wiki/File:Nervous_system_diagram-en.svg

PERIPHERAL NERVES (CONT'D)**MONONEUROPATHIES**

Nerve (origin)	Pathophysiology	Signs and symptoms	Comments
Axillary nerve (C5–6)	Lesion usually near shoulder joint	Motor: weakness of shoulder abduction, shoulder atrophy	
	Affects deltoid and teres minor	Sensory: deficit similar to C5 lesion	
Subscapular nerve (C5–6)	Lesion usually at suprascapular notch of scapula	Motor: weakness of external rotation of arm	
	Affects supraspinatus and infraspinatus	Sensory: intact	
Long thoracic nerve (C5–7)	Affects serratus anterior	Motor: winging of the scapula	
		Sensory: intact	
Radial nerve (C5–T1)	Lesion usually at spiral groove of humerus	Motor: wrist drop, weakness of finger and thumb extensors	Saturday night palsy (acute compression) is frequent cause
	Affects brachioradialis, triceps, wrist, finger and thumb extensors	Sensory: changes in dorsal surface of 1st-lateral 4th fingers, dorsal surface of arm/forearm	Cheiralgia paresthetica (entrapment of superficial branch of radial nerve to dorsum of hand)
Posterior interosseous branch of radial nerve (C7–8)	Lesion usually at the Arcade of Frohse	Motor: finger drop, wrist relatively spared	
	Affects finger and thumb extensors	Sensory: intact	
Ulnar nerve (C8–T1)	Lesion usually at cubital tunnel or ulnar groove at the elbow	Motor: weakness of finger adduction, abduction and thumb adduction (Froment sign), claw-hand and interosseous atrophy	
		Sensory: changes in both dorsal and palmar surfaces of 4th and 5th fingers. May have pain over median proximal forearm (cubital tunnel).	
		Tests: Tinel sign positive	
Ulnar nerve (C8–T1)	More distal lesion usually at medial base of palm	Motor: weakness of finger adduction and abduction. Interosseous atrophy	Cyclist's palsy
	Affects intrinsic hand muscles only	Sensory: changes in palmar surface of 4th and 5th fingers only	
Median nerve (C6–T1)	Lesion at carpal tunnel	Tests: Tinel sign negative	
		Motor: weakness, pain, numbness and tingling over thumb, 2nd and 3rd fingers	Carpal tunnel syndrome
	Affects abductor pollicis brevis, proximal muscles include forearm pronator, long finger, and thumb flexors	Sensory: changes in palmar surface of 1st-lateral 4th fingers	
Anterior interosseous branch of median nerve (C7–T1)	Lesion usually just below the elbow	Tests: square wrist sign, closed fist sign, Flick sign, Tinel sign and Phalen sign	
		Motor: weakness of pinch, pain in volar forearm	

PERIPHERAL NERVES (CONT'D)			
Nerve (origin)	Pathophysiology	Signs and symptoms	Comments
	Affects long flexors of thumb and index and middle fingers	Sensory: intact	
Femoral nerve (L2–4)	Lesion usually proximal to inguinal ligament	Motor: buckling of knee, absent knee jerk, weak anterior thigh muscles with atrophy.	Post-femoral catheterization or pelvic surgery with retroperitoneal hematoma, diabetes mellitus
	Affects iliopsoas (hip flexor) and quadriceps femoris (knee extensor)	Sensory: changes in lateral leg to medial malleolus	
Lateral femoral cutaneous branch of femoral nerve (L2–3)	Lesion usually at inguinal ligament	Motor: intact	Meralgia paresthetica (entrapment of lateral cutaneous femoral nerve to anterolateral aspect of thigh)
		Sensory: dysesthetic hyperpathia of lateral thigh (burning)	
Obturator nerve (L3–4)	Lesion usually at pubis or intrapelvic	Motor: weakness of hip adduction	
	Affects thigh adductors	Sensory: deficit of medial thigh	
Sciatic nerve (L4–S3)	Lesion usually near sciatic notch	Motor: severe lower leg and hamstring weakness, flail foot, difficulty walking	Overdose victims
	Affects hamstring muscles, hip abductor and all muscles below the knee	Sensory: changes in lower leg and foot	
Tibial nerve (L5–S2)	Lesion usually at tarsal tunnel or near medial malleolus	Motor: weak toe flexors	Tarsal tunnel syndrome
	Affects calf muscles (proximally), toe flexor, and other intrinsic foot muscles	Sensory: pain and numbness of sole	
Peroneal nerve (L4–S1)	Lesion usually at neck of fibula	Motor: weakness of foot eversion and foot drop	Cross-leg palsy
	Affects dorsiflexors of toes and foot and evertors of foot	Sensory: deficit similar to L5 lesion	

Muscle Weakness

DIFFERENTIAL DIAGNOSIS

INFLAMMATORY MYOPATHY—polymyositis, dermatomyositis, inclusion body myositis, juvenile dermatomyositis, vasculitis, overlap syndromes (SLE, scleroderma, rheumatoid arthritis, Sjögren), immune-mediated necrotizing myositis, antisynthetase syndrome

INFECTIOUS MYOPATHY

- **BACTERIAL**—pyomyositis, Lyme myositis
- **VIRAL**—influenza, parainfluenza, Coxsackie, HIV, CMV, echovirus, adenovirus, EBV
- **FUNGAL**
- **PARASITIC**—trichinosis, toxoplasmosis

DRUG/TOXIC MYOPATHY—steroid, alcohol, cocaine, heroin, colchicine, antimalarial, statins, fibrates, penicillamine, zidovudine, gemcitabine, immune check point inhibitors

DIFFERENTIAL DIAGNOSIS (CONT'D)

ENDOCRINE MYOPATHY—hypothyroidism, hyperthyroidism, Cushing, diabetes, acromegaly

METABOLIC MYOPATHY—hypokalemia, hypocalcemia, hypophosphatemia, hyponatremia, hypernatremia, disorders of carbohydrate/lipid/purine metabolism

NEOPLASTIC MYOPATHY

RHABDOMYOLYSIS

- **DRUGS**—alcohol, cocaine, statins, neuroleptic malignant syndrome, malignant hyperthermia
- **HYPERACTIVITY**—seizures, exertion
- **TRAUMA/OPERATION**
- **IMMOBILITY**

DIFFERENTIAL DIAGNOSIS (CONT'D)**NEUROLOGIC**

- **MOTOR CORTEX**—stroke, multiple sclerosis, brain tumor, abscess
- **CORTICOSPINAL TRACT/ANTERIOR HORN CELLS**—spinal cord injury, vitamin B12 deficiency, ALS, polio, lead
- **SPINAL NERVE ROOTS/PERIPHERAL NERVES**—Guillain-Barré, myeloma, amyloidosis, diabetes
- **NEUROMUSCULAR JUNCTION**—myasthenia gravis, botulism, Lambert-Eaton organophosphate poisoning
- **MUSCLES**—myopathies (see above)

Related Topics

Critical Illness Weakness (p. 108)

Dermatomyositis (p. 307)

Lambert-Eaton Syndrome (p. 355)

Myasthenia Gravis (p. 353)

CLINICAL FEATURES**APPROACH TO CLINICAL DIAGNOSIS**

- FUNCTIONAL VS. TRUE MUSCLE WEAKNESS?**
 - If functional, consider cardiopulmonary disease, arthritis, anemia, cachexia from malignancy or chronic disease, depression, deconditioning, fibromyalgia
 - If true muscle weakness, proceed to 2
- GENERALIZED VS. LOCALIZED MUSCLE WEAKNESS?**
 - If generalized, consider myasthenia gravis, long-standing periodic paralysis, advanced disuse atrophy from prolonged bed rest, or advanced muscle wasting from malignancy
 - If localized, proceed to 3
- ASYMMETRIC VS. SYMMETRIC MUSCLE WEAKNESS?**
 - If asymmetric, consider disease of central or peripheral nervous system (stroke, spinal cord injury, demyelinating disorders, compression neuropathy, mononeuropathy/neuritis), disuse atrophy, myasthenia gravis
 - If symmetric, proceed to 4
- DISTAL VS. PROXIMAL MUSCLE WEAKNESS?**
 - If distal, consider peripheral neuropathy, myasthenia gravis, motor neuron disease, myotonic dystrophy
 - If proximal, consider myopathies (see differential diagnosis), myasthenia gravis, muscular dystrophy

CLINICAL FEATURES (CONT'D)**MRC MUSCLE STRENGTH GRADING****0** = no contraction**1** = flicker**2** = possible only with gravity eliminated**3** = against gravity only**4** = power decreased but muscle contraction possible against resistance**5** = normal power resistance

MUSCLE STRENGTH—preserved in patients with cachexia despite advanced generalized muscle atrophy. In contrast, patients with true muscle weakness due to myopathy generally have normal muscle bulk at time of presentation

MUSCLE TENDERNESS—usually not associated with one of the causes of true muscle weakness, except for infectious myopathies, certain drug-induced myopathies, rhabdomyolysis, thyroid myopathy, and inherited metabolic myopathies

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, Cr, Ca, Mg, PO₄, CK, TSH, LDH, AST, ALT, ANA, ANCA, HBV/HBC serology, cryoglobulin, RF

SPECIAL

- **EMG AND NERVE CONDUCTION STUDY**
- **MUSCLE BIOPSY**—select mildly-affected muscle, not previously studied with EMG
- **INFLAMMATORY MYOSITIS ANTIBODIES**—polymyositis and antisynthetase (anti-Jo 1 and 2), necrotizing myositis (anti-SRP, anti-HMG-CoA), dermatomyositis (anti-Mi2, anti-SAE, anti-MDA5, anti-p155, anti-NXP2), inclusion body myositis (anti-NT5c1A)
- **MRI**—can be used to identify muscle for biopsy

MANAGEMENT**REHABILITATION****TREAT UNDERLYING CAUSE****SPECIFIC ENTITIES**

INFLAMMATORY MYOSITIS—steroids, IVIG
CRITICAL ILLNESS NEUROMUSCULAR DISORDERS

- **CRITICAL ILLNESS POLYNEUROPATHY**—muscle weakness and atrophy, ↓ deep tendon reflexes, ↓ peripheral sensation to light touch and pin prick. Associated with sepsis, systemic inflammation

SPECIFIC ENTITIES (CONT'D)

- **DELAYED REVERSAL OF NEUROMUSCULAR BLOCKADE**—non-depolarizing neuromuscular blocking agents (pancuronium, vecuronium) in susceptible patients
- **CRITICAL MYOPATHY**—muscle weakness and atrophy. Muscle damage second degree to sepsis and multi-system organ failure. Sensation invariably spared. EMG and muscle biopsy can be diagnostic
- **MYOPATHY ASSOCIATED WITH COMBINED USE OF STEROID AND NEUROMUSCULAR BLOCKING AGENT**—muscle weakness and atrophy, ↑ deep tendon reflexes

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

- **PATHOPHYSIOLOGY**—combined upper and lower motor neuronal degeneration → spread to involve multiple myotomes in multiple regions

Approach to Neuroimaging**MODALITIES**

CT HEAD (unenhanced)—particularly useful for **acute hemorrhage** (subarachnoid, subdural, intracerebral), **skull fractures/trauma, meningiomas, and subacute and chronic strokes**. Also used as initial workup of acute TIA or stroke and other brain tumors although not as sensitive as MRI. Advantages include easy accessibility. Disadvantages include insensitivity in detecting subtle structural pathology and changes in the posterior fossa

MRI HEAD—particularly useful for evaluation of **stroke** (acute, subacute, chronic), **hemorrhage** (subacute and chronic), **white matter lesions** (multiple sclerosis), and lesions of the **posterior fossa, brainstem, and spinal cord**. Also useful for most tumors, epilepsy, demyelinating diseases, inflammatory and infectious conditions (e.g. HSV encephalitis), degenerative diseases, and congenital abnormalities. Main disadvantage is difficulty scanning patients with claustrophobia

MRI WITH GADOLINIUM—certain lesions and pathological findings have characteristic enhancement patterns. Gadolinium enhancement may be seen in some infectious, inflammatory, and neoplastic conditions (from breakdown of blood-brain barrier)

CT/MR ANGIOGRAPHY—used for evaluation of occlusive cerebrovascular disease, dissection, and in the detection of intracerebral aneurysms as

SPECIFIC ENTITIES (CONT'D)

- (bulbar, cervical, and lumbosacral). No sensory deficit. Preserved cognition
- **CLINICAL FEATURES**—mixed upper motor neuron signs (hyperactive reflexes, extensor plantar responses, spasticity, pseudobulbar affect) and lower motor neuron signs (muscle weakness, atrophy, and fasciculations) in multiple regions
- **DIAGNOSIS**—EMG/NCS
- **TREATMENTS**—antiglutamate agent (riluzole), free radical scavenger (edaravone), emerging antisense oligonucleotides medications for familial ALS (SOD1 and C9ORF72)

DROP HEAD SYNDROME—persistent head flexion. May be due to myasthenia gravis, inflammatory myositis, ALS, Parkinson disease, isolated neck extensor myopathy, muscular dystrophy, myotonic dystrophy

MODALITIES (CONT'D)

small as 5 mm in diameter. However, conventional cerebral angiogram remains the gold standard

CT/MR VENOGRAPHY—extremely sensitive and specific in the diagnosis of venous sinus thrombosis

APPROACH TO CT HEAD**BRAIN PARENCHYMA**

- **ANY SUSPICIOUS, ASYMMETRIC LESIONS**—hypodensity within the parenchyma suggests infarction or fluid. Hyperdensity represents either hematoma (hemorrhage) or calcification. A hematoma will produce mass effect upon adjacent structures. Calcification will usually be punctate and have no mass effect
- **GRAY-WHITE DIFFERENTIATION**—the junction of gray matter and white matter adjacent to the cortex and the basal ganglia should be well defined. Poor delineation should raise suspicion of cerebral edema if the finding is global or acute infarction if the finding is localized
- **MIDLINE SHIFT**—measured by drawing a line from the anterior falx to the posterior falx, then comparing this line with the septum pellucidum

VENTRICLES AND SUBARACHNOID SPACES

(sulci and cisterns)—difficulty with visualization of the basal cisterns may indicate increased intracranial pressure and possibly brain herniation. Hyperdensity (white) within the subarachnoid

APPROACH TO CT HEAD (CONT'D)

spaces and the dependent portions of the ventricles suggests subarachnoid hemorrhage

DURA AND SUBDURAL SPACE—check for subdural hemorrhage in subdural window (crescent like), especially along the edges of the intracranial cavity

BONE AND AIR SPACES—check for fractures in bone window and fluid in sinuses

SKIN AND SUBCUTANEOUS TISSUES—check for swelling of extracranial soft tissues in subdural window

HEAD CT FINDINGS IN THE ELDERLY

SMALL VESSEL DISEASE—diffuse brain atrophy, hypodense periventricular white matter due to gliosis, and lacunar infarcts within the basal ganglia

LARGER VENTRICLES AND SUBARACHNOID SPACES—due to brain atrophy

FOCAL CALCIFICATION—common within the basal ganglia in the elderly and should not be confused with hemorrhage

HEAD CT FINDINGS IN STROKE

LOCALIZATION—the presenting symptoms can help focus evaluation. The majority of infarcts involve the MCA territory or subcortical region. Early signs of infarction include the following:

- **HYPERDENSE MCA**—the suspected MCA must be significantly denser than the contralateral MCA or basilar artery
- **EDEMA OF THE BASAL GANGLIA AND/OR INSULAR CORTEX**—involved lentiform nucleus will appear hypodense with indistinct lateral border. The insular cortex will appear swollen compared to the contralateral side
- **SULCAL EFFACEMENT**—the sulci along the cerebral convexity on the involved side will appear smaller than the other side

EVOLUTION—hypodense lesions may not appear until after 24 h. MRI is superior to CT for identifying acute stroke. Lesions may become more hypodense over time. Old infarcts are very black



CLASSIFICATION

TYPE 1 DIABETES—autoimmune destruction of β cells, prone to DKA

TYPE 2 DIABETES—insulin resistance and a relative or absolute insulin deficiency

GESTATIONAL DIABETES—glucose intolerance diagnosed during pregnancy

OTHER SPECIFIC TYPES

- **GENETIC DEFECTS OF β CELL FUNCTION**—maturity onset diabetes of the young (MODY)
- **GENETIC DEFECTS IN INSULIN ACTION**
- **OTHER GENETIC SYNDROMES ASSOCIATED WITH DIABETES**—Down, Klinefelter, Turner, Wolfram, and Prader-Willi syndromes
- **DESTRUCTIVE PANCREATOGENIC**—cystic fibrosis, hemochromatosis, neoplasia, pancreatitis, pancreatectomy
- **ENDOCRINOPATHIES**—acromegaly, Cushing syndrome, glucagonoma, hyperthyroidism, pheochromocytoma
- **INFECTIONS**—congenital rubella, CMV
- **OTHER FORMS OF IMMUNE-MEDIATED DIABETES**—autoimmune polyglandular syndrome type 2, anti-insulin receptor antibodies, immune checkpoint inhibitors
- **DRUG OR CHEMICAL INDUCED**—atypical antipsychotics, corticosteroids, nicotinic acid, phenytoin, protease inhibitors, thiazides

PATHOPHYSIOLOGY

CHRONIC COMPLICATIONS OF DIABETES

- **MACROVASCULAR DISEASE**—patients with diabetes have a 2–4 \times \uparrow in cardiovascular complications (coronary artery disease, stroke/TIA, peripheral vascular disease)
- **RETINOPATHY**
 - **BACKGROUND**—microaneurysms, dot and blot hemorrhages, hard exudates

PATHOPHYSIOLOGY (CONT'D)

- **PRE-PROLIFERATIVE**—soft exudates, macular edema, intra-retinal microvascular abnormality
- **PROLIFERATIVE**—increased new vessels around the optic disc, vitreous hemorrhage, detached retina, neovascular glaucoma
- **NEPHROPATHY**—glomerular basement membrane thickening, \uparrow glomerular pressure, microalbuminuria, overt proteinuria, nephrotic range proteinuria, end-stage renal disease
- **NEUROPATHY** (50% of all patients)
 - **MONONEUROPATHY**—cranial (III [commonly sparing pupil], IV, VI, VII), peripheral (median, ulnar, peroneal)
 - **MONONEURITIS MULTIPLEX**—combination of multiple mononeuropathies
 - **DISTAL SYMMETRIC POLYNEUROPATHY**—most common with classic stocking-glove distribution. Progressive loss of distal sensation due to axonal loss, followed by motor weakness and motor axonal loss. May be associated with Charcot foot
 - **PROXIMAL POLYNEUROPATHY**—also known as diabetic amyotrophy, diabetic polyradiculopathy, diabetic radiculoplexopathy, or Bruns-Garland syndrome. Usually involving L2–4 roots causing painful, asymmetric, proximal weakness in knee extension, hip flexion, and, importantly, hip adduction (obturator nerve involvement, distinguishing feature from femoral neuropathy)
 - **AUTONOMIC NEUROPATHY**—postural hypotension, gastroparesis, constipation, diarrhea, erectile dysfunction, atonic bladder, hypoglycemia unawareness, hyperhidrosis of upper extremities, anhidrosis of lower extremities, dry skin

PATHOPHYSIOLOGY (CONT'D)**REASONS WHY BLOOD GLUCOSE MAY FLUCTUATE**

- **LIFESTYLE**—diet (quantity/quality, timing), exercise
- **INSULIN**—injection site, technique, dose
- **ILLNESS**—infections, stress
- **NEUROPATHY**—hypoglycemic awareness, gastroparesis
- **DECREASED INSULIN REQUIREMENT**—renal failure, Addison disease
- **MEDICATIONS**—interactions
- **BLOOD GLUCOSE TESTING**—accuracy, timing
- **OTHER ENDOCRINE CAUSES OF HYPERGLYCEMIA**—Cushing syndrome, pheochromocytoma, hyperthyroidism

DKA vs. HYPEROSMOLAR HYPERGLYCEMIC STATE (HHS)—both have many overlapping features. DKA is characterized by anion gap metabolic acidosis (from ketones), volume contraction (mild to severe), elevated blood glucose (usually ≥ 14 mM [250 mg/dL] but can be lower, particularly if taking SGLT2 inhibitors), and plasma osmolality ≤ 320 mOsm/kg. In contrast, HHS is characterized by a greater elevation in blood glucose (typically ≥ 34 mM [>600 mg/dL]), severe volume contraction, and plasma osmolality >320 mOsm/kg, but minimal/no acidosis. Altered mentation may occur with HHS and severe DKA

PRECIPITATING FACTORS FOR DKA—infection, insulin omission, myocardial infarction, new-onset of type 1 diabetes, acute abdomen, drugs (e.g. SGLT2 inhibitors, corticosteroids)

CLINICAL FEATURES

HISTORY—duration and type of diabetes, **diabetic control** (frequency of monitoring, hypoglycemia [\pm awareness of adrenergic symptoms], hyperglycemia, previous HbA1C, previous DKA/hyperosmolar hyperglycemic state, prior hospitalization), **treatment** (insulin, oral hypoglycemic agents, healthy eating guidelines, exercise, education), **acute complications** (polyuria, polydipsia, blurred vision, numbness, weight loss, fatigue), **chronic complications** (see previous section). Risk factors for heart disease (hyperlipidemia, hypertension, smoking, family history of early cardiac events, obesity)

PHYSICAL—weight, BMI, vitals, fundi (diabetic or hypertensive retinopathy, cataracts), thyroid,

CLINICAL FEATURES (CONT'D)

chest, cardiac, abdominal examination, insulin injection sites (lipoatrophy or lipohypertrophy), peripheral pulses, check for carotid and femoral bruits, diabetic foot examination including neurological examination

EXAMINATION OF LOWER EXTREMITIES

- **INSPECTION**—shoes, diabetic dermopathy, dry atrophic skin, fissures, callus, necrobiosis lipoidica diabetorum, muscle atrophy, hair loss, pallor, ulcers (arterial, neuropathic, venous stasis), gangrene (look between toes), dystrophic nails, ingrown nails, fungal nail infections, Charcot foot (neuropathic arthropathy, characterized by collapse of the arch of the midfoot and bony prominences in distinctive places, acute painless episodes of swelling and erythema over ankle or foot)
- **PALPATION/CIRCULATION**—peripheral pulses, temperature, capillary refill, Buerger test, ankle/brachial index
- **NEUROLOGICAL**—10 g sensory monofilament, vibration, glove and stocking sensory loss (light touch, pain, temperature), power (dorsiflexion, plantar flexion), ankle reflex

INVESTIGATIONS**BASIC**

- **LABS**—fasting glucose, lytes, osmolality, ketones, creatinine, HbA1C, fasting lipids, urinalysis, urine albumin to creatinine ratio

SPECIAL

- **ABG**—if DKA
- **OTHER AUTOIMMUNE DISEASE WORK-UP**—TSH, celiac screen
- **ANTIBODIES**—insulin antibody, GAD65 antibody, islet cell antibody

Related Topics

Autonomic Neuropathy (p. 357)
 Coronary Artery Disease (p. 30)
 Gastroparesis (p. 131)
 Gestational Diabetes (p. 470)
 Osteomyelitis (p. 264)
 Peripheral Neuropathy (p. 355)
 Peripheral Vascular Disease (p. 67)

DIAGNOSTIC ISSUES**DIAGNOSTIC CRITERIA FOR DIABETES**

	Fasting BG	OGTT (75 g, 2 h)	HbA1C
Normal	<5.6 mmol/L [<100 mg/dL]	<7.8 mmol/L [<140 mg/dL]	<5.5%
Prediabetes ^a			6.0–6.4%
Impaired fasting glucose	6.1–6.9 mmol/L [110–125 mg/dL]		
Impaired glucose tolerance		7.8–11.0 mmol/L [140–199 mg/dL]	
Diabetes ^b	≥7.0 mmol/L [≥126 mg/dL]	≥11.1 mmol/L [≥200 mg/dL]	≥6.5%

BG blood glucose, OGTT oral glucose tolerance test

^aIf fasting BG 5.6–6.0 mmol/L [100–109 mg/dL] and/or HbA1C 5.5–5.9%, consider further testing with 75 g OGTT

^bRandom glucose ≥11.1 mmol/L [≥200 mg/dL] accompanied by classical symptoms (polyuria, polydipsia, unexplained weight loss) also sufficient for diagnosis. In the absence of compatible symptoms, a single laboratory test in the diabetes range should be repeated with a confirmatory test on another day

DIAGNOSTIC ISSUES (CONT'D)

FACTITIOUS LABORATORY ABNORMALITIES—DKA itself may cause ↑ WBC, ↓ Na, and ↓ amylase, which should correct with resolution of DKA

SELECTED FACTORS AFFECTING HEMOGLOBIN A1C

- **INCREASE**—iron deficiency, B12 deficiency, chronic renal failure (altered glycation)
- **DECREASE**—hemoglobinopathies, chronic renal failure (decreased erythrocyte span)

ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS

ACUTE—ABC, O₂, IV, may need intubation

CORRECT ACID/BASE ELECTROLYTES ABNORMALITIES

- **MONITOR**—continuous cardiac monitor until patient is stable. Create flow sheet with time vs. lytes, anion gap, glucose, insulin, IV fluids, urine output. Careful monitoring and frequent reassessment required
- **HYDRATION**—NS 15–20 mL/kg IV bolus (~1 L) then 4–14 mL/kg/h (~250–500 mL/h) to fluid resuscitate then decrease IV accordingly
- **POTASSIUM**—do not start insulin infusion unless K is ≥3.3 mEq/L. Once serum K is <5.0 mEq/L and patient is voiding, add supplemental potassium (see table on next page)

ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS (CONT'D)

- **INSULIN**—give 0.1 units/kg/h. Titrate insulin drip against anion gap. If anion gap still ↑, increase the rate (see table on next page). Try to keep glucose between 10 and 15 mM in first day. As anion gap falls, decrease insulin drip. Switch to SC insulin when (1) anion gap normalized, (2) insulin requirements reasonable, (3) patient able to eat, and (4) only in AM (to facilitate monitoring over the course of the day). Ensure overlap of SC insulin with insulin infusion by at least 1–2 h
- **GLUCOSE**—once serum glucose is less than 15 mM, add glucose to IV fluids (e.g. D5NS, D5½NS)
- **BICARB**—if pH <7, may be beneficial to give 1–2 amps of HCO₃ over 1–2 h. If pH. If pH ≥7.0, giving HCO₃ not necessary
- **PHOSPHATE**—no indication for replacement in the acute setting unless there is severe cardiac/respiratory depression; may consider when serum phosphate <0.32 mmol/L [1.0 mg/dL]
- **LABS**—obtain hourly lytes, bicarb, anion gap (calculated using measured Na⁺), glucose. Cerebral edema is a concern (particularly in children) if osmolality/sodium parameters are corrected too quickly. Avoid correcting blood glucose by >5 mmol/L/h [>90 mg/dL/h] or Na⁺ by >0.3–0.5 mmol/L/h

ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS (CONT'D)

	Hour 1	Hour 2	Hour 3-4	Hour 4-8	Hour 8-24
Potassium replacement (when voiding)	Serum potassium, potassium replacement	<3.3 mmol/L, give 40 mmol/h	3.3-4 mmol/L, give 30 mmol/h	4-5 mmol/L, give 20 mmol/h	5-5.5 mmol/L, give 10 mmol/h
Laboratory	Baseline: glucose, ketones, ABG, urinalysis, CBC, electrolytes, Cr, PO ₄ , Mg, ± lipase, CXR, cultures, troponin, ECG	Glucose (C/S), lytes (VBG) ABGs if pH <7.0	Glucose (C/S), lytes lytes (VBG) ABGs if pH <7.0	Glucose (C/S) hourly, lytes (VBG), PO ₄	Glucose (C/S) q1-2 h Lytes q4-8 h
Alkaline replacement	Rarely indicated unless severe acidosis (pH <7) with incipient circulatory collapse Dose 50-100 mEq, NaHCO ₃ in ½NS over 30-60 min Extra potassium may be needed with bicarbonate therapy				
Phosphate replacement	Consider if serum phosphorus <0.65 mmol/L (<2.0 mg/dL) and give if serum phosphorus <0.35 mmol/L (<1.1 mg/dL) 2.5-8 mmol/h [8-25 mg/dL] (1 mmol of phosphate = 31 mg of elemental phosphorus) (e.g. 10 mL of KPO ₄ in 1 L NaCl over 6 h (30 mM PO ₄ , 44 mEq K)				
General measures	Make flow sheet (ABGs, glucose, lytes, bicarb, AG, ±O ₂ , urine output), q1h vitals NG tube if unconscious, antibiotics if infection, cardiac monitor when acidotic, give fluid (6-8 L deficit) Foley to urometer if no urine for 4 h				

NOTE: this table should not replace individualized care and sound clinical judgment

Abbreviations: ABG arterial blood gas, AG anion gap, C/S chemstrips, NS normal saline, VBG venous blood gas

SPECIFIC ENTITIES

HYPEROSMOLAR HYPERGLYCEMIC STATE

- **PATHOPHYSIOLOGY**—may occur with severe uncontrolled hyperglycemia in type 2 diabetes
- **CLINICAL FEATURES**—characterized by profound dehydration, hyperosmolar state, severe elevation in blood glucose along with hypernatremia. Ketones may be absent (or mildly elevated). Patients often present with neurological deficit (decreased level of consciousness, coma)
- **TREATMENTS**—fluid resuscitation along with an insulin IV drip. To minimize risk of cerebral edema, serum Na should ideally drop by no more than 8–10 mmol/L/day, serum osmolality should drop by no more than 3 mmol/kg/h, and glucose should drop by no more than 3 mmol/L/h. Lower insulin requirement compared to DKA. Mortality 10–20%

EUGLYCEMIC DKA

- **PATHOPHYSIOLOGY**—SGLT2 inhibitors may lower threshold for developing DKA because of fall in insulin:glucagon ratio with increased fatty acid oxidation
- **CLINICAL FEATURES**—similar to hyperglycemic DKA but presenting with glucose <14 mmol/L [252 mg/dL]
- **TREATMENTS**—stop SGLT2 inhibitor and treat per DKA protocol

LONG-TERM MANAGEMENT

RISK REDUCTION ★ABCDEF★

- **ASA/ACE INHIBITOR/ARB**—ASA 81 mg PO daily for secondary prevention, controversial for primary prevention. ACE inhibitor or ARB should be started if albuminuria or clinical cardiovascular disease
- **BLOOD PRESSURE CONTROL**—aim for <130/80 mmHg
- **CHOLESTEROL CONTROL**—start statin if diabetes >15 years and >30-years old, or in those with established microvascular/macrovacular disease. May consider ezetimibe (↓ LDL), fibrates (↓ triglycerides, ↑ HDL), and/or PCSK9 inhibitor (↓ LDL) as add-on therapy
- **CARDIOVASCULAR DISEASE SCREENING**—consider the following tests for selected patients:
 - **ECG**—if age >40, have had diabetes for >15 years and >30-years old, presence of end organ damage, or multiple cardiovascular risk factors
 - **EXERCISE ECG STRESS TEST**—angina, atypical chest pain, dyspnea, abnormal ECG, peripheral artery disease, carotid bruits,

LONG-TERM MANAGEMENT (CONT'D)

transient ischemic attack, stroke, absolute coronary artery calcium score >400

- **STRESS MIBI**—individuals with an abnormal ECG (LBBB or ST-T wave changes) or who cannot exercise
- **DIABETIC CONTROL**—individualize treatment targets. **Aim for HbA1C ≤7.0% in most patients.** A target HbA1C of ≤6.5% may be considered in selected patients with type 2 diabetes to reduce risk of microvascular complications. Consider HbA1C of 7.1–8.5% in patients with limited life expectancy, high-level of functional dependency, extensive coronary artery disease, multiple comorbidities, or history of severe hypoglycemia. Target fasting/preprandial blood glucose 4.0–7.0 mmol/L [73–126 mg/dL], and 2 h postprandial blood glucose 5.0–10.0 mmol/L [91–182 mg/dL] (or 5.0–8.0 mmol/L [91–145 mg/dL] if HbA1C targets are not met). Diabetes Control and Complications Trial showed that intensive glycemic control of patients with type 1 diabetes reduces retinopathy, nephropathy, and neuropathy. HbA1C correlates with complications. Major side effects include 3 × ↑ in hypoglycemia (especially previous episodes, hypoglycemia unawareness) and increased weight gain
- **EDUCATION**—all patients should attend diabetes classes
- **EXERCISE**—150 min per week of moderate to vigorous aerobic physical activity and resistance exercise 3 times per week
- **EYE/NEUROLOGIC**—all patients with type 2 diabetes should be referred to an ophthalmologist/optometrist at the time of diagnosis and then annually. Patients with type 1 diabetes may have a baseline eye assessment 5 years after the diagnosis as long as they are aged 15 or greater. Eye exams may be done annually after that. All patients should have an annual assessment of neuropathy including the diabetic foot exam. Duloxetine, gabapentin, or pregabalin may be used for painful neuropathy. Domperidone, metoclopramide, erythromycin, or prucalopride may be used for gastroparesis
- **FAT REDUCTION**—all patients should follow healthy eating guidelines and try to attain an ideal body weight. Sustained weight loss of ≥5% of initial body weight for overweight or obese individuals may improve glycemic control and reduce CV risk. Remission of diabetes is possible with bariatric surgery for patients

LONG-TERM MANAGEMENT (CONT'D)

with morbid obesity. See OBESITY ISSUES (p. 449)

- **GET GOING TO QUIT SMOKING!**—there are many different options for patients, including nicotine gum, nicotine inhaler, nicotine patch, bupropion SR, and varenicline

NON-INSULIN ANTIHYPERGLYCEMIC AGENTS

BIGUANIDES (↓ hepatic glucose production, ↑ tissue insulin sensitivity)—*metformin* 500–1,000 mg PO BID; adverse effects include GI upset and possible lactic acidosis; contraindications include hypoxia, hepatic failure, severe renal failure, HF, poor LV function; hold before giving IV contrast and 48 h post-contrast

SULFONYLUREA (↑ insulin release)—*glipizide* [Diamicon®] 80 mg PO daily to 160 mg BID; *glipizide* [Diamicon® MR] 30–120 mg PO daily; *glimepiride* 1–8 mg PO daily, *glyburide* 2.5–10 mg PO BID; adverse effects include hypoglycemia. Caution in elderly

MEGLITINIDE (↑ pancreatic insulin release)—*repaglinide* 0.5–4 mg PO TID ac meals; adverse effects include hypoglycemia. May be used in CKD

DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS—*sitagliptin* 25–100 mg PO daily; *saxagliptin* 2.5–5 mg PO daily; *linagliptin* 5 mg PO daily; *alogliptin* 6.25–25 mg PO daily. Usually add-on therapy to metformin. Increases incretin levels, increases insulin release in response to glucose, and decreases glucagon resulting in improved postprandial control; weight neutral

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGUES—*liraglutide* 0.6–1.8 mg SC daily; *exenatide* 5–10 µg SC BID; *exenatide ER* 2 mg SC weekly; *dulaglutide* 0.75–1.5 mg SC weekly; *lixisenatide* 10–20 mcg SC daily; *semaglutide* 0.25–1 mg SC weekly; also available as *semaglutide* 3–14 mg PO daily to be taken with up to 120 mL of water at least 30 minutes before eating or other

NON-INSULIN ANTIHYPERGLYCEMIC AGENTS (CONT'D)

oral medications. Usually add-on therapy. Causes dose-dependent and glucose-dependent insulin secretion, delays gastric emptying, promotes weight loss, and suppresses glucagon. Long-term adverse effects are unknown. Nausea is a common adverse effect and pancreatitis has been reported

SODIUM-GLUCOSE COTRANSORTER 2 (SGLT2) INHIBITORS—*canagliflozin* 100–300 mg PO daily; *dapagliflozin* 5–10 mg PO daily; *empagliflozin* 10–25 mg PO daily; *ertugliflozin* 5–15 mg PO daily. Promotes renal excretion of glucose. Increased risk of urinary tract infections, vulvovaginal candidal infections, rarely euglycemic DKA

THIAZOLIDINEDIONES (↑ tissue insulin sensitivity, ↓ hepatic glucose production)—*pioglitazone* 15–45 mg PO daily. Adverse effect of fluid retention; contraindications include liver failure, fluid overload, HF, and CAD

α-GLUCOSIDASE INHIBITOR (↓ glucose absorption)—*acarbose* 25–100 mg TID ac meals; adverse effects include bloating and diarrhea

SPECIAL CONSIDERATIONS

- **RENAL FAILURE**—many antihyperglycemic medications need to be dose-adjusted (e.g. insulin, GLP-1 agonists, DPP-4 inhibitors, sulfonylureas, meglitinides); some may lack therapeutic efficacy with advanced renal failure (e.g. SGLT2 inhibitors); and others are contraindicated when GFR < 30 mL/min/1.72 m² (e.g. metformin)
- **SICK DAY MANAGEMENT**—during periods of intercurrent illness when unable to maintain adequate fluid intake (e.g. presence of vomiting or diarrhea), patients should be instructed to hold medications that may increase risk of renal failure (e.g. ACE inhibitors, ARBs, diuretics, SGLT2 inhibitors, NSAIDs) and those that are primarily renally-cleared (e.g. metformin, sulfonylureas)

Principles of Insulin Use**STARTING INSULIN FOR NEW PATIENTS****EDUCATION**

- **INSULIN STORAGE**—refrigerate until opened, then keep at room temperature for up to 28 days
- **ADMINISTRATION TECHNIQUE**—priming pen and site rotation

STARTING INSULIN FOR NEW PATIENTS (CONT'D)

- **HYPOGLYCEMIA MANAGEMENT**—monitoring for symptoms and treatment
- **DRIVING PRECAUTIONS**

STARTING INSULIN FOR NEW PATIENTS (CONT'D)**CALCULATE TOTAL DAILY DOSE**

- **STABLE PATIENTS**—in type 1 diabetes, total daily dose of insulin is approximately 0.5 units/kg/d (but may be ↑ with insulin resistance [puberty, obesity, pregnancy], or ↓ with residual β-islet cell function or illness [renal failure, adrenal insufficiency]). In type 2 diabetes, insulin dosages vary greatly; common starting dose is bedtime insulin (intermediate- or long-acting) at 0.1–0.2 units/kg/day (minimum 10 units) to improve control
- **BASAL-BOLUS REGIMENS**—multiple daily injections or continuous subcutaneous insulin infusion (insulin pump) is ideal for patients with type 1 diabetes. Treatment must be individualized. With multiple daily injections, approximately 50% of total insulin is given as basal (intermediate- or long-acting) either once daily (e.g. at bedtime) or BID (e.g. morning and bedtime). Remaining 50% is given as bolus (rapid- or short-acting) split between meals (breakfast, lunch, supper). With continuous subcutaneous insulin infusion (insulin pump) therapy, rapid-acting insulin is used for both basal and bolus components
- **TWO-THIRDS, ONE-THIRD RULE**—if a patient is unable to comply with multiple daily injections (e.g. children or those with difficulty self-administering), consider simplified “two-thirds, one-third rule.” Provides a rough estimate of the amount of insulin required. Morning dose (given before breakfast) = 2/3 of total daily insulin (2/3 = intermediate acting, 1/3 = short acting), supper dose = 1/3 of total daily insulin (2/3 = intermediate acting, 1/3 = short acting)

SPECIAL CONSIDERATIONS

- **PERI-PROCEDURAL**—insulin dosing strategies vary widely. Commonly, mealtime (rapid- or short-acting) insulin held when NPO; basal insulin (intermediate- or long-acting) reduced by 20–50% the evening before and on the morning of the test/procedure/surgery when NPO
- **RENAL FAILURE**—insulin is renally metabolized, thus its dose must be reduced in patients with advanced renal failure
- **METFORMIN AND INSULIN**—consider the use of metformin in conjunction with insulin in type 2 diabetics to increase insulin sensitivity and decrease insulin requirements

STARTING INSULIN FOR NEW PATIENTS (CONT'D)

- **THIAZOLIDINEDIONES AND INSULIN**—avoid using thiazolidinediones (e.g. rosiglitazone) in combination with insulin as these promote fluid retention
- **β-BLOCKERS**—non-selective β-blockers may mask signs and symptoms of hypoglycemia. Consider use of cardioselective β-blocker agents instead

REGULAR INSULIN DOSE ADJUSTMENT PRINCIPLES

INSULIN ADJUSTMENTS—understanding the pharmacokinetics of different insulin types is essential. Blood glucose is usually checked at least 4 times/day, before meals and at bedtime

- **HIGH AM BLOOD GLUCOSE**—check 3 AM glucose. If there is nocturnal hypoglycemia, bedtime basal insulin should be decreased. If the 3 AM glucose is elevated, bedtime basal insulin should be increased
- **HIGH LUNCH TIME BLOOD GLUCOSE**—should increase breakfast mealtime insulin dose
- **HIGH SUPPER TIME BLOOD GLUCOSE**—should increase noon mealtime insulin dose or morning basal dose
- **HIGH BEDTIME BLOOD GLUCOSE**—should increase supper insulin mealtime dose

INSULIN-CARBOHYDRATE RATIO—in type 1 diabetes, meal-time insulin can be dosed according to the content of the meal. Insulin-carbohydrate ratio is the number of grams of carbohydrate that 1 unit of rapid-acting insulin will cover. Commonly 1:10–1:15, but must be individualized for each patient, and may vary with each meal. Insulin-carbohydrate ratio is usually empirically derived, but can be roughly estimated as 500 divided by total daily dose of insulin. Matching insulin dosage with the amount of carbohydrate consumed allows for flexibility around meals (e.g. if insulin-carbohydrate ratio is 1:10 and meal contains 90 g of carbohydrate, then 9 units of rapid-acting insulin should be taken)

INSULIN-SENSITIVITY FACTOR (CORRECTION FACTOR)—in type 1 diabetes, a correction factor can be used to estimate the amount the blood glucose expected to drop with 1 unit of rapid-acting insulin. Correction factor is calculated as 100 divided by total daily dose of insulin (e.g. if sum of basal and bolus insulin over 24 h is 50

REGULAR INSULIN DOSE ADJUSTMENT PRINCIPLES (CONT'D)

units, then the correction factor is $100 \div 50 = 2$; therefore, for every 1 unit of rapid-acting insulin, the blood glucose is expected to \downarrow by 2 mmol/L. Correction dose of insulin is calculated by “(measured blood glucose – target blood glucose) \div correction factor” (e.g. if pre-meal blood glucose is 10 mmol/L and the target blood glucose is 6 mmol/L, then $[10 - 6] \div 2 = 2$ units; therefore, 2 units of rapid-acting insulin is expected to \downarrow blood glucose from 10 to 6 mmol/L)

REGULAR INSULIN DOSE ADJUSTMENT PRINCIPLES (CONT'D)

COMBINING INSULIN-CARBOHYDRATE RATIOS WITH INSULIN-SENSITIVITY FACTOR—total amount of bolus (rapid-acting) insulin that should be administered at mealtime is the sum of the insulin required for the carbohydrate content of the meal (based on the insulin-carbohydrate ratio) and the correction dose (based on the insulin-sensitivity factor)

TYPES OF INSULIN

Insulin	Onset	Peak	Duration
Rapid-acting (clear)			
NovoRapid (insulin aspart)	9–20 min	1–1.5 h	3–5 h
Apidra (insulin glulisine)	10–15 min	1–1.5 h	3.5–5 h
Humalog (insulin lispro) U-100, U-200	10–15 min	1–2 h	3–4.75 h
Fiasp (faster insulin aspart)	4 min	0.5–1.5 h	3–5 h
Short-acting (clear)			
Humulin-R (insulin regular)	30 min	2–3 h	6.5 h
Novolin ge Toronto (insulin regular)	30 min	2–3 h	6.5 h
Entuzity (insulin regular)	15 min	4–8 h	17–24 h
Intermediate-acting (cloudy)			
Humulin-N (insulin neutral protamine Hagedorn)	1–3 h	5–8 h	Up to 18 h
Novolin ge NPH (insulin neutral protamine Hagedorn)			
Long-acting (clear)			
Insulin detemir (Levemir)	90 min	Not applicable	16–24 h
Insulin glargine biosimilar (Basaglar)			24 h
Insulin glargine (Lantus) U-100			24 h
Insulin glargine (Toujeo) U-300			>30 h
Degludec (Tresiba) U-100, U-200			42 h
Premixed regular insulin-NPH (cloudy)			
Humulin 30/70			
Novolin ge 30/70			
Novolin ge 40/60			
Novolin ge 50/50			
Premixed insulin analogues (cloudy)			
Novo Mix 30			
Humalog Mix 25			
Humalog Mix 50			

2018 Diabetes Canada Guidelines. NOTE: most insulin is U-100 (100 units/mL), but more concentrated formulations exist such as U-200 (200 units/mL), U-300 (300 units/mL), and U-500 (500 units/mL). Be careful with dosing of concentrated formulations because volumes do not correspond with U-100 and pharmacokinetic profile may also differ (e.g. regular insulin U-500 resembles intermediate-acting insulin)

MANAGEMENT ISSUES

LOCAL COMPLICATIONS OF INSULIN INJECTION—lipoatrophy (human insulin), lipohypertrophy (animal insulin), edema, itching, pain or warmth at injection site, scar tissue

LONG-TERM COMPLICATIONS OF INSULIN USE—weight gain and risk of hypoglycemia

GLUCOSE MONITORING TECHNOLOGIES—continuous glucose monitoring and flash glucose monitoring provide real-time data that may help improve glycemic control and quality of life

CONTINUOUS SUBCUTANEOUS INSULIN THERAPY—portable pumps that deliver rapid-acting insulin continuously

- **ADVANTAGES**—flexible and customizable for basal/bolus patterns, decreased risk of hypoglycemia, and ability to deliver very small amounts of insulin
- **DISADVANTAGES**—risk of ketoacidosis quickly if insulin delivery interrupted, need accurate carbohydrate counting, need frequent blood glucose monitoring at least 4–6 times/day, costly, and resource-intensive
- **BEFORE STARTING PUMP**—give 50% (minimum 10 units) of usual basal dose of insulin the night before pump start. If basal insulin typically given in the morning, can start pump at the time when SC dose was meant to be given

MANAGEMENT ISSUES (CONT'D)

- **PUMP INITIATION**—calculate 75% of the typical total daily dose of insulin and divide this into a 50/50 ratio where half will be the starting basal dose over 24 hours. Assess glycemic control every few days and adjust settings (basal rate, insulin-carbohydrate ratio, and sensitivity factor) as needed. Remind patient that changes in basal rate will be apparent after 2 hours, whereas boluses will take effect within 10–15 minutes. Even with a pump, patient still needs pen (or syringes) with insulin on hand at all times in case of an emergency or pump failure
- **KETONE TESTING**—check for ketones if blood glucose >15 mmol/L on several occasions spaced 1–2 hours apart despite usual correction dose, or if symptoms of ketosis (e.g. nausea, vomiting, lethargic). If ketones detected, use a pen (or syringe) and give 50% more than usual correction and recheck blood glucose. Change infusion site
- **TRANSITIONING BETWEEN IV INSULIN AND PUMP**—if pump has been suspended for IV insulin (e.g. surgery), consider restarting insulin pump when the patient is alert and well while overlapping with insulin infusion for at least 1–2 h

Hypoglycemia**DIFFERENTIAL DIAGNOSIS**

↑ **INSULIN** AND ↓ **C-PEPTIDE**—exogenous insulin, insulin autoantibodies

↑ **INSULIN** AND ↑ **C-PEPTIDE**—drugs (sulfonylurea, meglitinide, pentamidine, quinine), β-cell tumor (insulinoma), non-insulinoma pancreatogenous hypoglycemia syndrome (nesidioblastosis, dumping syndrome post-bariatric surgery)

↓ **INSULIN** AND ↓ **C-PEPTIDE**—alcohol, sepsis, adrenal insufficiency, panhypopituitarism, severe liver failure, chronic renal failure, anorexia, inborn errors of metabolism, drugs (fluoroquinolones, β-blockers, salicylates, haloperidol), starvation (inanition), IGF-II-secreting tumors

PATHOPHYSIOLOGY

DEFINITION OF HYPOGLYCEMIA—plasma glucose <4.0 mmol/L [<72 mg/dL]

PATHOPHYSIOLOGY (CONT'D)

REACTIVE HYPOGLYCEMIA—hypersecretion of insulin postprandially (hypoglycemia occurring within 4 h after meals)

CLINICAL PEARL—the most common reason for a patient to have a low glucose is too much insulin or exposure to oral hypoglycemic agents. However, in patients without diabetes who are presenting with hypoglycemia, it is important to rule out alcoholism, severe sepsis, adrenal insufficiency, and panhypopituitarism. Insulinoma is rare and should be a diagnosis of exclusion. Always consider surreptitious use if no obvious cause found, especially if there is possibility of access to diabetic drugs. Plasma glucose less than 4.0 mmol/L [72 mg/dL] can occasionally be present in normal healthy individuals after prolonged fasting, strenuous exercise, or with pregnancy, but uncommonly goes lower than 2.8 mmol/L [50 mg/dL]

CLINICAL FEATURES

ADRENERGIC (AUTONOMIC) SYMPTOMS—trembling, sweating, palpitations, anxiety

NEUROGLYCOPENIC SYMPTOMS—dizziness, blurred vision, headaches, mental deficits, drowsiness, altered level of consciousness

WHIPPLE TRIAD—measured hypoglycemia (<2.8 mmol/L [50 mg/dL]), corresponding symptoms of hypoglycemia, reversal of symptoms with glucose. Further investigations usually only recommended for individuals with Whipple triad with unexplained hypoglycemia

INVESTIGATIONS**BASIC**

- **LABS**—collected when glucose is low: plasma glucose, insulin, and C-peptide. Consider cortisol, ketones, liver function studies, and renal function. If sepsis is suspected, order CBC, blood cultures, and urine cultures

SPECIAL

- **SERUM SULFONYLUREA SCREEN**—at the time of hypoglycemia
- **INSULIN ANTIBODIES**
- **PROLONGED FASTING STUDY**—may help in the diagnosis of insulinoma if spontaneous hypoglycemic episodes are infrequent. Consult endocrinology

INVESTIGATIONS (CONT'D)

- **MIXED MEAL CHALLENGE TEST**—may help in the diagnosis of non-insulinoma pancreatogenous hypoglycemia syndrome for post-prandial hypoglycemic episodes. Consult endocrinology
- **IMAGING**—CT or MRI abd, endoscopic US if pancreatic tumor suspected

MANAGEMENT

ACUTE—*glucose tablets* 15 g PO, ensure snack or meal afterward. If hypoglycemia is severe and/or patient is unresponsive, give D50W 25–50 mL IV push. If unavailable, give *glucagon* 1 mg SC/IM \times 1 dose, but may be ineffective for patients with heavy alcohol use, advanced liver disease, or sulfonyleurea overdose. Monitor chemstrips q1h to ensure glucose normalizes

TREAT UNDERLYING CAUSE

- **UNINTENTIONAL INSULIN OVERDOSE**—education; reduction of insulin dose; advise having snacks available (e.g. juice); consider *glucagon* 1 mg IM kit as a precaution for treatment of severe hypoglycemia
- **FACTITIOUS**—consult psychiatry
- **DUMPING SYNDROME**—advise small frequent meals; avoidance of simple sugars, increasing fiber and complex carbohydrates; consider *acarbose* 25–100 mg PO tid with meals
- **INSULINOMA**—consult surgery

Hypothyroidism**DIFFERENTIAL DIAGNOSIS****PRIMARY HYPOTHYROIDISM**

- **THYROIDITIS**—Hashimoto, subacute, lymphocytic (silent, postpartum), irradiation
- **IATROGENIC**—radioactive I¹³¹, thyroidectomy
- **DRUGS**—methimazole, propylthiouracil, lithium, amiodarone
- **CONGENITAL**—thyroid agenesis, thyroid dysgenesis, Pendred syndrome
- **OTHERS**—iodine deficiency (endemic goiter), infiltration (amyloidosis, hemochromatosis, sarcoidosis, Riedel thyroiditis/IgG4-related disease)

CENTRAL HYPOTHYROIDISM—diseases of the pituitary or hypothalamus (tumor, surgery, infarction, infection, infiltration, irradiation)

CLINICAL FEATURES

HISTORY—fatigue, dry skin, cold intolerance, depression, confusion, memory loss, goiter, constipation, weakness, carpal tunnel syndrome, menorrhagia, amenorrhea, weight gain, medications, family history of thyroid disease

PHYSICAL—bradycardia, bradypnea, diastolic hypertension, hypothermia, cool and dry skin, orange skin (from carotenemia), carpal tunnel syndrome, thinning hair, periorbital edema, anemia, goiter, pleural effusion, pericardial effusion, proximal myopathy, pseudomyotonia, delayed relaxation phase of the reflexes, edema (non-pitting)

INVESTIGATIONS**BASIC**

- **LABS**—TSH (see note below regarding free T4 and free T3)

SPECIAL

- **ANTI-TPO ANTIBODY**—non-specific

DIAGNOSTIC ISSUES

TSH—usually all that is required to make a diagnosis. Free T4 and free T3 not routinely measured. If central hypothyroidism suspected, check TSH with free T4. In sick euthyroid, biochemical lab abnormalities may occur even though patient is clinically euthyroid

ANTI-TPO ANTIBODY—may be associated with Hashimoto thyroiditis, but non-specific and elevated in up to 20% of general population. Not useful for monitoring disease activity

THYROGLOBULIN ANTIBODY—unhelpful for diagnosing hypothyroidism or hyperthyroidism. Generally only ordered for follow-up of differentiated thyroid cancer post-total thyroidectomy

INTERPRETATION

	TSH	ft4	ft3
Subclinical hypothyroidism	↑	N	N
Primary hypothyroidism	↑	↓	↓
Central hypothyroidism	N/↓	↓	↓
Sick euthyroid syndrome	N/↑/↓	N/↓	↓

MANAGEMENT

MYXEDEMA COMA—ABC, O₂, IV. **Hydrocortisone** 100 mg IV q6h (**give hydrocortisone first** in case of concurrent adrenal insufficiency). **Levothyroxine** 200–500 µg IV, then 100 µg IV daily initially (and if IV continued, give 80% of appropriate PO dose, but not more than 1.4 µg/kg of ideal body weight). **Warming blankets**. Important to rule out adrenal insufficiency as levothyroxine can cause severe decompensation in patients with untreated hypocortisolism. Rule out infection

MANAGEMENT (CONT'D)

TREAT UNDERLYING CAUSE—*levothyroxine* dosage highly variable, but commonly 75–112 µg PO daily for women and 125–200 µg PO daily for men (1.6 µg/kg/day). But in elderly or those with heart disease, initiate treatment at a dose of 25–50 µg PO daily and titrate up by 12.5–25 µg increments every 4–6 weeks as needed

TREATMENT ISSUES

SUBCLINICAL HYPOTHYROIDISM—treatment controversial but should be considered if at high risk of progressing to overt hypothyroidism (e.g. significantly ↑ TSH and ↑ TPO-Ab). Treatment associated with iatrogenic thyrotoxicosis, especially in the elderly, with no apparent benefit for most individuals

PRIMARY HYPOTHYROIDISM—aim to normalize TSH with dosage adjustments no sooner than every 4–6 weeks; *levothyroxine* has half-life of 7 days, and it takes 4–6 weeks for serum TSH to equilibrate after each dose adjustment. When stable dose achieved, check TSH yearly

CENTRAL HYPOTHYROIDISM—free T4 should be used to follow treatment progress in patients with central hypothyroidism, targeting upper half of normal range. No dose adjustments should be made on basis of TSH

SPECIFIC ENTITIES

SICK EUTHYROID SYNDROME—in medically sick but clinically euthyroid patients! Secondary to hypothalamic–pituitary axis disruption, with ↓ T4 → T3 conversion. Mildly altered N/↓ free T4, ↓ free T3, and N/↓ TSH (but may ↑ during recovery phase). Thyroid replacement is not needed. Repeat TSH 1–2 months after acute illness resolved

Related Topic

Hypothyroidism in Pregnancy (p. 472)

Hyperthyroidism**DIFFERENTIAL DIAGNOSIS OF THYROTOXICOSIS**

GRAVES DISEASE (diffuse toxic goiter)—most common cause of hyperthyroidism

TOXIC ADENOMA/TOXIC MULTINODULAR GOITER—more common in elderly

THYROIDITIS—subacute thyroiditis, lymphocytic thyroiditis (silent, postpartum), Hashimoto thyroiditis (“Hashitoxicosis”), radiation-induced

DIFFERENTIAL DIAGNOSIS OF THYROTOXICOSIS (CONT'D)

thyroiditis, drug-induced thyroiditis (lithium, amiodarone, interferon)

IODINE EXPOSURE—kelp, seaweed, radiocontrast dye

EXOGENOUS—*levothyroxine* or *liothyronine* ingestion, hamburger thyrotoxicosis

DIFFERENTIAL DIAGNOSIS OF THYROTOXICOSIS (CONT'D)

ECTOPIC—struma ovarii (thyroid tissue present in an ovarian tumor), hydatidiform mole

CENTRAL—pituitary TSHoma (rare)

PATHOPHYSIOLOGY

GRAVES DISEASE—circulating IgG that binds to and activates the TSH receptor, resulting in follicular hyperplasia (diffuse thyroid enlargement) and overproduction of thyroid hormones. Graves disease occurs more frequently in women (10:1) and may be precipitated by stress, infections, and recent labor/delivery

CLINICAL FEATURES

HISTORY—fatigue, sweating, heat intolerance, psychosis, agitation, confusion, anxiety, goiter, dyspnea, palpitations, diarrhea, amenorrhea, weight loss, medications, family history. Subacute thyroiditis associated with painful goiter

PHYSICAL—vitals (tachycardia, atrial fibrillation, tachypnea, systolic hypertension, fever), systolic flow murmur, thyroid acropachy (clubbing, Graves only), onycholysis (Plummer nails), palmar erythema, tremor, warm and moist skin (“velvet skin”), proptosis, proximal myopathy, hyperreflexia, pretibial myxedema (Graves only), splenomegaly

- **GOITER**—present along with thyroid bruits in Graves. Thyroid enlargement may be found in other types of hyperthyroidism or hypothyroidism as well
- **GRAVES OPHTHALMOPATHY**—protrusion of eyes from the orbits. Features include upper and lower lid retraction, lid lag and stare, ophthalmoplegia, diplopia, conjunctivitis, chemosis, corneal ulceration, optic atrophy, loss of vision. Check visual acuity and visual fields, measure exophthalmos with exophthalmometer

THYROID STORM—may be precipitated by anesthetics, surgery, trauma, systemic illness (especially sepsis), iodine load, and parturition. Clinical manifestations include fever, CNS (delirium), CVS (tachycardia, hypotension), and/or GI (vomiting, jaundice, diarrhea, ↑ LFT) symptoms. The presence of thyrotoxicosis along with dysfunction in 2 of 4 systems would be highly suggestive of a thyroid storm

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A GOITER?

NORMAL—15–20 g. Abnormal if each lateral thyroid lobe has volume greater than the individual's terminal phalanx of thumb

CLINICAL FEATURES (CONT'D)

INSPECTION—slightly extend the neck, observe from front and side, observe the patient swallow, measure amount of prominence with a ruler (>2 mm AP diameter on lateral exam below cricothyroid membrane has very high LR+ for goiter; non-visible gland suggests absence of goiter)

PALPATION—locate thyroid isthmus by palpating between cricoid cartilage and suprasternal notch. Feel the left lobe with neck slightly flexed and rotated to left, and then right lobe. Ask patient to swallow sips of water and repeat palpation. Describe the size of the thyroid, its texture, and consistency; comment on the presence or absence of nodules or tenderness

AUSCULTATION—listen for bruits over each lobe and the isthmus

APPROACH—perform both inspection and palpation (LR+ 0.15 if normal exam, LR+ 1.9 if 1–2 × size, LR+ 25 if >2 × size)

**Siminoski JAMA 1995;273(10)
Simel et al. *The Rational Clinical Examination* McGraw-Hill; 2009**

INVESTIGATIONS**BASIC**

- **LABS**—TSH, free T4, free T3, TSH receptor antibody (Graves), CRP (↑ if thyroiditis), CBC, ALT, AST, ALP, ECG

SPECIAL

- **THYROID US**—to assess for vascular flow (↑ with hyperthyroidism vs. ↓ with thyroiditis) and nodularity; useful when nuclear studies are contraindicated (e.g. pregnancy)
- **RADIOACTIVE IODINE UPTAKE**—to differentiate between hyperthyroidism from increase hormone synthesis (↑ uptake with Graves and functioning nodules) vs. destructive thyroiditis (↓ uptake). Must be thyrotoxic at time of testing; contraindicated if pregnant or breastfeeding
- **THYROID SCAN (SCINTIGRAPHY)**—to determine functional status of nodule(s). Diffuse homogeneous increased iodine uptake suggests Graves disease. Multifocal uptake suggests toxic multinodular goiter. Increased single focus suggests toxic adenoma. Decreased global uptake suggests thyroiditis or factitious hyperthyroidism. Decreased localized uptake may suggest cold nodule. Must be thyrotoxic at time of testing; contraindicated if pregnant or breastfeeding
- **THYROID STIMULATING IMMUNOGLOBULIN**—for Graves disease

DIAGNOSTIC ISSUES			
THYROID HORMONE INTERPRETATION	LEVELS	AND	
	TSH	ft4	ft3
Subclinical hyperthyroidism	↓	N	N
Primary hyperthyroidism	↓	↑	↑
T3 thyrotoxicosis	↓	N	↑
Central hyperthyroidism	↑/N	↑	↑

MANAGEMENT

THYROID STORM—ABC, O₂, IV. **Propylthiouracil** 1,000 mg PO/NG/PR STAT, then 200 mg PO/NG/PR q4h × 1 week then 200 mg PO BID. **Inorganic iodide** with **Lugol solution** 5–7 drops PO q8h or **saturated potassium iodide** (SSKI) 1–2 drops PO q8h, to be given 1 h **after** each dose of propylthiouracil. **Glucocorticoids** with **hydrocortisone** 100 mg IV q8h. **Propranolol** 20–80 mg PO q6–8h. **Supportive care** with IV saline, cooling blankets, and acetaminophen

TREAT UNDERLYING CAUSE

- **ANTITHYROID DRUGS**—inhibit thyroid hormone synthesis; for Graves, toxic adenoma, and multinodular goiter. **Methimazole** 10–30 mg PO daily for most cases of hyperthyroidism, or **propylthiouracil** 50–300 mg PO BID–TID. Initial treatment course commonly 12–18 months (to be stopped if TSH normal). Methimazole associated with better safety profile, more convenient dosing, and less ¹³¹I failure rates than propylthiouracil. However propylthiouracil preferred in first trimester of pregnancy. Side-effects include rash, hepatotoxicity, and agranulocytosis

MANAGEMENT (CONT'D)

- **RADIOIODINE ¹³¹ABLATION**—for Graves, toxic adenoma, and multinodular goiter. Give once thyroid levels have been stabilized. Must discontinue antithyroid drugs 3–7 days in advance. Avoid ¹³¹I if severe ophthalmopathy, smoking, severe thyrotoxicosis, pregnant, or breastfeeding as may make eye disease worse or lead to thyroid storm. Euthyroidism or hypothyroidism within 2–4 months is expected. Many develop permanent hypothyroidism and require thyroid hormone replacement
- **THYROIDECTOMY**—usually for patients with a toxic adenoma or multinodular goiter, or patients with Graves who fail medical therapy, are unable to receive radioactive ablation (e.g. severe ophthalmopathy), have compressive goiter, or have another indication for surgery (e.g. nodule suspicious for malignancy)

SPECIFIC ENTITIES

APATHETIC (MASKED) THYROTOXICOSIS—in the elderly, thyrotoxicosis may manifest as isolated congestive HF, unexplained weight loss, or atrial fibrillation without other classical symptoms and signs

THYROIDITIS—supportive care for the majority. Initial thyrotoxicosis from release of pre-formed hormone, then a period of hypothyroidism, followed by recovery to euthyroid state for most patients

Related Topics

Hyperthyroidism in Pregnancy (p. 473)

Amiodarone-associated Thyrotoxicosis (see Important Toxicities of Amiodarone (p. 51))

Thyroid Nodules

2015 ATA Thyroid Nodule and Differentiated Thyroid Cancer Guidelines
2009 ATA Medullary Thyroid Cancer Guidelines

DIFFERENTIAL DIAGNOSIS

BENIGN (95%)—colloid nodule, benign follicular neoplasm (adenoma), cyst, thyroiditis

MALIGNANT (5%)—thyroid carcinoma (papillary, follicular, medullary, anaplastic), lymphoma

CLINICAL FEATURES

RISK FACTORS FOR THYROID CANCER

- **CLINICAL RISK FACTORS**—family history of medullary thyroid carcinoma or MEN2, rapid growth, fixated/firm/hard nodule, extremes of age 60,

CLINICAL FEATURES (CONT'D)

male sex, prior head and neck irradiation, nodule >4 cm [>1.6 in.] in diameter, symptoms of compression (dysphagia, dysphonia, hoarseness, dyspnea, cough), regional lymphadenopathy, distant metastases

- **SUSPICIOUS (HIGH-RISK) ULTRASOUND FINDINGS**—hypoechoic lesion, absence of cystic elements, irregular/infiltrative margins, microcalcifications, absence of halo, increased central vascularity, appearance taller than wide on transverse view, pathologic lymph nodes

INVESTIGATIONS**BASIC**

- **LAB TESTS**—TSH
- **IMAGING**—thyroid US
- **FNA**—with US-guidance

SPECIAL

- **THYROID SCAN**—if thyrotoxic to determine hot vs. cold nodule
- **THYROGLOBULIN LEVEL**—for follow-up of follicular-cell derived thyroid cancer
- **CALCITONIN LEVEL**—for follow-up of medullary thyroid cancer

DIAGNOSTIC ISSUES

OVERALL APPROACH—main goals are to determine whether nodule is functioning vs. non-functioning, benign vs. malignant, obstructive vs. non-obstructive

- **FUNCTIONAL EVALUATION**—if \downarrow TSH \rightarrow obtain thyroid scan. If hot nodule(s) with radiotracer trapping \rightarrow toxic adenoma(s). If N/\uparrow TSH \rightarrow no functional testing needed
- **EVALUATION FOR MALIGNANCY**—select patients for FNA based on combination of clinical risk factors, presence of suspicious US findings, size of nodule, and results of functional evaluation (i.e., hot nodules very rarely malignant)

THYROID FUNCTION AND CANCER RISK—thyroid nodules have a 5–15% risk of being malignant; 1/3 of all nodules are cold and less than 1/3 of cold nodules are malignant. Cold nodules in the setting of autoimmune thyroid disease have a higher risk of malignancy. Functioning nodules are almost always benign and usually require no evaluation for malignancy

SIZE CUTOFF FOR MALIGNANCY EVALUATION—most lesions <1 cm [<0.4 in.] require no further testing. Recommend FNA for most nodules ≥ 1.5 cm [≥ 0.6 in.], or ≥ 1 cm [≥ 0.4 in.] for nodules with suspicious (i.e., high-risk) US features

DIAGNOSTIC ISSUES (CONT'D)

BETHESDA CLASSIFICATION OF FNA BIOPSIES—standardized classification system with six categories: (I) non-diagnostic or unsatisfactory (e.g. cyst fluid only, acellular specimen) with 1–4% risk of malignancy; (II) benign (e.g. benign follicular nodule) with $\leq 3\%$ risk of malignancy; (III) follicular lesion of undetermined significance (FLUS) or atypia of undetermined significance (AUS) with 5–15% risk of malignancy; (IV) follicular neoplasm or suspicious for follicular neoplasm (e.g. Hurthle cell neoplasm) with 15–30% risk of malignancy; (V) suspicious for malignancy with 60–75% risk of malignancy; and (VI) malignant (e.g. papillary, medullary, anaplastic thyroid cancer) with $>95\%$ risk of malignancy

MANAGEMENT

PURELY CYSTIC NODULE—drain if symptomatic, but recurrences common

NON-FUNCTIONING NODULE <1 cm—usually no further testing required if no suspicious features

NON-FUNCTIONING NODULE 1–4 cm—evaluate thyroid function then proceed to FNA if indicated

- **NON-DIAGNOSTIC FNA**—repeat FNA with US (after 3–6 mo interval)
- **BENIGN NODULE**—follow-up US 6–18 mo after initial FNA. If size stable, clinical follow-up. If size \uparrow ($\geq 20\%$ with at least ≥ 2 mm in ≥ 2 dimensions in solid component), repeat FNA
- **FOLLICULAR NEOPLASM/SUSPICIOUS FOR FOLLICULAR NEOPLASM**—diagnostic lobectomy \pm follow-up completion thyroidectomy if necessary
- **SUSPICIOUS FOR MALIGNANCY/MALIGNANT**—total thyroidectomy \pm postoperative I^{131} remnant ablation

NON-FUNCTIONING NODULE (>4 cm)—consider surgical removal, especially in younger patients, presence of compressive symptoms, or clinical concern

MULTINODULAR GOITERS (>2 CLINICALLY-RELEVANT NODULES)—similar algorithm as solitary nodules with selected FNA of suspicious or high risk nodules

OBSTRUCTIVE (OR SUBSTERNAL) GOITER—surgical removal if symptomatic (e.g. positional dyspnea, dysphagia, dysphonia), suspected malignancy, or clinical concern. If surgery not possible, consider I^{131} ablation but beware transient increase in size!

Pituitary Tumors

Schlechte *NEJM* 2003;349(21)

DIFFERENTIAL DIAGNOSIS OF PITUITARY TUMORS

FUNCTIONAL ADENOMA—prolactinoma is most common, Cushing disease (pituitary ACTH-secreting tumor) and acromegaly are rare, functional TSH tumors are exceedingly rare

NON-FUNCTIONAL ADENOMA

OTHER TUMORS—meningioma, craniopharyngioma, dysgerminoma, optic glioma, lymphoma, metastases, infiltrative disorders (lymphocytic hypophysitis, sarcoidosis, hemochromatosis)

DIFFERENTIAL DIAGNOSIS OF PITUITARY HORMONE DEFICIENCY

IATROGENIC—neurosurgery, irradiation

TRAUMATIC—traumatic brain injury

INFILTRATIVE—lymphocytic hypophysitis, sarcoidosis, hemochromatosis, immune checkpoint inhibitor-related hypophysitis

INFECTION—TB, histoplasmosis

VASCULAR—apoplexy, Sheehan syndrome

NEOPLASTIC—metastasis, lymphoma, craniopharyngioma

FUNCTIONAL—excessive exercise, anorexia, critical illness

CONGENITAL

DIFFERENTIAL DIAGNOSIS OF HYPERPROLACTINEMIA

PHYSIOLOGIC—pregnancy, lactation, exercise, coitus, stress

TUMORS—pituitary (prolactinoma, other functional tumors [acromegaly], non-functional tumor with stalk compression [macroadenoma]), non-pituitary

DRUGS—metoclopramide, domperidone, phenothiazines, risperidone, TCA, SSRI, labetalol, verapamil, ranitidine, estrogen, opioids

OTHERS—hypothyroidism (\uparrow TRH), chronic kidney disease, chest wall irritation (trauma, surgery, zoster)

IMPORTANT—prolactin secretion is normally inhibited by dopamine. Therefore, anything that interferes with dopamine secretion/delivery (e.g. pituitary stalk compression) can lead to \uparrow prolactin secretion

CLINICAL FEATURES

★GO LOOK FOR THE ADENOMA PLEASE★—A compressive pituitary adenoma usually affects hormone secretion in this order: \downarrow GH, \downarrow LH and FSH, \downarrow TSH, \downarrow ACTH, and \uparrow Prolactin

CLINICAL FEATURES (CONT'D)

MASS EFFECT—visual field abnormalities (bitemporal hemianopsia), blurred vision (\downarrow visual acuity), headaches, cranial nerve palsies, loss of color (red) discrimination

SYMPTOMS—inquire about hormonal excess, hormonal deficiencies, and mass effect (see below)

HYPERPROLACTINEMIA

♀—amenorrhea, oligomenorrhea, galactorrhea, infertility, sexual dysfunction, osteoporosis

♂—erectile dysfunction, infertility, osteoporosis
GROWTH HORMONE DEFICIENCY—nonspecific symptoms (obesity, \downarrow exercise capacity, weakness, low mood, fatigue)

GROWTH HORMONE EXCESS (ACROMEGALY)—mass effect (especially headaches), increased hand/foot/head size (\uparrow ring, glove, shoe, and hat size), increased sweating, painful osteoarthritis (DIP, PIP, CMC, wrists), nerve entrapment (carpal tunnel syndrome, foot drop), coarse facial features, frontal bossing, prognathism (prominent mandible), wide-spaced teeth, enlarged tongue, low-pitched voice, skin tags, acanthosis nigricans (insulin resistance), cardiomegaly with or without HF, sleep apnea, hypertension

CORTISOL DEFICIENCY (ADRENAL INSUFFICIENCY)—see section on Adrenal Insufficiency (p. 383) for details

CORTISOL EXCESS (CUSHING SYNDROME)—see section on Adrenal Incidentaloma (p. 382) for details

THYROID HORMONE DEFICIENCY (HYPOTHYROIDISM)—see section on Hypothyroidism (p. 375) for details

THYROID HORMONE EXCESS (HYPERTHYROIDISM)—see section on Hyperthyroidism (p. 376) for details

LH/FSH DEFICIENCY—hypogonadism

INVESTIGATIONS

BASIC

- **LABS**—prolactin, IGF-1 (simpler than GH to interpret), LH, FSH, TSH, ACTH, AM cortisol, free T4 \pm AM testosterone, estrogen, progesterone
- **IMAGING**—MRI sella

DIAGNOSTIC ISSUES

MICROADENOMA (<10 mm [<0.4 in.])—evaluate for hormonal hypersecretion (e.g. prolactin, IGF-1 \pm free T4 if clinically hyperthyroid \pm 1 mg

DIAGNOSTIC ISSUES (CONT'D)

dexamethasone suppression test [or 24 h urinary free cortisol, or late night salivary cortisol]) if Cushing disease suspected

MACROADENOMA (≥ 10 mm [≥ 0.4 in])—evaluate for hormonal hypersecretion (see above) and hyposecretion (e.g. AM cortisol, free T4 \pm AM testosterone [if ♂] \pm LH and FSH [if ♀; may omit if regular menses] \pm IGF-1 if GH deficiency suspected). Refer to ophthalmologist for formal visual field testing if optic chiasm compression

HYPERPROLACTINEMIA—if prolactin $< 2 \times$ upper limit of normal, repeat at least two more times (fasting and at rest) as most cases will normalize spontaneously. If persistent \uparrow prolactin confirmed, look for potential offending medications, check pituitary function, renal function, liver function, β -hCG (in ♀), TSH, IGF-1, MRI sella \pm macroprolactin assay

MANAGEMENT

NON-FUNCTIONAL MICROADENOMA (< 10 mm)—expectant observation (e.g. MRI q1y for 2–3 years to monitor; if size stable, \downarrow frequency)

NON-FUNCTIONAL MACROADENOMA (≥ 10 mm)—replace any hormone deficiencies. Expectant observation (e.g. MRI q1y for 5 years to monitor; if size stable, \downarrow frequency) with monitoring of vision. If ≥ 20 mm and/or vision threatened, transsphenoidal surgery

SPECIFIC ENTITIES

PROLACTINOMA—**dopamine agonists** (*cabergoline* 0.25–1 mg PO 2 \times /week, *bromocriptine* 1.25–7.5 mg PO BID). Consider baseline echocardiogram for patients starting cabergoline and repeat echocardiogram at 5 years

SPECIFIC ENTITIES (CONT'D)

for those taking ≤ 2 mg/week, or yearly for those taking > 2 mg/week. **Transsphenoidal surgery** (if resistant to medical therapy or visual field compromise)

GH DEFICIENCY

- **DIAGNOSIS**—serum IGF-1 (insensitive). Consider glucagon-stimulation test or insulin tolerance test to confirm (serum GH levels remain low after 3–4 h)
- **TREATMENT**—**human growth hormone** (may potentially improve quality of life, body composition, and exercise capacity)

ACROMEGALY

- **DIAGNOSIS**—serum IGF-1. Also check prolactin. Consider 75 g oral glucose tolerance test to confirm (serum GH levels remain elevated after 2 h)
- **TREATMENTS**—**transsphenoidal surgery** (preferred, 5–20% recurrence). **Octreotide** (long-acting analogue of somatostatin). **Cabergoline** or **bromocriptine** may be combined with somatostatin analogue. **Pegvisomant** (growth hormone receptor antagonist) if somatostatin analogue ineffective. **Irradiation** of pituitary as adjuvant when surgery and/or medical management unsuccessful

CUSHING DISEASE—**transsphenoidal surgery**. See p. 384 for details

TSH-SECRETING ADENOMA (TSHoma)—**transsphenoidal surgery** (first line but cure rates low). Consider **octreotide** and/or treatment with antithyroid medications. See section on Hyperthyroidism (p. 376) for details

Melmed *NEJM* 2006;355(24)

Diabetes Insipidus**DIFFERENTIAL DIAGNOSIS**

OSMOTIC DIURESIS—glucose, mannitol
WATER DIURESIS

- **CENTRAL DIABETES INSIPIDUS**—**iatrogenic** (neurosurgery), **granulomatous infiltration** (sarcoidosis, TB, histiocytosis X), **trauma** (closed head injury), **tumor** (craniopharyngioma, metastatic breast cancer, metastatic lung cancer), **autoimmune** (infundibulo-neurohypophysitis), **congenital**
- **NEPHROGENIC DIABETES INSIPIDUS**—hypercalcemia, hypokalemia, lithium, demeclocycline, obstructive uropathy, congenital

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **DIABETES INSIPIDUS OF PREGNANCY**
- **PRIMARY POLYDIPSIA**

PATHOPHYSIOLOGY

DEFINITION OF POLYURIA—urine > 3 L/day

INVESTIGATIONS**BASIC**

- **LABS**—lytes, Cr, glucose, serum osmolality (if diabetes insipidus, > 290 mOsm/kg), 24 h urine volume, urine osmolality (if diabetes insipidus, < 275 mOsm/kg)

INVESTIGATIONS (CONT'D)

SPECIAL

- **WATER DEPRIVATION TEST**—consult endocrinology. In the dehydrated state, the body normally concentrates urine, but in diabetes insipidus, the urine remains dilute. Serial measurements of urine output, urine and serum lytes and osmolality, weight. Administration of 1 µg desmopressin/DDAVP IV/SC causes concentration of the urine in central DI but not nephrogenic DI (unreliable if medullary gradient has been washed-out)
- **MRI PITUITARY**—if central diabetes insipidus
- **COPEPTIN**—cosecreted with ADH with longer half-life (easier to interpret)

MANAGEMENT OF DIABETES INSIPIDUS

TREAT UNDERLYING CAUSE

- **CENTRAL DIABETES INSIPIDUS**—(*desmopressin/DDAVP* 10–20 µg intranasally daily–BID, or 0.5–2 µg SC/IV daily–BID, or 0.2 mg PO BID–TID, 60–120 µg SL daily–BID). Goal of treatment is to improve quality of life (↓ polydipsia, ↓ polyuria) while allowing occasional breakthrough. Note risk of hyponatremia
- **NEPHROGENIC DIABETES INSIPIDUS**—low solute diet. **Thiazide** or **thiazide-like diuretic** (*hydrochlorothiazide* 25 mg PO daily–BID or *chlorthalidone* 25 mg PO qd–BID) ± **NSAIDs** (*indomethacin* 25–50 mg PO BID–TID) if needed

Adrenal Incidentaloma

Young Jr. *NEJM* 2007;356(6)

DIFFERENTIAL DIAGNOSIS

BENIGN

- **NON-FUNCTIONAL ADENOMA**
- **FUNCTIONAL ADENOMA**—cortisol-secreting (Cushing syndrome), aldosterone-secreting (Conn syndrome), androgen-secreting (rare)
- **PHEOCHROMOCYTOMA/PARAGANGLIOMA**—may be benign or malignant
- **OTHER**—myelolipomas, hamartomas, granulomas

MALIGNANT

- **CARCINOMA**—adrenocortical carcinoma
- **METASTASES**—lung, breast, GI, renal, melanoma

PATHOPHYSIOLOGY

CATECHOLAMINES—tyrosine is precursor, forming dopamine, then norepinephrine, then epinephrine. Adrenal medulla produces 85% epinephrine and 15% norepinephrine. Epinephrine has equal effect on α and β receptors. Norepinephrine acts mainly on α receptors

- **ACTIVATION OF α RECEPTORS**—peripheral vasoconstriction, mydriasis, and sweating
- **ACTIVATION OF β RECEPTORS**—vasodilation, cardiac stimulation, bronchodilation, smooth muscle relaxation

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM—renin release is stimulated by ↓ effective circulating volume, ↓ tubular [Na], and the sympathetic nervous system. It converts angiotensinogen to angiotensin I, which is then converted to angiotensin II by ACE. Aldosterone

PATHOPHYSIOLOGY (CONT'D)

release is then stimulated by angiotensin II, hyperkalemia, and ACTH. Aldosterone's effects include ↑ Na reabsorption and ↑ K secretion at the distal tubule

CLINICAL FEATURES

HISTORY

- **SYMPTOMS OF PHEOCHROMOCYTOMA**—episodic spells of palpitations, pallor, tremor, headache, diaphoresis, hypertension (sustained or episodic)
- **SYMPTOMS OF CORTISOL EXCESS**—see section on Cushing syndrome (p. 384) for details
- **SYMPTOMS OF ALDOSTERONE EXCESS**—hypokalemia, hypertension, nocturia
- **SYMPTOMS OF ANDROGEN EXCESS** (in ♀)—hirsutism, virilization, acne, amenorrhea
- **SYMPTOMS OF ADRENOCORTICAL CARCINOMA**—features of rapid hormone excess (cortisol, androgen, or both), abdominal pain, weight loss, anorexia, fever, palpable abdominal mass

INVESTIGATIONS

BASIC

- **LABS**—1 mg dexamethasone suppression test preferred (or 24 h urine cortisol, late night salivary cortisol), lytes, plasma renin and aldosterone (if hypertensive), plasma or 24 h urine for metanephrines ± ACTH, DHEAS, androstenedione, testosterone
- **IMAGING**—CT or MRI adrenals

INVESTIGATIONS (CONT'D)**SPECIAL**

- **ADRENAL VEIN SAMPLING**—for primary hyperaldosteronism
- **METAIODOBENZYLGUANIDINE (MIBG) SCAN**—for pheochromocytoma

DIAGNOSTIC ISSUES

APPROACH TO DIAGNOSIS OF ADRENAL INCIDENTALOMA—start with history and physical, and baseline labs to determine if tumor is functioning, then proceed with imaging to look for suspicious features suggestive of malignancy. FNA **unhelpful** (cannot distinguish benign adenoma from adrenal carcinoma)

DISTINGUISHING FEATURES OF ADRENAL TUMORS ON CT SCAN

- **BENIGN ADENOMA**—smooth border, homogeneous density, absolute CT contrast washout usually >60% at 10–15 min
- **ADRENOCORTICAL CARCINOMA**—irregular, heterogeneous density, commonly >6 cm [>2.4 in.], very high unenhanced attenuation (>20 HU), absolute CT contrast washout <50% (especially <10%) at 10–15 min
- **PHEOCHROMOCYTOMA**—cystic, hemorrhagic, variable size, may be bilateral, high enhanced attenuation (>10 HU)
- **METASTATIC DISEASE**—irregular, heterogeneous density, bilateral, high unenhanced attenuation

MANAGEMENT

TREAT UNDERLYING CAUSE—determine functional vs. non-functional tumor and benign vs. malignant tumor. All functional tumors, tumors >4 cm [>1.6 in.], and lesions suspicious for malignancy should be resected

SPECIFIC ENTITIES**PRIMARY ALDOSTERONISM**

- **DIAGNOSIS**—↑ aldosterone-to-renin ratio (↑ aldosterone, ↓ renin) ± confirmatory test

SPECIFIC ENTITIES (CONT'D)

with volume expansion (non-suppressibility of aldosterone) ± subtype classification with CT and/or adrenal vein sampling. Beware of medications that alter lab test results (e.g. ACE inhibitor, ARB, diuretics)

- **TREATMENTS**—for unilateral disease amenable to surgery, consider adrenalectomy. Otherwise, consider medical therapy (*spironolactone* 12.5–100 mg PO daily or *eplerenone* 25–100 mg PO BID). See Hypertension section for more details (p. 70)

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

- **PATHOPHYSIOLOGY**—commonly termed pheochromocytoma when arising from adrenal gland, and paraganglioma when elsewhere. May be sporadic or associated with genetic syndromes like MEN2A (medullary thyroid cancer, primary hyperparathyroidism), MEN2B (medullary thyroid cancer, muccutaneous neuromas, marfanoid), Von Hippel-Lindau (hemangioblastomas, renal cell carcinoma, pancreatic tumors), neurofibromatosis (neurofibromas, *café-au-lait* spots), and SDH mutations (renal cell carcinoma, gastrointestinal stromal tumors)
- **DIAGNOSIS**—plasma or 24-h urinary metanephrines. Beware of medications that predispose to false positive results (e.g. TCAs, venlafaxine, bupropion, buspirone, amphetamines)
- **TREATMENTS**—**volume and salt repletion** (reduce postural hypotension) with **α-blockade** (*phenoxybenzamine* 10 mg PO BID and ↑ dose as needed, or *doxazosin* 2 mg PO daily and ↑ dose as needed). Consider **β-blockade** only after well α-blocked (to control tachycardia). Avoid initial β-blockade to prevent unopposed α-constriction. Medical therapy precedes surgery by 1–2 weeks. Refer for **genetic testing**

Adrenal Insufficiency**DIFFERENTIAL DIAGNOSIS****PRIMARY**

- **AUTOIMMUNE**—Addison disease
- **INFECTION**—TB, histoplasmosis, coccidioidomycosis, CMV, HIV
- **HEMORRHAGE**—anticoagulants, sepsis (Waterhouse-Friderichsen syndrome, associated with meningococemia), trauma, anticardiolipin antibodies

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **INFILTRATION**—metastases, sarcoidosis, amyloidosis
- **CONGENITAL**—congenital adrenal hyperplasia, adrenoleukodystrophies

SECONDARY/TERTIARY—exogenous glucocorticoid therapy, pituitary or hypothalamic tumor (panhypopituitarism), traumatic brain injury, infarction, infection, infiltration, irradiation

DIFFERENTIAL DIAGNOSIS (CONT'D)

tion, drugs (high dose progestins, opiates), idiopathic

CLINICAL FEATURES

HISTORY—fatigue, weight loss, abdominal pain, N&V, postural lightheadedness (presyncope), muscle weakness, hypoglycemia, dehydration, salt cravings (Addison only), visual field changes (pituitary tumor), evidence of steroid use, medical history (TB, cancer, sarcoidosis), medications (anticoagulation)

PHYSICAL—orthostatic hypotension, hyperpigmentation (Addison only)

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY/TERTIARY ADRENAL INSUFFICIENCY

	Primary	Secondary/ tertiary
Affected hormones	Cortisol, DHEAS, aldosterone	Cortisol, DHEAS
ACTH	↑	↓
Electrolytes	↓ Na, ↑ K	↓ Na
Symptoms	Salt craving, hyperpigmentation	Normal skin pigment. GI symptoms and hypotension often less prominent

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, glucose, creatinine, AM cortisol, ACTH
- **MICROBIOLOGY**—blood and urine cultures if suspect sepsis

DIAGNOSTIC ISSUES**ACTH STIMULATION TEST**

- **STANDARD DOSE**—obtain cortisol and ACTH at baseline, give cosyntropin 250 µg IV push, measure cortisol at 30 and 60 min. Peak cortisol >300–550 nmol/L (cutoff variable depending on local lab assay) excludes most cases of adrenal insufficiency

MANAGEMENT

ACUTE ADRENAL CRISIS—ABC, IV fluids (NS or D5NS 1–2 L IV bolus, then 100–200 mL/h), and glucose as needed. **Corticosteroid** (*hydrocortisone* 100 mg IV q6–8 h) and **treat precipitant**

LONG-TERM TREATMENT—**physiologic replacement** (*hydrocortisone* 10–15 mg PO qAM and 5–10 PO qPM or *prednisone* 5 mg PO qAM and 2.5 mg PO qPM, plus *fludrocortisone* 0.1 mg PO daily [if primary adrenal insufficiency]). Advise **medical alert bracelet** and **sick day management ± emergency prefilled hydrocortisone syringe**

STRESS DOSING—if patients have been taking suppressive (supraphysiologic) doses of glucocorticoids for >3 weeks during the preceding year, consider stress dosing during illnesses or surgical procedures

- **MINIMAL STRESS** (e.g. routine dental work, skin biopsy)—usual dosage (no change)
- **MINOR STRESS** (e.g. flu, surgeries under local anesthetic)—double to triple the regular dose of glucocorticoids, then resume usual dosage when well
- **MODERATE STRESS** (e.g. orthopedic surgery, most abdominal surgeries)—*hydrocortisone* 25 mg IV q8h × 3 doses with first dose on call to OR, then resume usual dosage when well
- **HIGH STRESS** (e.g. major trauma, septic shock, cardiac surgery)—*hydrocortisone* 50 mg IV q8h × 3 doses with first dose on call to OR, then 25 mg IV q8h until recovered, then resume usual dosage when well

Cushing Syndrome

2008 Endocrine Society Cushing Syndrome Guideline

DIFFERENTIAL DIAGNOSIS

IATROGENIC (↓ ACTH)

PITUITARY (↑ ACTH)—Cushing disease

ECTOPIC (↑ ACTH)—small cell lung cancer, bronchial carcinoids, neuroendocrine tumors

ADRENAL (↓ ACTH)—adenoma, carcinoma

CLINICAL FEATURES**SIGNS AND SYMPTOMS OF CUSHING SYNDROME**

- **NEUROLOGICAL**—euphoria, depression, psychosis, restlessness, irritability, insomnia
- **OPHTHALMIC**—glaucoma, cataracts
- **CARDIOVASCULAR**—hypertension, fluid retention

CLINICAL FEATURES (CONT'D)

- **GASTROINTESTINAL**—gastritis, ulcers, GI bleed
- **HEMATOLOGICAL**—leukocytosis, immunosuppression
- **ENDOCRINE**—hyperglycemia, insulin resistance, hypogonadism, menstrual irregularity, central obesity, hirsutism, weight gain
- **MUSCULOSKELETAL**—osteoporosis, avascular necrosis, proximal myopathy
- **DERMATOLOGICAL**—purple striae, round face, supraclavicular and/or dorsocervical fat pad, skin thinning, easy bruising, acne, poor wound healing

Note that typical symptoms and signs of Cushing may be absent or minimal with ectopic ACTH production. Hypokalemic alkalosis may be the only obvious initial finding

INVESTIGATIONS**BASIC**

- **LABS**—begin initial evaluation with 1 of 3 possible screening tests (24 h urine cortisol, 1 mg overnight dexamethasone suppression test, or late night salivary cortisol), ACTH, CBC, lytes, urea, Cr, glucose, HbA1C, fasting lipid profile

SPECIAL

- **CT ADRENAL**—unilateral mass suggests adrenal lesion. Bilateral adrenal hyperplasia suggests ACTH oversecretion (central or ectopic lesion)
- **CT CHEST/ABDO/PELVIS**—to look for ectopic ACTH producing tumors
- **MRI SELLA**—if suspect Cushing disease
- **INFERIOR PETROSAL SINUS SAMPLING**—to differentiate pituitary vs. ectopic tumor
- **OCTREOTIDE SCAN**—to localize ectopic ACTH producing tumors

DIAGNOSTIC ISSUES

INITIAL SCREENING TESTS—begin initial evaluation with 1 of 3 sensitive screening tests (i.e., 1 mg overnight dexamethasone suppression test, 24 h urine cortisol, or late night salivary cortisol). Follow-up abnormal test result with second test. If multiple abnormal tests, consult Endocrinology

DIAGNOSTIC ISSUES (CONT'D)**1 MG OVERNIGHT DEXAMETHASONE SUPPRESSION TEST**

- **PROTOCOL**—give 1 mg dexamethasone between 11 PM and midnight, then measure 8-9 AM serum cortisol the next morning
- **INTERPRETATION**—8-9 AM serum cortisol <50 nmol/L following 1 mg of dexamethasone effectively rules out Cushing syndrome
- **ADVANTAGES**—convenient
- **PROBLEMS**—needs accurate timing; false positives with oral contraceptives, alcohol, rifampin, phenytoin, carbamazepine

24 H URINARY FREE CORTISOL

- **ADVANTAGES**—not affected by oral contraceptives or shift work
- **PROBLEMS**—inconvenient; false positives with proteinuria and polyuria; false negatives with moderate to severe renal impairment

LATE NIGHT SALIVARY CORTISOL

- **ADVANTAGES**—not affected by oral contraceptives
- **PROBLEMS**—collection technique difficult; false positives with cigarettes, chewing tobacco, licorice, and shift work

MANAGEMENT**TREAT UNDERLYING CAUSE**

- **IATROGENIC**—discontinue or reduce the dose of steroids if possible
- **PITUITARY**—first-line transsphenoidal surgery (90% cure rate). For refractory or recurrent cases, consider repeat transsphenoidal surgery, pituitary irradiation, medical therapy, or bilateral adrenalectomies
- **ADRENAL**—unilateral adrenalectomy
- **ECTOPIC**—resection of ectopic source if appropriate; otherwise, bilateral adrenalectomies and medical therapy (ketoconazole, pasireotide, metyrapone) may be considered

TREATMENT ISSUES

GLUCOCORTICOID REPLACEMENT—required in the post operative period. May take months to years for HPA axis to recover after transsphenoidal surgery or unilateral adrenalectomy. If bilateral adrenalectomy, lifelong replacement is needed. Do not forget to stress dose!

TREATMENT ISSUES (CONT'D)

EQUIVALENT DOSING TABLE

	Half-life (h)	Equivalent anti-inflammatory potency ^a	Equivalent mineralocorticoid potency ^a
Glucocorticoids			
Short acting			
Hydrocortisone	8–12	1	1
Cortisone	8–12	0.8	0.8
Intermediate acting			
Methylprednisolone	18–36	5	0.5
Prednisolone	18–36	4	0.8
Prednisone	18–36	4	0.8
Long acting			
Dexamethasone	36–54	30	0
Mineralocorticoid			
Fludrocortisone	12–24	12	125

^aRelative to cortisol; higher number indicates greater potency

SPECIFIC ENTITIES

PSEUDO-CUSHING SYNDROME—hypercortisolism associated with severe stress, depression, obesity, alcoholism, pregnancy, and poorly-controlled diabetes. May mimic Cushing syndrome clinically, but rarely associated with dermatologic and muscular complications (e.g. bruising, thinning of skin, proximal muscle weakness)

SPECIFIC ENTITIES (CONT'D)

MILD AUTONOMOUS CORTISOL EXCESS (SUBCLINICAL CUSHING SYNDROME)—usually detected in work-up of adrenal incidentaloma. Associated with an increased rate of diabetes mellitus, hypertension, and vertebral compression fracture

Hypocalcemia

DIFFERENTIAL DIAGNOSIS

PTH-RELATED (↓ PTH, ↑ PO4)

- **HYPOPARATHYROIDISM**—surgery, irradiation, autoimmune, infiltrative, congenital (e.g. DiGeorge syndrome)
- **FUNCTIONAL HYPOPARATHYROIDISM**—hypomagnesemia

PTH RESISTANCE (↑ PTH)—pseudohypoparathyroidism

NON-PTH-RELATED

- **VITAMIN D ABNORMALITIES (↑ PTH)**—vitamin D deficiency (nutritional, malabsorption), altered vitamin D metabolism (cirrhosis, chronic renal failure, anticonvulsants), vitamin D resistance

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **DRUGS**—severe hyperphosphatemia, bisphosphonates, calcitonin, loop diuretics
- **CALCIUM SEQUESTRATION**—hungry bone syndrome, acute pancreatitis, rhabdomyolysis, large transfusions of citrate-containing blood products, osteoblastic malignancies
- **OTHERS**—renal calcium wasting (e.g. Bartter syndrome, Fanconi syndrome)

PATHOPHYSIOLOGY

DEFINITION OF HYPOCALCEMIA—corrected serum Ca <2.1 mM [<8.4 mg/dL]. For every 10 mg/L [1 g/dL] ↓ in albumin, correct serum Ca by adding 0.2 mM [0.8 mg/dL]

PATHOPHYSIOLOGY (CONT'D)**PTH AND VITAMIN D**

- **VITAMIN D FORMATION**—7-dehydrocholesterol → skin with UV → cholecalciferol (vitamin D₃ may be obtained via diet as well) → liver → 25OH D (used to determine vitamin D status) → kidney (stimulated by PTH or hypo-PO₄) → 1,25(OH)₂D₃ (also known as calcitriol, the active form of vitamin D)
- **1,25(OH)₂D₃**—↑ Ca reabsorption at gut, kidney, and bone, ↑ PO₄ reabsorption at gut, ↓ PTH
- **PTH ACTION**—↑ Ca reabsorption at distal tubule and bone, ↓ PO₄ reabsorption at proximal tubule, ↑ 1,25(OH)₂D₃

CLINICAL FEATURES

HISTORY—perioral paresthesias, tingling of fingers and toes, tetany, stridor (laryngospasm), seizures, confusion, weakness, past medical history (neck surgery), medications (loop diuretics, bisphosphonates, calcitonin, anticonvulsants)

PHYSICAL—hypotension, Trousseau sign, Chvostek sign, carpal/pedal spasm, weakness

INVESTIGATIONS**BASIC**

- **LABS**—Ca, albumin, ionized Ca, Mg, PO₄, PTH, 25(OH)D, creatinine

SPECIAL

- **ECG**—may show prolonged QT interval, ST changes

MANAGEMENT

ACUTE MANAGEMENT—if severe symptoms, *Ca gluconate* 1 amp slow IV push, then run a calcium drip 0.5–1.5 mg/kg/h, checking serum calcium q4–6h; if hypomagnesemia, *MgSO₄* 5 g IV over 4 h. If mild symptoms, *elemental calcium* 1–2 g PO divided BID–TID apart from meals ± *calcitriol* 0.25–0.5 µg daily–BID

TREAT UNDERLYING CAUSE**SPECIFIC ENTITIES****VITAMIN D DEFICIENCY**

- **CAUSES**—vitamin D deficient diet and/or lack of exposure to sunlight, fat malabsorption syndromes, extensive burns (decreased skin conversion), nephrotic syndrome, medications (anticonvulsants, glucocorticoids,

SPECIFIC ENTITIES (CONT'D)

immunosuppressants and antiretroviral therapy may lead to increased inactivation of 1,25(OH)₂D₃, chronic kidney disease (decreased 1-OH activation), liver failure (decreased 25-OH activation)

- **CLINICAL FEATURES**—hypocalcemia, hypophosphatemia, osteomalacia with associated bone pain, osteoporosis with fractures
- **DIAGNOSIS**—25-hydroxyvitamin D is used to determine the level of vitamin D. A level <50–80 nmol/L is considered low
- **TREATMENTS**—treat underlying cause. For severe vitamin D deficiency (<25 nmol/L [<10 ng/mL]), *vitamin D3* 50,000 IU PO per week × 6–8 weeks initially, then 50,000 IU PO q2–4 weeks × 6–8 weeks, then reassess. For moderate deficiency (25–50 nmol/L [10–20 ng/mL]), *vitamin D3* 50,000 IU PO per week × 6–8 weeks then 800–2,000 IU PO daily. For mild deficiency (50–75 nmol/L [20–30 ng/mL]), long-term use of *vitamin D3* 800–2,000 IU PO daily. For renal failure or hypoparathyroidism, *calcitriol* 0.25–1 µg PO BID should be given

HYPOPARATHYROIDISM

- **CAUSES**—parathyroid gland injury or destruction (surgery, radiation, autoimmune, infiltration), abnormal parathyroid gland development (agenesis, dysgenesis), impaired PTH secretion (hypomagnesemia), defect in calcium sensing receptor (gain-of-function), or idiopathic
- **CLINICAL FEATURES**—hypocalcemia, hyperphosphatemia, extraskeletal calcifications (intracerebral, renal), above-average BMD
- **DIAGNOSIS**—hypocalcemia with ↓ PTH; chronic if sustained >6 months
- **TREATMENTS**—*elemental calcium* 1–2 g PO divided BID–TID, plus *calcitriol* 0.25–0.5 µg daily–BID ± *vitamin D3* 800–2,000 IU PO daily. Recombinant PTH may be considered in severe refractory cases
- **GOALS**—prevent symptomatic hypocalcemia; **maintain serum calcium in slightly ↓/↓-N range; avoid hypercalcemia**; keep Ca × PO₄ product <4.4 mmol²/L² (55 mg²/dL²); avoid extraskeletal calcifications

Holick NEJM 2007;357(3)

Hypercalcemia

DIFFERENTIAL DIAGNOSIS

PTH-MEDIATED (\uparrow -N/ \uparrow PTH)

- **HYPERPARATHYROIDISM (MOST COMMON AMONG OUTPATIENTS)**—parathyroid adenoma, parathyroid hyperplasia, parathyroid carcinoma (rare)
- **FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FHH)**
- **DRUGS**—lithium, thiazides (shifts PTH response curve)

NON-PTH-MEDIATED (\downarrow / \downarrow -N PTH)

- **MALIGNANCY**—lung, breast, prostate, renal, thyroid, GI, melanoma, sarcoma, multiple myeloma, lymphoma, leukemia
- **VITAMIN D-MEDIATED**—vitamin D intoxication, granulomatous disease (TB, sarcoidosis, lymphoma)
- **DRUGS**—vitamin A intoxication, milk alkali syndrome, thiazides (\uparrow calcium reabsorption)
- **OTHER**—adrenal insufficiency, hyperthyroidism, acute kidney injury, immobilization, hereditary hypophosphatemic rickets with hypercalciuria (HHRH)

PATHOPHYSIOLOGY

DEFINITION OF HYPERCALCEMIA—corrected serum Ca >2.6 mmol/L [10.4 mg/dL]. For every 10 g/L (1 g/dL) \downarrow in albumin, correct serum Ca by adding 0.2 mmol/L [0.8 mg/dL]

PTH ACTION— \uparrow Ca reabsorption at distal tubule and bone, \downarrow PO_4 reabsorption at proximal tubule, \uparrow $1,25(OH)_2D_3$

MALIGNANCY-RELATED MECHANISMS—local osteolytic bone lesions, humoral hypercalcemia of malignancy (PTH-related peptide, PTHrP), $1,25(OH)_2D_3$ -secretion (lymphomas), ectopic hyperparathyroidism (very rare)

GRANULOMATOUS DISEASE MECHANISM—unregulated synthesis of $1,25(OH)_2D_3$ from PTH-independent 1-hydroxylase activity in macrophages

CLINICAL FEATURES

SYMPTOMS

- **GI**—N&V, abdominal pain from constipation, pancreatitis, or peptic ulcer disease (**moans**)
- **MSK**—bony pain (**groans**), osteoporotic fractures (**bones**)
- **RENAL**—polyuria, calculi (**stones**)
- **CNS**—fatigue, depression, apathy, delirium (**psychiatric overtones**)

INVESTIGATIONS

BASIC

- **LABS**—Ca, albumin, ionized Ca, PO_4 , PTH, $25(OH)D$, creatinine

SPECIAL

- **HYPERPARATHYROIDISM WORKUP**—US neck/thyroid, Tc-sestamibi parathyroid scan, DEXA (for osteoporosis), US renal (for renal calculi)
- **FAMILIAL HYPOCALCIURIC HYPERCALCEMIA WORKUP**—24 h urine Ca and creatinine
- **VITAMIN D-MEDIATED HYPERCALCEMIA WORKUP**— $1,25(OH)_2D_3$
- **MALIGNANCY WORKUP**—serum protein electrophoresis \pm urine protein electrophoresis, PSA, PTHrP, CXR, bone scan (if metastatic bone disease), skeletal survey (if multiple myeloma)
- **MEN 2A WORKUP**—plasma or 24 h urinary metanephrines
- **OTHER**—TSH (if thyrotoxicosis), AM cortisol (if adrenal insufficiency), ECG (for bradycardia, heart block, ST changes, shortened QT interval)

DIAGNOSTIC ISSUES

PTH LEVEL— \uparrow in hyperparathyroidism, \uparrow /N in familial hypocalciuric hypercalcemia, \downarrow in vitamin D excess or PTHrP

DISTINGUISHING FEATURES BETWEEN IMPORTANT CAUSES OF HYPERCALCEMIA

	Primary PTH	Granulomatous disease	PTHrP	FHH
Ca	\uparrow	\uparrow	$\uparrow\uparrow$	\uparrow
PO_4	\downarrow	\uparrow	\downarrow /N	\downarrow
PTH	\uparrow /N	\downarrow	\downarrow	\uparrow /N
PTHrP	—	—	\uparrow	—
Calcitriol	\uparrow	\uparrow	—	\downarrow /N
24 h urine Ca	\uparrow	\uparrow /N	\uparrow	\downarrow

MANAGEMENT

ACUTE SEVERE HYPERCALCEMIA—early rehydration, **NS** 200–500 mL/h IV \pm **furosemide** 20–40 mg IV q8h PRN (use with caution and only when fully hydrated; hypercalcemia exacerbated if dehydrated) \pm **calcitonin** 4–8 IU/kg SC q12h. If malignancy-related hypercalcemia or prolonged immobilization, consider **bisphosphonates** (*pamidronate* 60–90 mg in 500 mL NS IV over 4 h or *zoledronate* 4 mg in 100 mL NS IV over 15 min), but ineffective for hyperparathyroidism. If vitamin D-mediated hypercalcemia (e.g. sarcoidosis, lymphoma), consider **steroids** (*prednisone* 20–30 mg PO daily \times 7–10 days). Consider **dialysis** in patients with advanced renal failure where bisphosphonates are contraindicated and fluid challenge is difficult. Monitor urine output and renal function

TREAT UNDERLYING CAUSE**SPECIFIC ENTITIES****PRIMARY HYPERPARATHYROIDISM**

- **PATHOPHYSIOLOGY**—autonomous production of PTH from one or more parathyroid glands. Mostly from solitary parathyroid adenoma, less commonly from gland hyperplasia or multiple adenomas, rarely parathyroid cancer

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—hypercalcemia with \uparrow -N/ \uparrow PTH, \downarrow PO_4 , \uparrow urinary calcium
- **INDICATIONS FOR PARATHYROIDECTOMY**—age 0.25 mmol/L [>1 mg/dL] above upper limit of normal, GFR 10 mmol/d (400 mg/d)
- **MEDICAL MANAGEMENT**—for those not eligible for surgery, medical monitoring (e.g. annual calcium and creatinine \pm q2–3y DEXA). Avoid medications that worsen hypercalcemia (e.g. thiazides) and maintain hydration. If symptomatic or severe hypercalcemia, consider *cinacalcet* 30–60 mg PO daily–BID. Dietary calcium restriction *not* necessary; treat vitamin D deficiency if present

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FHH)

- **PATHOPHYSIOLOGY**—autosomal dominant inactivating mutation of the calcium sensing receptor, leading to a higher calcium set point needed to suppress PTH release
- **CLINICAL FEATURES**—usually asymptomatic
- **DIAGNOSIS**—hypercalcemia with \uparrow -N/ \uparrow PTH, \downarrow PO_4 , \downarrow urinary calcium. Family history helpful. Important to differentiate from primary hyperparathyroidism as FHH does not respond to parathyroidectomy
- **TREATMENTS**—counseling and reassurance

Osteoporosis

2010 Osteoporosis Canada Guidelines

2019 Endocrine Society Osteoporosis Post-Menopausal Women Guideline

Tatangelo et al. *J Bone Miner Res* 2019;34(4)**CAUSES****PRIMARY**—hereditary**ENDOCRINE**—hypogonadism (e.g. anorexia nervosa, athletic amenorrhea, testicular/ovarian failure), hyperthyroidism, hyperparathyroidism, Cushing syndrome, diabetes mellitus**HEMATOLOGICAL DISORDERS**—multiple myeloma, leukemia, lymphoma, sickle cell disease**GASTROINTESTINAL DISORDERS**—malabsorption syndromes (e.g. celiac disease), inflammatory bowel disease, liver disease (primary biliary cirrhosis)**DRUGS**—glucocorticoids, heparin, cyclosporine, anticonvulsants (phenytoin, carbamazepine, barbiturates), LHRH agonists and antagonists, long-acting progestins, proton pump inhibitors, alcohol**CAUSES (CONT'D)****OTHERS**—age >50 , renal disease, immobilization, small frame, decreased BMI <21 kg/m², Caucasian, Asian, Indo-Asian, family history, smoking, caffeine**PATHOPHYSIOLOGY****DEFINITION**—a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Diagnosis based on reduced bone mineral density (BMD) measurements, relative to a normal young adult population of the same sex and ethnicity, and/or the presence of a fragility fracture. T-score is the number of standard deviations above/below the mean BMD compared to normal young adults, while Z-score compares with peers (of the same age, sex, and ethnicity)

PATHOPHYSIOLOGY (CONT'D)

Status	T-score
Normal	+2.5 to -1.0 (inclusive)
Low bone mass	Between -1.0 and -2.5
Osteoporosis	≤ -2.5
Severe osteoporosis	≤ -2.5 and fragility fracture

CLINICAL FEATURES

HISTORY—history of fragility fractures, height loss, thoracic kyphosis, milk/calcium consumption, sedentary lifestyle, past medical history, menstrual and reproductive history (for ♀), estrogen exposure (for ♀), medications (steroids, heparin, cyclosporine, anticonvulsants), family history of fragility fractures, smoking, alcohol, and caffeine intake

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS WOMAN HAVE OSTEOPOROSIS?

	LR+	LR-
History		
Self-reported humped back	3.0	0.85
Physical		
Weight <51 kg	7.3	0.8
BMI <25	4.5	0.5
Wall-occiput distance >0 cm (indicative of spinal fracture)	3.8	0.6
Rib-pelvis distance ≤2 finger breadths (indicative of spinal fracture)	3.8	0.6
Tooth count <20	3.4	0.8
Kyphosis	1.5	0.7
Decision Rules		
Simple calculated osteoporosis risk estimation (score ≥6)	1.2	0.02
Osteoporosis risk assessment instrument (score ≥9)	1.4	0.1

CLINICAL FEATURES (CONT'D)

	LR+	LR-
National Osteoporosis Foundation (score ≥1)	1.2	0.2
Age/body size/no estrogen (score ≥2)	1.6	0.3

APPROACH—"No single physical examination finding or combination of findings is sufficient to rule in osteoporosis or spinal fracture without further testing. ... Several convenient examination maneuvers including low body weight (<51 kg [<112 lb]), inability to place the back of the head against a wall when standing upright, low tooth count, self reported humped back, and rib-pelvis distance can significantly increase the likelihood of osteoporosis or spinal fracture and identify additional women who would benefit from earlier screening."

Green et al. JAMA 2004;292(23)

UPDATE—"A BMI less than 25 in older women is the single best finding for detecting women with osteoporosis, performing better than decision rules. However, a BMI greater than 25 is not as informative as the decision rules for identifying women at the lowest risk of osteoporosis."

Simel et al. The Rational Clinical Examination McGraw-Hill; 2009

INVESTIGATIONS**BASIC**

- **LABS**—Ca, PO₄, albumin, 25(OH)D, PTH, ALP, CBC, creatinine, serum protein electrophoresis, TSH
- **IMAGING**—dual-energy X-ray absorptiometry (DEXA)

SPECIAL

- **IMAGING**—lateral thoracic and lumbar spine XR
- **BONE TURNOVER**—serum CTX or urine NTX

DIAGNOSTIC AND PROGNOSTIC ISSUES**WHO SHOULD BE SCREENED WITH DEXA?****Older adults (≥50 years)**

Age ≥65 years irrespective of risk factors

Risk factors for fracture *plus* age 50–64 years (♂) or post-menopausal (♀)

- Fragility fracture after age 40
- Prolonged glucocorticoid use (≥3 mo cumulative exposure at prednisone-equivalent dose of ≥7.5 mg/day)
- Use of high-risk medication (e.g. androgen deprivation therapy, aromatase inhibitor)
- Parental hip fracture
- Current smoking
- High alcohol intake
- <60 kg body weight or major weight loss
- Height loss >10 cm
- Rheumatoid arthritis
- Presence of disorder strongly associated with osteoporosis (e.g. hypogonadism, malabsorption syndrome, primary hyperparathyroidism)

Younger adults (<50 years)

Fragility fracture (ever)

Prolonged glucocorticoid use (≥3 m cumulative exposure at prednisone-equivalent dose of ≥7.5 mg/day)

Use of high-risk medication (e.g. androgen deprivation therapy, aromatase inhibitor)

Hypogonadism or premature menopause (<45 years)

Malabsorption syndrome

Primary hyperparathyroidism

Presence of disorder strongly associated with rapid bone loss and/or fracture

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

FRACTURE RISK ASSESSMENT—estimate 10-year risk of a major osteoporotic fracture using a validated risk calculator such as the online (country specific) Fracture Risk Assessment tool (**FRAX**®) developed by the University of Sheffield, UK

PROGNOSIS—an average 50-year-old Caucasian woman has a remaining lifetime risk of 40% of developing hip, vertebra, or wrist fracture

MANAGEMENT

LIFESTYLE CHANGES—calcium or vitamin D alone does not prevent hip fractures, but the combination of calcium and vitamin D appears beneficial. Recommend **calcium** through diet ± supplementation; advise *elemental calcium* 1000 mg/d if ♀ 19–50 years or ♂ 19–70 years; and *elemental calcium* 1200 mg/d if ♀ >50 years or ♂ >70 y. **Vitamin D** 800–2,000 IU PO daily. **Physical activity** >30 min 3 × /week (weight bearing, core strengthening, and balance training). Consider **hip protectors** and **fall prevention strategies**. **Avoid excess caffeine** (>4 cups/day). **Smoking cessation**

MEDICATIONS—**bisphosphonates** (patients over the age of 50 should be stratified by their 10-year fracture risk. Patients who are at high risk

MANAGEMENT (CONT'D)

[i.e., >20% risk of major osteoporotic fracture in the next 10 years, or prior history of fragility fracture] should be started on bisphosphonates. May also consider treating patients at moderate risk. Bisphosphonates should be taken with water >60 min before first meal, and remain upright ×30 min. **Alendronate** 70 mg PO weekly, **risedronate** 35 mg PO weekly, **zoledronic acid** 5 mg IV yearly). **RANKL antibody** (denosumab, an anti-resorptive agent). Patients should be counselled on risks of atypical femoral fracture and osteonecrosis of the jaw particularly with prolonged use of antiresorptive medications. **Recombinant PTH** (teriparatide, anabolic). **PTHrP analogue** (abaloparatide, anabolic). **Sclerostin inhibitor** (romosozumab, anabolic). **Selective estrogen receptor modulators** (raloxifene). **Hormone replacement** (not for treatment of osteoporosis as primary indication, but sometimes used for treatment of menopausal vasomotor symptoms)

DRUG HOLIDAY—duration of bisphosphonate therapy is controversial. Consider reassessment of fracture risk after 3–5 years of treatment, followed by possible “drug holiday” (i.e., temporary discontinuation of therapy for up to 5 years) in those at low-to-moderate risk vs. prolonged therapy in those at highest risk

SPECIFIC ENTITIES**PAGET DISEASE OF BONE**

- **PATHOPHYSIOLOGY**—second most common metabolic bone disease (after osteoporosis). Focal, accelerated bone remodeling from highly active osteoclasts (skull, pelvis, vertebra, femur, tibia) followed by imperfect bone repair
- **CLINICAL FEATURES**—usually asymptomatic and incidental finding. Bone pain (achy, deep), bony deformity (femur, tibia), headaches and hearing loss (skull), and even neurological symptoms and paralysis (spine) possible. Usually presents around age 50–60

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—↑ ALP is an excellent marker of disease extent and activity and can be used to follow treatment. X-rays (“disorganized matrix of woven bone”) and bone scan to assess involved sites
- **TREATMENTS**—indicated for bone pain; benefits of treatment for other complications less clear. Supportive care (NSAIDs, acetaminophen, opioids for pain). *Zoledronic acid* 5 mg IV × 1 dose ± surgery (for long bone deformity, fracture fixation, joint arthroplasty, spinal decompression, and bone tumors)

HypertensionAmarenco et al. *NEJM* 2006;355(6)

See HYPERTENSION (p. 70)

Hyperlipidemia

See HYPERLIPIDEMIA (p. 75)

Amenorrhea**DIFFERENTIAL DIAGNOSIS****PRIMARY AMENORRHEA**

- **HYPOTHALAMIC DYSFUNCTION**—constitutional delay, stress (emotional, physical, nutritional), idiopathic hypogonadotropic hypogonadism (Kallman syndrome), septo-optic dysplasia
- **PITUITARY DYSFUNCTION**—tumor, iatrogenic (surgery, radiation), isolated gonadotropin deficiency
- **OVARIAN FAILURE**—Turner syndrome (XO), gonadal agenesis/dysgenesis
- **ABSENT UTERUS**—Mullerian agenesis, complete androgen insensitivity syndrome, disorders of sex development (DSD)
- **OUTFLOW TRACT DISORDER**—imperforated hymen, transverse vaginal septum, isolated absence of cervix or vagina
- **OTHERS**—Mullerian agenesis, complete androgen insensitivity syndrome (XY), constitutional delay, causes of secondary amenorrhea

SECONDARY AMENORRHEA

- **PREGNANCY**
- **THYROID DYSFUNCTION**—hyperthyroidism, hypothyroidism
- **ESTROGEN DEFICIENCY**—hypothalamic anovulation (physical/emotional stress, strenuous

DIFFERENTIAL DIAGNOSIS (CONT'D)

- exercise, weight loss, anorexia nervosa, chronic disease, CNS disease [infection, trauma, tumor]), hyperprolactinemia, primary ovarian insufficiency, menopause
- **ANDROGEN EXCESS**—PCOS, ovarian tumors, adrenal tumors, Cushing syndrome, non-classic congenital adrenal hyperplasia, medications (testosterone, danazol)
- **ANATOMICAL ENDOMETRIAL DISORDERS**—adhesions (Asherman syndrome), endometrial cancer, endometrial polyps, adenomyosis, leiomyomas

PATHOPHYSIOLOGY**DEFINITION OF AMENORRHEA**

- **PRIMARY AMENORRHEA**—absence of menarche by age 15–16 years (in the presence of normal secondary sexual development), or absence of menarche by age 13–14 (without normal secondary sexual development). Note: absence of menarche within 4 years of breast development always warrants investigation
- **SECONDARY AMENORRHEA**—absence of menses for >3 cycles or 6 months in a woman who previously had menses

CLINICAL FEATURES

HISTORY—characterize amenorrhea (onset, duration, previous menstruation), pregnancy and related symptoms, puberty milestones, headaches, visual field defects, fatigue, polyuria, polydipsia, weight change, physiologic or emotional stressors, galactorrhea, hot flashes, vaginal dryness, poor sleep, decreased libido, hirsutism, acne, past medical history (PCOS, obesity, hyperthyroidism, hypothyroidism, D&C), medications (oral contraception)

PHYSICAL—height and weight, vitals, visual fields, galactorrhea, Tanner staging (breasts, genitalia, pubic hair). Also assess for hirsutism, acne, striae, acanthosis nigricans, vitiligo, and signs of hypothyroidism/hyperthyroidism. Perform pelvic examination

INVESTIGATIONS**BASIC**

- **LABS**— β hCG, prolactin, FSH, LH, TSH
- **IMAGING**—US pelvis (if suspect ovarian tumor or uterine disorder), CT abd (if suspect adrenal tumor)

SPECIAL

- **KARYOTYPE**—Turner syndrome, androgen insensitivity, gonadal dysgenesis
- **FMRT (FRAGILE X) GENE TESTING**—primary ovarian insufficiency
- **HYSTEOSALPINGOGRAM**—Asherman syndrome
- **MRI SELLA**—hypogonadotropic hypogonadism
- **PROGESTIN CHALLENGE TEST**—first rule-out pregnancy, then administer progesterone for 7–10 days. If sufficient estrogen present, withdrawal bleeding will occur within a

INVESTIGATIONS (CONT'D)

week, and suggests chronic anovulation (e.g. PCOS). Absence of withdrawal bleed suggests hypogestrogenism, endometrial disease, or outflow tract obstruction

- **HYPERANDROGENISM WORKUP**—17-hydroxyprogesterone (for non-classic congenital adrenal hyperplasia), total testosterone, DHEAS, androstenedione

MANAGEMENT**TREAT UNDERLYING CAUSE**

POLYCYSTIC OVARIAN SYNDROME—see section on Hirsutism p. 393 for details

HYPOTHALAMIC ANOVULATION—if eating disorder, refer to psychiatry and consider hormone replacement therapy (transdermal estrogen with cyclic progesterone). If functional hypothalamic anovulation, reverse primary cause if possible (e.g. stress management, reduction of exercise, weight correction) and consider hormone replacement therapy (transdermal estrogen with cyclic progesterone) if amenorrhea persists. If hyperprolactinemia, give dopamine agonist (bromocriptine or cabergoline; see section on Pituitary Tumors p. 380 for details). Refer to Endocrinology if fertility desired

PRIMARY OVARIAN INSUFFICIENCY (PREMATURE OVARIAN FAILURE)

—hormone replacement therapy (estrogen with progesterone) to improve symptoms (e.g. vasomotor instability, dyspareunia) and for bone protection. Consider treating until expected natural menopause (late 40s to early 50s). Counsel and monitor for associated conditions (e.g. hypothyroidism, adrenal insufficiency, type 1 diabetes)

Hirsutism**DIFFERENTIAL DIAGNOSIS****TESTOSTERONE EXCESS**

- **POLYCYSTIC OVARY SYNDROME**—most common, insulin resistance with hyperinsulinemia
- **IDIOPATHIC HIRsutISM**—common
- **OVARIAN TUMORS**—Sertoli–Leydig cell tumor, granulosa-theca cell tumor
- **ADRENAL TUMORS**—carcinoma, adenoma
- **ANDROGEN THERAPY**—testosterone

DHEAS EXCESS

- **CONGENITAL ADRENAL HYPERPLASIA**
- **CUSHING DISEASE**

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **ADRENAL TUMORS**—carcinoma, adenoma
- **ANDROGEN THERAPY**—DHEA, danazol

PATHOPHYSIOLOGY

HIRSUTISM—androgen excess leading to excessive male pattern hair growth (terminal body hairs on face, chest, abdomen, and back). There may be associated acne and male-pattern balding

VIRILIZATION—significant androgen excess causing not only hirsutism but also deepening of

PATHOPHYSIOLOGY (CONT'D)

voice, breast atrophy, increased muscle bulk, clitoromegaly, and increased libido

HYPERTRICHOSIS—excessive hair growth (soft, non-sexual areas) that is androgen independent. Most commonly familial, but may also be caused by systemic disorders (hypothyroidism, anorexia nervosa, malnutrition, porphyria, and dermatomyositis) or medications (phenytoin, penicillamine, diazoxide, minoxidil, or cyclosporine)

CLINICAL FEATURES

HISTORY—time course of symptoms, hirsutism and virilization symptoms, menstrual history, weight history, medications, family history

DIAGNOSTIC ISSUES**DISTINGUISHING FEATURES**

	PCOS	CAH	Idiopathic	Ovary tumor
Age	Puberty	Puberty	Puberty	Any age
Menstruation	Altered	May be altered	Normal	Normal
Hirsutism	+	+	+	+++ virilization
Course	Slow	Slow	Slow	Acute
Testosterone/DHEAS	+	+	Normal	++
17-OH progesterone	—	+	—	—

MANAGEMENT

TREAT UNDERLYING CAUSE—to eliminate excessive androgen production. Suppression of androgen only prevents new hair growth. After hyperandrogenism resolved, consider terminal hair removal (e.g. electrolysis)

SPECIFIC ENTITIES**POLYCYSTIC OVARIAN SYNDROME**

- PATHOPHYSIOLOGY**—androgen excess mostly from peripheral conversion of androstenedione (ovaries) to testosterone. Associated increased insulin resistance leads to maturation arrest of developing primary and secondary follicles. Cycles are anovulatory
- CLINICAL FEATURES**—menstrual irregularity (since puberty), hyperandrogenism (hirsutism, acne, male pattern balding), infertility, metabolic syndrome (central obesity, insulin resistance), elevated testosterone levels
- DIAGNOSIS**—2 out of 3 Rotterdam 2003 criteria: oligomenorrhea/anovulation, hyperandrogenism, and polycystic ovaries on US. Exclude other causes of menstrual irregularity/hyperandrogenism

CLINICAL FEATURES (CONT'D)

PHYSICAL—BMI, skin and hair growth pattern, signs of virilization, abdominal and pelvic examination

INVESTIGATIONS**BASIC**

- LABS**—total testosterone, DHEAS, 17-OH progesterone, androstenedione

SPECIAL

- IMAGING**—US pelvis (if suspect ovarian tumor), CT abd (if suspect adrenal tumor)
- CUSHING WORKUP**—1 mg dexamethasone suppression test (or 24 h urinary free cortisol, or late night salivary cortisol)

SPECIFIC ENTITIES (CONT'D)

- TREATMENTS**—treat hirsutism (low-dose combination oral contraceptive pill, spironolactone, electrolysis, laser therapy), provide endometrial protection (low-dose combination oral contraceptive pill, progesterone), treat metabolic syndrome (diet, exercise, weight loss, metformin if prediabetes/diabetes), and advise regarding fertility (clomiphene, letrozole)

NON-CLASSIC CONGENITAL ADRENAL HYPERPLASIA

- PATHOPHYSIOLOGY**—21-hydroxylase deficiency, which leads to increased production of both 17-hydroxyprogesterone (the substrate for 21-hydroxylase and an androgen precursor) and androstenedione
- CLINICAL FEATURES**—sometimes menstrual irregularity, hirsutism, no cortisol deficiency. May be indistinguishable from PCOS
- DIAGNOSIS**—elevated 17-OH progesterone level
- TREATMENTS**—highly individualized therapy. Treat hirsutism (low-dose oral contraceptive pill, spironolactone, electrolysis, laser therapy) and advise regarding fertility (low-dose glucocorticoid to turn off ACTH stimulation to

SPECIFIC ENTITIES (CONT'D)

restore fertility). Refer to Endocrinology for prenatal counseling and therapy

IDIOPATHIC HIRSUTISM

- **CLINICAL FEATURES**—no menstrual irregularity, hirsutism

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—normal androgen levels, diagnosis of exclusion
- **TREATMENTS**—hair removal (electrolysis, laser therapy) and antiandrogen therapy (low-dose oral contraceptive pill, spironolactone, cyproterone acetate)

Male Hypogonadism**DIFFERENTIAL DIAGNOSIS****PRIMARY HYPOGONADISM**

- **CONGENITAL OR DEVELOPMENTAL DISORDERS**—Klinefelter syndrome, Down syndrome, Prader-Willi syndrome, uncorrected cryptorchidism, testosterone biosynthetic defect
- **ACQUIRED**—testicular trauma, irradiation, surgery, drugs (spironolactone, ketoconazole, cyclophosphamide, alcohol), mumps orchitis, autoimmune polyglandular syndrome, myotonic dystrophy, cirrhosis, CKD, sickle cell disease, malignancy, spinal cord injury, vasculitis, infiltrative disease

SECONDARY HYPOGONADISM

- **CONGENITAL OR DEVELOPMENTAL DISORDERS**—constitutional delay, hypogonadotropic hypogonadism (Kallman syndrome, congenital adrenal hyperplasia)
- **ACQUIRED**—hyperprolactinemia, drugs (opioids, marijuana, alcohol, cocaine, anabolic steroids, progesterone, GnRH agonists/antagonists), pituitary or suprasellar tumor, infiltrative disorders (hemochromatosis), excessive exercise, chronic systemic illness (e.g. cirrhosis, HF, CKD, Cushing syndrome), morbid obesity

CLINICAL FEATURES

HISTORY—drugs, delayed puberty (and family history of delayed puberty), loss of smell (Kallman syndrome), decreased erections, decreased libido, decreased volume of ejaculate, infertility, decreased energy and motivation, reduced frequency of shaving, loss of body hair, decreased muscle bulk and strength, hot flashes

PHYSICAL—height and weight, visual fields, galactorrhea, GU examination (hypospadias, microphallus, cryptorchidism, testicular size [normal adult volume 12–25 mL]). Also assess for facial hair, eunuchoidal body proportions (arm span > height), and signs of systemic illness (e.g. Cushing syndrome)

INVESTIGATIONS**BASIC**

- **LABS**—total testosterone

SPECIAL

- **FREE TESTOSTERONE**—if liver disease, obesity, or diabetes mellitus
- **KARYOTYPE**—Klinefelter syndrome
- **SECONDARY HYPOGONADISM WORKUP**—prolactin, ferritin, LH, FSH, MRI sella
- **SEMEN ANALYSIS**

DIAGNOSTIC ISSUES

INDICATIONS FOR TESTING—presence of symptoms/signs of hypogonadism or high index of suspicion (e.g. unexplained anemia, osteoporosis). Diagnosis of hypogonadism requires ↓ testosterone *and* compatible history. Testosterone should never be used for asymptomatic screening, but only to supplement a clinical diagnosis

INITIAL TESTING—initial testing with testosterone between 8–10 AM, fasting, and not at time of intercurrent illness. Follow-up abnormal test result with second test, preferably 3–6 months apart. Diagnosis of hypogonadism cannot be made during acute/subacute illnesses. If multiple abnormal tests, conduct further workup for underlying cause of hypogonadism prior to empiric treatment

MANAGEMENT

TREAT UNDERLYING CAUSE—exclude reversible illness, confounding drugs, nutritional deficiencies, and strenuous exercise

PRIMARY HYPOGONADISM—mostly irreversible and treated with testosterone replacement for secondary sexual characteristics, bone protection, and performance

SECONDARY HYPOGONADISM—If constitutional delay, no treatment needed for most cases. If hypopituitarism, testosterone replacement ± replacement of other deficient pituitary hormones (see section on Pituitary Tumors p. 380)

MANAGEMENT (CONT'D)

for details). If hyperprolactinemia, give dopamine agonist (bromocriptine or cabergoline; see section on Pituitary Tumors p. 380 for details). If exogenous anabolic steroids, discontinue offending medications. If obesity, recommend weight loss (but beware of using testosterone, which may induce or worsen OSA)

SPECIFIC ENTITIES**GYNECOMASTIA**

- **PATHOPHYSIOLOGY**—palpable breast tissue in a male. Commonly occurs in neonatal and pubertal stages (transient, physiologic). May occur in adults because of testosterone deficiency and/or estrogen excess (pathologic). Often idiopathic, but may be due to drugs (e.g. testosterone [aromatized to estrogen], spironolactone), increased aromatase activity (e.g. hyperthyroidism, cirrhosis), and estrogen-/hCG-producing tumors
- **CLINICAL FEATURES**—may be unilateral or bilateral. Assess for duration of onset, symptoms (pain, tenderness, discharge), associated

SPECIFIC ENTITIES (CONT'D)

lymphadenopathy, and presence of testicular tumor

- **DIAGNOSIS**—review medications carefully, check for systemic illness, and rule out pseudogynecomastia (adipose tissue). Mild, asymptomatic gynecomastia detected incidentally usually does not require further workup. Investigate if recent, rapid-onset, and/or large with testosterone, estradiol, LH, FSH, PRL, β hCG, TSH, creatinine, ALT, ALP \pm anabolic steroid screen. Suspect breast cancer if unilateral, firm, indurated, and fixed.
- **TREATMENTS**—treat underlying disorder (e.g. discontinue offending medication, treat hyperthyroidism, resect testicular tumor). If gynecomastia persists, consider testosterone replacement in the setting of androgen deficiency, or selective estrogen receptor modulators for estrogen excess \pm surgery for long-standing symptomatic gynecomastia. If asymptomatic (with no identifiable underlying disorder), give reassurance as most do not require treatment



Eczema

DIFFERENTIAL DIAGNOSIS OF PRURITUS

INFLAMMATORY

- **DERMATITIS**—atopic dermatitis, asteatotic eczema, nummular eczema, dyshidrotic eczema, seborrheic dermatitis, stasis dermatitis, irritant contact dermatitis, allergic contact dermatitis, lichen simplex chronicus (neurodermatitis)
- **PSORIASIS**
- **PITYRIASIS LICHENOIDES**
- **URTICARIA**
- **DERMATITIS HERPETIFORMIS**
- **BULLOUS PEMPHIGOID**
- **LINEAR IMMUNOGLOBIN A DISEASE**
- **GRAFT VS HOST DISEASE**

INFECTIONS—tinea, scabies, pediculosis corporis and pubis, pityriasis rosea, varicella

NEOPLASTIC—lymphoma (mycosis fungoides, Hodgkin lymphoma), myeloma, solid tumors, polycythemia vera

IATROGENIC

- **DRUG ERUPTION**—antibiotics, anti-epileptics
- **DRUG-INDUCED PRURITUS**—opiates, steroids, aspirin, antimalarials

SYSTEMIC

- **ENDOCRINE**—diabetes, hypothyroidism, hyperthyroidism, carcinoid syndrome
- **HEPATOBIILIARY**—PBC, cholestasis
- **RENAL**—uremia, hemodialysis
- **NEUROLOGIC**—brachioradial pruritus, notalgia paresthetica, postherpetic neuralgia, multiple sclerosis
- **INFECTIONS**—HCV, HIV
- **AUTOIMMUNE**—sarcoidosis, dermatomyositis, Sjögren syndrome
- **PSYCHOGENIC**—delusional infestation, psychogenic excoriation, anorexia nervosa
- **OTHERS**—iron deficiency, idiopathic xerosis, burns and scars

PATHOPHYSIOLOGY

PATHOGENESIS—chronic inflammatory skin disorder characterized by dry skin and pruritus. Rubbing and scratching the skin promotes inflammation and leads to an itch–scratch cycle. It follows a relapsing course characterized by alternating periods of flares and remissions. Mutations in filaggrin and deficiency in ceramides play a key role in pathogenesis. Patients often have a personal or family history of eczema, asthma, or allergic rhinitis. Exacerbating factors may include cold weather, dust mites, pollens, infection, wool, pet fur, emotional stress, chemical irritants, and other allergens

CLINICAL FEATURES

FINDINGS—ill-defined pruritic erythematous plaques with excoriations. Neck and flexural prominence in adults and children. Extensor prominence in infants. Pustules, honey-colored crusts, and weeping may be a sign of secondary infection

TYPES OF ECZEMA

- **ASTEATOTIC ECZEMA**—dry irritable skin in the elderly
- **NUMMULAR ECZEMA**—acral, coin-shaped patches of eczema usually on extremities
- **DYSHIDROTIC ECZEMA**—acute vesicular eczema of the palms and soles
- **XEROSIS/WINTER ITCH**—eczema secondary to dry conditions in winter

INVESTIGATIONS

SPECIAL (not typically performed)

- **LABS**—CBC (eosinophilia) and IgE level (elevated)
- **BACTERIAL AND VIRAL CULTURES**—if there is a suspicion of a secondary infection

MANAGEMENT

TREATMENTS—dry skin care (unscented, hypoallergenic soaps, daily moisturizers). **Topical corticosteroids** BID×3 weeks, off 1 week, repeat PRN (typically hydrocortisone 1–2.5% or desonide 0.05% for the face, triamcinolone 0.1% for the body), and topical calcineurin inhibitors (tacrolimus 0.1%, pimecrolimus 1%). **Antihistamines** (diphenhydramine, loratadine, fexofenadine, hydroxyzine, and doxepin). **Oral antibiotics** × 7 days for superimposed *Staphylococcus aureus* infections (typically flucloxacillin or other penicillinase-resistant penicillin for MSSA and clindamycin, doxycycline or trimethoprim-sulfamethoxazole for MRSA)

SPECIFIC ENTITIES**DERMATITIS HERPETIFORMIS**

- **ASSOCIATIONS**—celiac disease, IgA nephropathy, autoimmune thyroid disease, autoimmune hepatitis, type 1 diabetes, SLE, Sjögren syndrome, sarcoidosis, Addison disease, atrophic gastritis, vitiligo, and alopecia areata. Strong linkage to HLA-B8, DR3, and DQw2. Increased risk of non-Hodgkin lymphoma
- **CLINICAL FEATURES**—pruritic erythematous papulovesicles on extensor surfaces and buttocks, rarely mucous membranes. Lesions tend to be symmetrically distributed
- **TREATMENTS**—dapsone and gluten-free diet. If dapsone cannot be tolerated, sulfonamides such as sulfasalazine can be used. See Celiac Disease (p. 142)

STASIS DERMATITIS

- **CLINICAL FEATURES**—erythematous pruritic and burning lesions found on lower limbs of older patients due to compromised venous or lymphatic return. With increased extravasation of

SPECIFIC ENTITIES (CONT'D)

blood into the surrounding tissues, the lesions become darker, scaly, and may even form stasis ulcers and lipodermatosclerosis in late disease. Accompanying localized hair loss may be seen

- **TREATMENTS**—treat underlying cause. Encourage weight reduction, daily walking/exercise, and leg elevation as tolerated. Graduated compression stockings (after ankle–brachial index [ABI] checked). Topical steroids for acute exacerbations. Pharmacologic systemic therapy, such as venoactive or phlebotonic drugs, pentoxifylline, and flavonoids have been used. Varicose veins may be treated with surgery, endovenous laser therapy or via sclerotherapy

SCABIES

- **CLINICAL FEATURES**—excoriations, eczematized and urticarial papules over trunk. Linear white burrows over finger webs, sides of hand, and flexural aspects of wrists. Confirmed by skin scrapings for ectoparasitic mites and eggs. Crusted scabies is a severe form seen in HIV and immunosuppressed patients
- **TREATMENTS**—first-line therapy with *permethrin* 5% cream × 1 dose, applied to the entire body from chin to soles, rinse off after 8–14 h. Second-line treatments include *ivermectin* 200 mcg/kg PO × 1 dose and repeat PO × 1 dose 1–2 weeks later, *lindane* 1% lotion or cream × 1 dose, rinse off after 8 h, and *benzyl benzoate* 10 or 25% lotions × 1 dose, rinse off after 24 h. Simultaneous treatment of patient and close contacts is recommended

Chosidow NEJM 2006;354(16)

Thomas et al. J Am Acad Dermatol 2020;82(3)

Psoriasis Vulgaris**DIFFERENTIAL DIAGNOSIS OF PAPULOSQUAMOUS LESIONS**

INFLAMMATORY—psoriasis vulgaris, lichen planus, nummular eczema, discoid lupus

INFECTIONS—tinea, pityriasis rosea, secondary syphilis, seborrheic dermatitis

MALIGNANCY—mycosis fungoides, basal cell carcinoma (BCC), squamous cell carcinoma (SCC)

IATROGENIC—drug eruption

PATHOPHYSIOLOGY

INFLAMMATION—a chronic inflammatory skin disorder with a polygenic predisposition and sometimes an environmental triggering factor (trauma/Koebner phenomenon, infections, drugs, smoking, alcohol ingestion, emotional stress)

CLINICAL FEATURES

FINDINGS—well-circumscribed, bright salmon red color, silvery micaceous scaly plaques. Predilection for the scalp and extensor regions. Nails may show pitting changes, “oil spots”, onycholysis, and subungual debris that may be helpful in making the diagnosis. All patients regardless of skin severity should be screened for inflammatory arthritis that is worse in the mornings, associated with joint stiffness and swelling \pm dactylitis. Consider screening for hyperlipidemia, coronary artery disease, and diabetes in patients with risk factors as there is an increased predilection in patients with psoriasis

SUBTYPES

- **CHRONIC PLAQUE PSORIASIS**—predilection for scalp, elbows, and knees. Symmetric, sharply demarcated erythematous plaques with silvery scales that when scratched off reveal punctate blood droplets (Auspitz sign)
- **GUTTATE PSORIASIS**—predilection for trunk. May follow a streptococcal infection. Multiple discrete erythematous papules with silvery scales
- **PALMOPANTAR PSORIASIS**—mild to severe forms. Well-demarcated erythematous plaque with silver scales. Cracking, fissures, or bleeding may be seen. Pustular variant also found
- **INVERSE PSORIASIS**—perianal, genital, and axillary well-demarcated erythematous plaques that are more likely to be macerated and fissured due to location in a moist and warm environment
- **ERYTHRODERMIC PSORIASIS**—generalized erythema \pm characteristic erythematous plaques with white-silver scale and nail changes. Often spares the face
- **PUSTULAR PSORIASIS**—initial stinging and burning in area may promote scratching, followed by eruption of sterile pustules. Hypocalcemia is a risk factor
- **NAIL PSORIASIS**—multiple small nail pits, leukonychia, red macules on nail lunula, and degradation of the nail plate. Associated with psoriatic arthritis

INVESTIGATIONS

SPECIAL (not typically performed)

- **MICROBIOLOGY**—throat C&S (if guttate psoriasis)
- **KOH PREPARATION**—if suspect tinea
- **SKIN BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE—**topical therapy** with corticosteroids (triamcinolone/fluocinolone, fluocinonide, betamethasone dipropionate and clobetasol), emollients, and vitamin D analogs. **Topical calcineurin inhibitors** may be used on the face and intertriginous areas. If unable to control, **light therapy** with either UVB or PUVA may be considered but requires 2–3 visits/week for months. Traditional **systemic therapies** including acitretin, cyclosporine, apremilast, and methotrexate should be considered in patients with moderate to severe psoriasis with >10% body surface involvement or severe functional impairment (hands, feet, arthritis, and genitals). If unresponsive or unable to tolerate these, **biologic therapy** such as the **TNF α inhibitors** (infliximab, adalimumab, golimumab, etanercept), **IL-17 pathway inhibitors** (secukinumab, ixekizumab, brodalumab), or **IL-23 pathway inhibitors** (ustekinumab, guselkumab, tildrakizumab) should be considered for psoriatic arthritis. Avoid systemic steroids as discontinuation may cause generalized pustular psoriasis

SPECIFIC ENTITIES**PITYRIASIS ROSEA**

- **PATHOPHYSIOLOGY**—human herpesvirus-6/7 may be the etiologic agent, although this disorder does not seem to be contagious
- **CLINICAL FEATURES**—herald plaque (2–5 cm, round, redder, scaly) followed by many smaller oval plaques in a “Christmas tree” configuration involving the trunk and extremities. Resolves spontaneously after 2–5 weeks
- **TREATMENTS**—no treatment needed usually. Topical steroid to relieve pruritus

LICHEN PLANUS

- **PATHOPHYSIOLOGY**—autoimmune disease with lymphocytic infiltration in epidermis
- **ASSOCIATIONS**—drugs (β -blockers, methyl dopa, penicillamine, NSAIDs, ACE inhibitors, carbamazepine, gold, lithium), HCV infection
- **CLINICAL FEATURES** ★5 P's★—Purple, Pruritic, Polygonal, Planar (flat-topped) Papules. May also see fine white lines on the surface (Wickham striae). Commonly seen in flexor wrists, forearms, and buccal mucosal (lacy white reticular lesions). Lesions may last for a year

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—no treatment needed usually. Topical or intralesional steroids, antihistamines, and anti-inflammatories to relieve pruritus. Investigate for associated causes

SEBORRHEIC DERMATITIS

- **PATHOPHYSIOLOGY**—a common skin disorder affecting areas rich in sebaceous glands such as the scalp, face, mid-chest, and intertriginous areas. It is caused by the yeast *Malassezia furfur* (formerly known as *Pityrosporum ovale*), *M. restricta*, and *M. globosa*, with increased host response leading to dermatitis. It is also known as “dandruff” in adults. Severe seborrheic dermatitis is associated with stress, neurologic disease (e.g. Parkinson disease), and immunosuppression (e.g. HIV/AIDS)
- **CLINICAL FEATURES**—pink to erythematous plaques with yellow scales or greasy crusts, which may occasionally be pruritic
- **TREATMENTS**—gentle emollients, ketoconazole shampoo or cream, 1–2.5% hydrocortisone cream, or topical calcineurin inhibitors. Severe scalp involvement in an adult may also be treated with shampoos containing selenium sulfide, zinc pyrithione, and stronger steroid liquids

Related Topic

Psoriatic Arthritis (p. 302)

URTICARIA (HIVES)

- **PATHOPHYSIOLOGY**—an acute (<6 weeks) or chronic (>6 weeks) type I hypersensitivity reaction. Most cases are idiopathic but triggers may include infections, insect bites, certain foods, medications, and emotional stress
- **CLINICAL FEATURES**—characterized by superficial transient edema with pink highly pruritic papules or plaques (wheals) with individual lesions having rapid onset and resolution within 24 h. Dermatographism is common where wheals may be induced after stroking the skin
- **TREATMENTS**—identification and elimination of eliciting factors, non-sedating antihistamines

SPECIFIC ENTITIES (CONT'D)

during the day and scheduled sedating antihistamines at night. Systemic glucocorticoids may be used when severe, but courses should be tapered over 5–7 days

DERMATOPHYTE (TINEA) INFECTIONS

- **PATHOPHYSIOLOGY**—*Trichophyton*, *Epidermophyton*, *Microsporum* are fungi that can uniquely dissolve keratin
- **CLINICAL FEATURES**—asymptomatic, scaling erythematous patches/plaques that slowly enlarge over scalp (tinea capitis), feet (tinea pedis), hand (tinea manuum), groin (tinea cruris), body (tinea corporis), and nails (onychomycosis). May be associated with pruritus and vesicles
- **DIAGNOSIS**—skin and nail lesions may be difficult to distinguish from psoriasis, eczematous conditions, and lichen planus. KOH examination from skin scrapings shows segmented hyphae and spores
- **TREATMENTS**—**tinea capitis** (*griseofulvin* 20–25 mg/kg/day for 6–8 weeks, *terbinafine*, *itraconazole*), **tinea pedis or cruris** (*terbinafine* 1% cream daily-BID, *clotrimazole/Lotrimin** 1% cream BID), **onychomycosis** (*terbinafine* 250 mg PO daily×6–12 weeks, *itraconazole* 200 mg PO daily×8–12 weeks. Need to monitor liver enzymes)

TINEA VERSICOLOR

- **PATHOPHYSIOLOGY**—*Malassezia furfur*
- **CLINICAL FEATURES**—young adult with hypopigmented, light brown, or salmon-colored scaly macules coalescing into patches
- **DIAGNOSIS**—KOH examination from skin scrapings show classic “spaghetti and meatballs” pattern representing hyphae and spores
- **TREATMENTS**—**topical** (*terbinafine* 1% cream daily BID, *clotrimazole* 1% cream BID, selenium sulfide 2.5% shampoo or lotion), **systemic** (ketoconazole, fluconazole, itraconazole)

GROIN SKIN LESIONS—common causes include tinea cruris, candidiasis, erythrasma (*Corynebacterium minutissimum*), and inverse psoriasis

Acne Vulgaris

James *NEJM* 2005;352(14)
 Zaenglein *NEJM* 2018;379(14)

DIFFERENTIAL DIAGNOSIS OF ACNEIFORM LESIONS

ACNE VULGARIS

ROSACEA

PERIORIFICAL DERMATITIS

DRUGS—**EGFR inhibitors** (erlotinib, gefitinib, cetuximab, panitumumab) and **oral corticosteroids** (prednisone, dexamethasone) can cause pustular folliculitis

PSEUDOFOLLICULITIS BARBAE

FACIAL ANGIOFIBROMAS—tuberous sclerosis, multiple endocrine neoplasia type 1, Birt-Hogg-Dubé syndrome

PATHOPHYSIOLOGY

PATHOGENESIS—condition affecting pilosebaceous units, commonly seen during puberty. Pathogenesis involves androgens, follicular keratinization, and the Gram-positive bacteria *Propionibacterium acnes*. Lesions may present as non-inflammatory comedones or inflammatory papules. Inflammatory cysts may leave behind hyperpigmentation and sometimes scarring

RISK FACTORS—**drugs** (steroids, phenytoin, lithium), **androgen excess** (PCOS, Cushing disease, congenital adrenal hyperplasia), skin trauma, family history. Diet, stress, insulin resistance, and body mass index may contribute to lesion development

CLINICAL FEATURES

SEVERITY OF ACNE VULGARIS

- **MILD**—mainly comedones with few papules/pustules
- **MODERATE**—moderate papules and pustules (10–40) and comedones (10–40)
- **MODERATELY SEVERE**—numerous papules and pustules (40–100) and many comedones (40–100). May have nodular inflamed lesions (up to 5). Widespread involvement of face, chest and back
- **SEVERE**—nodulocystic acne and acne conglobata with many nodular or pustular lesions

TYPICAL PRESENTATION—teenager with open comedones (blackheads), closed comedones (whiteheads), erythematous papules, pustules, cysts and scarring over face, shoulders, upper chest, and back

INVESTIGATIONS

SPECIAL (not typically performed)

- **ENDOCRINE WORKUP**—testosterone, 24-h urinary cortisol

MANAGEMENT

TREAT UNDERLYING CAUSE

- **MILD CASES**—topical agents include benzoyl peroxide 2.5–10% daily-BID, sulfur-based washes, topical retinoids (*tretinoin* 0.025–0.1% qhs, *tazarotene* qhs), and topical antibiotics (*clindamycin* daily-BID, *erythromycin* daily-BID)
- **MODERATE CASES**—in addition to above agents for mild cases, oral antibiotic (*minocycline* 50–100 mg daily-BID, *doxycycline* 50–100 mg daily-BID, *trimethoprim-sulfamethoxazole* 160/800 BID, *tetracycline* 250–500 mg daily-BID, *erythromycin* 250–500 mg BID–QID) or antiandrogen therapy such as birth control pills may be used in female patients
- **SEVERE CASES**—respond well to oral *isotretinoin* 0.5–1 mg/kg/day, with a cumulative dose of 120 mg/day. Close monitoring with laboratory and clinical follow-up. High risk for teratogenicity

TREATMENT ISSUES

RETINOIDS—inhibit sebum excretion and *P. acnes*. Reserved for severe nodulocystic acne. Topical retinoids may cause irritation and dryness of the skin. Retinoids should never be used in pregnant women as highly teratogenic. Fertile women should take oral contraceptive pills 2 months before treatment continuing until 1 month after discontinuing oral retinoids

SPECIFIC ENTITIES

ROSACEA

- **CLINICAL FEATURES**—middle age adults with central facial telangiectasias, flushing (especially after ingestion of hot liquids, alcohol, spicy foods, heat, and other triggers), and acneiform papulopustules on cheeks, nose, forehead, and chin. No comedones. May be associated with rhinophyma (more in men), conjunctivitis, iritis, and keratitis
- **TREATMENTS**—oral antibiotics (tetracycline, erythromycin), topical antibiotics (metronida-

SPECIFIC ENTITIES (CONT'D)

zole 0.75%), sulfur-based products (sodium sulfacetamide lotion 10%), pulsed dye laser. Advanced phymatous skin changes can be treated with laser ablation. Avoidance of flushing triggers and daily sun protection are advised

PERIORAL (PERIORIFICAL) DERMATITIS

- **CLINICAL FEATURES**—young woman with papules and pustules over chin, upper lip, and nasal labial folds

Exanthematous Lesions**DIFFERENTIAL DIAGNOSIS OF EXANTHEMATOUS LESIONS****INFECTIONS**

- **VIRAL**—HCV, HIV, EBV, parvovirus B19, measles, rubella, roseola
- **BACTERIAL**—toxic shock, staphylococcal scalded skin syndrome, streptococcal toxic shock syndrome, scarlet fever, meningococcus, Rocky Mountain spotted fever, typhus

IATROGENIC—medications (see DRUG ERUPTIONS p. 412)

CLINICAL FEATURES

TYPICAL PRESENTATION—widespread erythematous maculopapular lesions that may be accompanied by fever and malaise

MANAGEMENT

TREAT UNDERLYING CAUSE—discontinue any offending drugs. Usually resolve spontaneously

Related Topic

Fever and Rash (p. 248)

SPECIFIC ENTITIES

PARVOVIRUS B19—slapped cheek rash on face and erythematous eruption on trunk, neck, and extremities, which is most common in children. Also called fifth disease or erythema infectiosum. Self-limiting. Fever may be present. Parvovirus B19 is also associated with aplastic anemia, polyarthritis, and fetal hydrops

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—topical therapeutic options include *pimecrolimus* 1% cream or *erythromycin* 2% gel applied twice daily. *Metronidazole* 1% lotion or gel can be applied once daily. Oral tetracyclines may be used for moderate to severe disease. Discontinuation of topical corticosteroids and other topical irritants if relevant

SPECIFIC ENTITIES (CONT'D)**STAPHYLOCOCCAL SCALDED SKIN SYNDROME (SSSS)**

- **PATHOPHYSIOLOGY**—exfoliatins produced by specific strains of staphylococci leading to desquamative disorder with cleavage at the granular layer of the dermis and acute epidermolysis. Most common in infants
- **CLINICAL FEATURES**—fever, malaise, generalized macular erythematous rash that evolves rapidly into a scarlatiniform (sandpaper-like) rash, followed by an exfoliative phase with perioral exudation and crusting. Large radial fissures “sunburst” around the mouth and are one of the diagnostic features. Nikolsky sign positive. Increased risk in children/infants, renal failure, immunocompromised
- **DIAGNOSIS**—culture from a site other than the blisters (blood, conjunctivae, nasopharynx) demonstrating staphylococci
- **TREATMENTS**—hospitalization for supportive care, culture for antibiotic susceptibility, and IV antibiotics for treatment of staphylococci (nafcillin/oxacillin first line, vancomycin if failing therapy or high prevalence or risk of MRSA)

SCARLET FEVER

- **PATHOPHYSIOLOGY**—erythrogenic toxin by specific strains of group A *Streptococcus* leading to cleavage at the granular layer of the dermis
- **CLINICAL FEATURES**—children with fever, sore throat, petechiae, and punctate red macules on hard and soft palate and uvula (Forchheimer spots), circumoral pallor, strawberry tongue, erythematous patches involving ears and chest, extend to trunk and extremities and accentuate in skin folds (Pastia lines). Evolves

SPECIFIC ENTITIES (CONT'D)

to sandpaper-like appearance. Desquamation occurs 7–10 days after resolution of rash

- **TREATMENTS**—antibiotics to treat scarlet fever symptoms, prevent contagious spread of

SPECIFIC ENTITIES (CONT'D)

group A *Streptococcus*, and to prevent acute rheumatic fever. Penicillin V is first-line. Fluid resuscitation as needed

Stevens–Johnson Syndrome/Toxic Epidermal Necrolysis**DIFFERENTIAL DIAGNOSIS OF VESICLES/BULLOUS LESIONS**

INFLAMMATORY—bullous pemphigoid*, pemphigus vulgaris*, porphyria cutanea tarda*, lupus*, dermatitis herpetiformis, erythema multiforme, contact dermatitis, linear IgA bullous dermatosis, epidermolysis bullosa acquisita, pemphigoid gestationis

INFECTIONS

- **BACTERIAL**—bullous impetigo*, staphylococcal scalded skin syndrome, toxic shock syndrome
- **VIRAL**—HSV, VZV, molluscum contagiosum, Coxsackie virus

NEOPLASTIC—paraneoplastic pemphigus

IATROGENIC—Stevens–Johnson syndrome*, toxic epidermal necrolysis*

*bullous lesions may be seen with or without vesicles

PATHOPHYSIOLOGY

HYPERSENSITIVITY REACTION—Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) lie on a spectrum of serious, life-threatening illness characterized by extensive epidermal necrosis. By definition, SJS involves less than 10% of the body surface area (BSA) and TEN involves greater than 30% of the BSA. Involvement of 10–30% BSA is an overlap between the two. Drugs are the most common offending agents, but *Mycoplasma pneumoniae*, viruses, various chemicals and immunizations have also been associated with SJS/TEN

COMMONLY ASSOCIATED DRUGS ★4A'S★

- **ALLOPURINOL**
- **ANTIBIOTICS**—sulfamethoxazole, cephalosporins, penicillins, quinolones, macrolides
- **ANTI-INFLAMMATORY DRUGS**—NSAIDs, salicylates
- **ANTICONSULSANTS**—carbamazepine, phenytoin, lamotrigine, phenobarbital

RISK FACTORS—HIV infection, malignancy (particularly hematologic cancers), certain HLA types, SLE, high doses of the drugs listed above

CLINICAL FEATURES

TYPICAL PRESENTATION—patients usually develop symptoms within 2–3 weeks after drug exposure, more rapidly in previously exposed patients. The prodrome involves a flu-like syndrome with fever, malaise, arthralgias, myalgias, and mucous membrane lesions. This is followed by the development of irregular target-like lesions often with necrotic centers that coalesce over time. Flaccid blisters form that spread with pressure (Nikolsky sign), resulting in sheet-like loss of epidermis and exposure of the underlying dermis. Ninety percent of patients have mucous membrane involvement, 60% have ocular involvement, and up to two-thirds of patients may develop urethritis or have other urogenital involvement

NIKOLSKY SIGN—pressing on the edges of an intact blister helps to discriminate between an intraepidermal blistering process (pemphigoid vulgaris, blister extends and breaks easily) and a subepidermal process (TEN, bullous pemphigoid, blister would not advance)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, Cr, urea
- **MICROBIOLOGY**—fluid C&S, HSV serology, VZV serology
- **SKIN BIOPSY**

PROGNOSTIC ISSUES

PROGNOSIS—mortality rates for SJS and TEN are approximately 5% and 30–50%, respectively, typically from sepsis and multi-organ failure. The risk of death can be predicted using the TEN specific severity-of-illness score (SCORTEN). Prognostic factors are each assigned a score of 1 and then added together to determine the predicted mortality

PROGNOSTIC ISSUES (CONT'D)

Prognostic factor	Weight	SCORTEN total	Predicted mortality
Age ≥ 40	1	0-1	3.2%
Heart rate ≥ 120 /min	1	2	12.1%
Associated malignancy	1	3	35.8%
Initial BSA skin detachment $>10\%$	1	4	58.3%
Serum urea >10 mmol/L [27 mg/dL]	1	5 or more	90%
Serum glucose >14 mmol/L [252 mg/dL]	1		
Bicarbonate >20 mmol/L [20 mEq/L]	1		

Bastuji-Garin et al. *J Invest Dermatol* 2000;115(2)

MANAGEMENT

TREAT UNDERLYING CAUSE—identifying and stopping the offending drug. **Corticosteroids** may be helpful but can be deleterious in severe forms of SJS/TEN. **High-dose IVIG** is controversial but may halt progression. Corticosteroids and IVIG in combination therapy may reduce mortality in TEN and SJS/TEN overlap. Systemic antibiotics may be necessary, but prophylactic systemic antibiotics are not empirically used. Infection control is employed with sterile handling, antiseptic solutions (although silver sulfadiazine should not be used if sulfonamides are thought to be the cause of SJS/TEN), and repeated skin, blood and catheter cultures every 48 hours. Promising newer treatments include cyclosporine and etanercept

SUPPORTIVE MEASURES—patients should be managed in a burn unit or ICU, as electrolyte abnormalities, renal failure, and pulmonary edema may occur. Pain control, wound and ocular care, adequate fluid replacement, prevention of infection and vulvovaginal complications, nasogastric tube feeding, heated room temperature to 30°C to 32°C

Seminario-Vidal et al. *J Amer Acad Dermatol* 2020;82(6)

SPECIFIC ENTITIES**ERYTHEMA MULTIFORME**

- **PATHOPHYSIOLOGY**—immune-mediated hypersensitivity reaction involving the skin and potentially mucous membranes (very limited)
- **ASSOCIATIONS**—infections (HSV, HBV, HCV, *Mycoplasma*, bacterial, fungal), drugs, pregnancy, malignancy
- **CLINICAL FEATURES**—skin lesions usually preceded by a few weeks of viral prodrome. Macules or papules evolve to form targetoid

SPECIFIC ENTITIES (CONT'D)

lesions. Palms, soles, forearms, legs most commonly affected

- **TREATMENTS**—discontinue offending drugs. Treat suspected HSV infection with appropriate antivirals. Topical corticosteroids or oral antihistamines are appropriate symptomatic therapies, and intra-oral lesions may be palliated with an anesthetic mouthwash. Patients with significant ocular involvement should be referred to an ophthalmologist. Patients who fail systemic antiviral therapy may be treated with mycophenolate, dapson, mofetil, azathioprine, or cyclosporine. Tofacitinib and apremilast are newer treatment options for refractory cases

BULLOUS IMPETIGO

- **PATHOPHYSIOLOGY**—intra-epidermal infection by *S. aureus* or β -hemolytic streptococci
- **CLINICAL FEATURES**—in bullous form, flaccid, pus-filled lesions often found in intertriginous areas and on the trunk, which rupture to form a golden-brown crust. More commonly found in children. Management of bullous impetigo in an adult should include a work-up for HIV infection

- **TREATMENTS**—limited impetigo can be treated with topical therapy (mupirocin TID or retapamulin BID \times 5 days); however extensive impetigo warrants systemic antibiotics (cephalexin, dicloxacillin, and clindamycin)

BULLOUS PEMPHIGOID

- **PATHOPHYSIOLOGY**—autoimmune blistering disease with IgG binding to subepidermal proteins (BP antigen 180 or 230), leading to separation of epidermis from dermis
- **ASSOCIATIONS**—furosemide, captopril, thiazide, spironolactone, penicillamine, phenothiazines, tricyclic antidepressants, benzodiazepines

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—multiple chronic, pruritic, tense blisters in the elderly. Commonly affecting flexural areas, axillae, and groin. Mucous membranes affected in <1/3 of cases, but rarely presenting feature. Nikolsky sign negative
- **TREATMENTS**—discontinue offending drugs. In mild or localized disease, treat with Class I topical steroids (clobetasol propionate 0.05% cream). Treat with anti-inflammatories and immunosuppressants, including tetracycline in conjunction with niacinamide. *Prednisone* 1–2 mg/kg PO daily. Methotrexate, azathioprine and mycophenolate mofetil are glucocorticoid-sparing options

PEMPHIGUS VULGARIS

- **PATHOPHYSIOLOGY**—autoimmune blistering disease with IgG binding to intraepidermal proteins (desmoglein 1 and 3), leading to separation of keratinocytes in epidermis
- **ASSOCIATIONS**—penicillamine, captopril, enalapril, penicillins, cephalosporins, malignancies (paraneoplastic)
- **CLINICAL FEATURES**—acute onset of multiple flaccid blisters. Mucous membranes usually affected first, with spread to scalp, face, chest, and groin. Nikolsky sign positive. Lesions prone to rupture and infections. May be life-threatening. May be paraneoplastic
- **TREATMENTS**—discontinue offending drugs. Consider burn unit admission, supportive fluids. *Prednisone* 1–2 mg/kg PO daily.

SPECIFIC ENTITIES (CONT'D)

Azathioprine, cyclosporine, mycophenolate mofetil, rituximab, plasmapheresis, IVIG

HERPES SIMPLEX VIRUS (HSV) 1 OR 2

- **CLINICAL FEATURES**—vesicles followed by ulcers in oral (gingivostomatitis) or genital areas
- **DIAGNOSIS**—scraping of vesicle stained with Wright–Giemsa stain shows acantholytic ballooned and multi-nucleated cells. Viral culture, PCR, direct fluorescent antibody, and serologic antibody testing are other diagnostic tools
- **TREATMENTS**—acyclovir, valacyclovir, famciclovir

VARICELLA ZOSTER VIRUS (VZV)

- **CLINICAL FEATURES**—crops of vesicles over entire body (varicella) or specific dermatome with reactivation (zoster, also known as shingles)
- **TREATMENTS**—acyclovir, valacyclovir, famciclovir. Amitriptyline, gabapentin, and opioids may be useful for post-herpetic neuralgia
- **PREVENTION**—vaccination in immunocompetent patients at least 50 years old is recommended, even in patients with prior herpes zoster infections (however, must delay vaccination for 1 year after infection). The two types of zoster vaccines are the recombinant zoster vaccine (RZV) (Shingrix[®]) and the live attenuated vaccine (ZVL) (Zostavax[®]). RZV is the recommended choice for most patients because the evidence suggests it has greater efficacy over a longer period of time. However, ZVL requires one dose, while RZV is a two-part series, and ZVL has a lower incidence of systemic side effects than RZV

Ulcers**DIFFERENTIAL DIAGNOSIS OF ULCERS****VENOUS HYPERTENSION**

- **STASIS**—immobility, CHF, incompetent valves, pregnancy
- **DVT**

ATHEROSCLEROTIC—ischemic ulcers, hypertensive ulcers (Martorell hypertensive ulcer)

NEUROPATHIC—diabetes, leprosy, syphilis, syringomyelia, peripheral neuropathy

VASCULITIC—temporal arteritis, polyarteritis nodosa, systemic sclerosis

INFECTIONS

- **BACTERIAL**—gumma, mycobacteria
- **VIRAL**—chronic ulcerative herpes simplex
- **FUNGAL**—deep fungal infections
- **PARASITIC**—cutaneous leishmaniasis, cutaneous amebiasis

DIFFERENTIAL DIAGNOSIS OF ULCERS (CONT'D)

TUMOR—squamous cell carcinoma, basal cell carcinoma, melanoma, Kaposi sarcoma

TRAUMA—pressure-induced skin injury, burns

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, glucose, urea, Cr, HbA1C
- **MICROBIOLOGY**—wound Gram stain, AFB, C&S, TB culture
- **ANKLE BRACHIAL INDEX**—<0.8 indicates arterial origin
- **IMAGING**—doppler US, venous plethysmography

INVESTIGATIONS (CONT'D)

SPECIAL (workup for pyoderma gangrenosum specifically)

- **COLONOSCOPY**—if suspect IBD
- **MALIGNANCY WORKUP**—serum protein electrophoresis, CXR
- **INFLAMMATORY WORKUP**—ESR, antiphospholipid antibody, antineutrophil cytoplasmic antibodies, cryoglobulins
- **SKIN BIOPSY**—mainly to rule out possible skin malignancies in the ulcer and to exclude other diagnoses. Include inflamed border for histologic evaluation and ulcer edge for bacterial, fungal, and mycobacterial culture

MANAGEMENT

See **SPECIFIC ENTITIES** for details

SPECIFIC ENTITIES**VENOUS ULCERS**

- **PATHOPHYSIOLOGY**—result from chronic increases in venous pressure due to either incompetent valves, failure of pump activity from immobility or obesity, or venous outflow obstruction. Increased pressure in the venous system results in dilatation of the capillary beds and chronic inflammation that breaks down the extracellular matrix
- **RISK FACTORS**—obesity, HF, history of DVT and/or thrombophlebitis, varicose veins, prolonged standing, and multiple pregnancies
- **CLINICAL FEATURES**—shallow, irregular borders, relatively painless, and typically located from the mid-calf to the ankle, classically on the medial malleolus. Other common lower extremity findings include edema, lipodermatosclerosis (firm and indurated skin), hyperpigmentation, and dermatitis
- **TREATMENTS**—compression stockings (need to rule out arterial insufficiency), leg elevation, walking/physiotherapy. Occlusive dressing (DuoDerm) weekly if not infected vs. twice daily if infected). Diuretics (decrease leg edema). Antibiotics if super-infected. Superficial vein surgery may prevent recurrence in some patients

ATHEROSCLEROTIC ULCERS

- **PATHOPHYSIOLOGY**—result from peripheral artery disease or vasculitis that prevents adequate blood flow to the lower extremity. Inadequate oxygen and nutrient delivery results in tissue breakdown and arterial necrosis
- **RISK FACTORS**—atherosclerosis, peripheral artery disease, diabetes mellitus, obesity,

SPECIFIC ENTITIES (CONT'D)

smoking, rheumatic disease, Buerger disease, hemoglobinopathies

- **CLINICAL FEATURES**—ulcers tend to be well defined and appear “punched out” with a gray or black necrotic base. Lesions occur over distal sites such as toes and bony prominences and are very painful. Associated features include intermittent claudication, diminished peripheral pulses, and prolonged capillary refill (greater than 3 to 4 seconds)
- **TREATMENTS**—treat underlying cause, such as surgical bypass for peripheral arterial disease. Avoidance of trauma. Apply moist occlusive dressings. Surgical debridement and systemic antibiotics may be necessary if infected. See **PERIPHERAL VASCULAR DISEASE** (p. 67)

NEUROPATHIC ULCERS

- **PATHOPHYSIOLOGY**—most common in diabetic patients. A combination of sensory and motor neuropathy due to enzymatic glycosylation impairs protective sensation and alters the distribution of forces on the lower extremity during normal movement. Many diabetic patients have a combination of neuropathic and arterial ulcers
- **RISK FACTORS**—diabetes mellitus, syphilis, leprosy, and peripheral neuropathies
- **CLINICAL FEATURES**—a pure neuropathic ulcer is painless. There is diminished sensation in the lower extremity. Patients have warm extremities with palpable pulses, as opposed to arterial ulcers
- **TREATMENTS**—diabetic patients require tight glucose control. Treat infection with systemic antibiotics. Debridement of the ulcer, hyperbaric oxygen therapy, and occlusive dressings are applied to promote wound healing. Immobilization and orthotic devices are used to alleviate pressure on the wound. Amputation may be required in severe cases

PYODERMA GANGRENOSUM

- **PATHOPHYSIOLOGY**—chronic condition that involves neutrophilic destruction of tissue
- **RISK FACTORS**—approximately 50% of patients have an underlying systemic illness, including ulcerative colitis (most common), Crohn disease, rheumatoid arthritis, lymphoproliferative disorder (lymphoma, leukemia, MDS), Behçet disease, and active hepatitis
- **CLINICAL FEATURES**—initially lesions appear as small, painful, erythematous papules that spread concentrically, evolving into pustules. Tissue breakdown and ulceration occur rapidly. Ulcers classically have dusky-red, violaceous,

SPECIFIC ENTITIES (CONT'D)

irregular borders with a purulent exudate and undermining. Lesions are typically solitary but may be multiple and coalesce into larger ulcers. It is typically found on the lower extremity, but other common sites include the buttocks, abdomen, and face. Exhibits pathergy, often arising in sites of injury (surgical incision, needle prick, insect bite). ESR may be elevated. Classically worsens with attempted biopsy or debridement

- **TREATMENTS**—treat underlying causes where possible and maintain a moist wound environment to facilitate healing. Immunosuppressive

SPECIFIC ENTITIES (CONT'D)

and immunomodulator therapy with systemic corticosteroids (*prednisone* 60–80 mg PO daily, *pulse methylprednisolone* 1 g IV daily × 3 days), cyclosporine, and biologics such as infliximab and canakinumab have the greatest evidence for treatment. Adjuvant treatment with intralesional steroids injected at active border sites and topical calcineurin inhibitors (tacrolimus) may improve outcomes. Other options include IVIG, sulfasalazine, sulfones, minocycline and dapsone

Wenig et al. *NEJM* 2002;347(18)
Partridge et al. *Br J Dermatol* 2018;179(2)

Melanoma and Skin Tumors**2019 AAD Guideline Primary Cutaneous Melanoma****DIFFERENTIAL DIAGNOSIS OF PIGMENTED LESIONS**

BENIGN—**nevus** (congenital, acquired), freckle, seborrheic keratosis, *café-au-lait*

PRE-MALIGNANT—**dysplastic nevi syndrome**

MALIGNANT—**melanoma** (superficial spreading, nodular, lentigo maligna, acral lentiginous), **pigmented basal cell carcinoma**

PATHOPHYSIOLOGY**RISK FACTORS OF MELANOMA**

- **GENETICS**—fair skin/ethnicity, red/blonde hair, blue eyes, family history
- **NEVI**—number of common/atypical nevi (marker of sun exposure), familial dysplastic nevus syndrome, previous melanoma
- **EXPOSURE**—intermittent intense sun exposure, phototherapy, immunosuppression

HISTOLOGIC TYPE

- **SUPERFICIAL SPREADING (70%)**—fifth decade of life, both sexes, initial radial growth, common on back, posterior legs of women
- **NODULAR (15%)**—grows rapidly vertically. More common in men
- **LENTIGO MALIGNA (10–15%)**—sun-damaged skin, older patients, 5–20-year radial growth phase
- **ACRAL LENTIGINOUS**—most common melanoma in non-whites, who are at relatively lower risk for sun-exposure subtypes of melanoma. Affects palms, soles, and nails

CLINICAL FEATURES

DISTRIBUTION—more common on the trunk in men and extremities in women. Typically occur in relatively non-pigmented areas in non-whites. Unusual primary sites for melanoma include CNS, eyes, mucosa (respiratory, GI, GU), palate, gingival, vulva and anus

SYMPTOMS

- **LOCOREGIONAL**—skin lesion (see *JAMA* series below)
- **METASTATIC**—depending on location (lung, GI tract, liver, brain, subcutaneous, skin, bone, heart)
- **PARANEOPLASTIC**—vitiligo, melanosis syndrome (slate gray skin discoloration), dermatomyositis, gynecomastia, Cushing, hypercalcemia, neurological

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A MOLE OR A MELANOMA?

CHECKLIST ★ABCDE★—**A**symmetry, **B**order irregularity, **C**olor variegation, **D**iameter >6 mm, **E**volution/Enlargement (change in lesion)

CHECKLIST FOR SUBUNGUAL MELANOMA ★ABCDEF★—**A**ge, **B**lack patients, **A**sians, and **N**ative Americans, **B**rown to black band, **C**hange in the nail bed, **D**igit most commonly involved (great toe and thumb), **E**xtension of the pigment onto the nail-fold, **F**amily or personal history of melanoma

REVISED 7-POINT CHECKLIST—major: change in size or new lesion, change in color/

CLINICAL FEATURES (CONT'D)

irregular color, change in shape/irregular shape; minor: presence of inflammation, diameter ≥ 7 mm, crusting or bleeding, sensory change (sens 79–100%, spc 30–37%, depending on how many criteria used)

	LR+	LR–
ABCDE Criteria for Melanoma		
Asymmetry	2.1	0.59
Border irregularity	2.1	0.59
Color variegation	1.6	0.59
Dimension >6 mm	2.3	0.17
Enlargement	11	0.18
Combination of ABCDE Criteria		
5 positive findings	98	–
≥ 4 positive findings	8.3	–
≥ 3 positive findings	3.3	–
≥ 2 positive findings	2.6	–
≥ 1 positive finding	1.5	–
0 findings	0.07	–

APPROACH—using either checklist, misdiagnosing a melanoma as a benign lesion appears to be unlikely. The revised 7-point checklist has higher chance of classifying benign lesions as malignant. Non-dermatologists' examinations are less sensitive than those performed by dermatologists

UPDATE—combination of increasing ABCDE criteria increases the likelihood of melanoma; enlargement of a skin lesion is the single most powerful univariate predictor

Whited et al. JAMA 1998;279(9)
Simel et al. The Rational Clinical Examination McGraw-Hill; 2009

INVESTIGATIONS**BASIC**

- EXCISIONAL BIOPSY**—all lesions suspicious for melanoma should be biopsied with caution to obtain the total depth of the melanoma, with a 1–3mm margin of normal skin and some subcutaneous fat if possible. Breslow depth is the most important prognostic indicator

SPECIAL

- LABS**—CBC, lytes, urea, Cr, LDH, AST, ALT, ALP, bilirubin as part of staging workup after pathology confirmation

INVESTIGATIONS (CONT'D)

- IMAGING**—CXR as part of staging workup after pathology confirmation

DIAGNOSTIC AND PROGNOSTIC ISSUES**CLARK LEVELS (LIMITED UTILITY FOR SMALL LESIONS)**

Level	TNM	5-year survival (%)
I	Intraepidermal (in situ)	100
II	Invasion into papillary dermis	95
III	Extensive invasion of papillary dermis	81
IV	Invasion into reticular dermis	68
V	Invasion into subcutaneous tissue	47

TNM STAGING

T stage (Breslow depth/thickness)

- T1**— ≤ 1 mm
 - T1A**— <0.8 mm and without ulceration
 - T1B**— <0.8 mm and with ulceration, or 0.8–1 mm with or without ulceration
- T2**—1.01–2 mm
 - T2A**—without ulceration
 - T2B**—with ulceration
- T3**—2.01–4 mm
 - T3A**—without ulceration
 - T3B**—with ulceration
- T4**— >4 mm
 - T4A**—without ulceration
 - T4B**—with ulceration

N stage

- N1**
 - N1A**—one clinically occult node (i.e. detected by sentinel lymph node biopsy)
 - N1B**—one clinically detected lymph node
 - N1C**—microsatellite metastases **and** no regional lymph node
- N2**
 - N2A**—2–3 clinically occult node (i.e. detected by sentinel lymph node biopsy)
 - N2B**—2–3 lymph nodes, at least one was clinically detected
 - N2C**—microsatellite metastases **and** 1 clinically occult or clinically detected lymph node

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **N3**
 - **N3A**— ≥ 4 clinically occult node (i.e. detected by sentinel lymph node biopsy)
 - **N3B**— ≥ 4 lymph nodes, at least one was clinically detected, or presence of matted nodes
 - **N3C**—microsatellite metastases **and** ≥ 2 clinically occult or clinically detected lymph node, or presence of matted nodes
- **M stage** (lungs, bone, liver, skin, and essentially any organ. Biologically heterogeneous with variable course)
 - **M1A**—distant metastasis to skin, soft tissue or non-regional nodes
 - **M1B**—distant metastasis to lung
 - **M1C**—distant metastasis to non-CNS visceral sites
 - **M1D**—distant metastasis to CNS sites

SENTINEL LYMPH NODE BIOPSY—usually done if primary melanoma is 1–4 mm thick or ulcerated

MANAGEMENT

PREVENTION—**sun avoidance** (sun-protective clothing, wide-brimmed hat, sunscreens)

SURVEILLANCE—particularly for high-risk individuals

STAGE I–III—standard of care is **wide local excision**. Mohs micrographic surgery may be used. Excision margin 1 cm for lesions ≤ 1 mm thick, 1–2 cm for lesions 1.01–2 mm, and 2 cm for lesions > 2 mm thick). **Sentinel lymph node biopsy** for lesions > 1 mm thick. If palpable node or sentinel lymph node positive, consider **lymph node dissection** and **adjuvant therapies**. For desmoplastic melanoma with high risk features, consider **adjuvant radiation**. Adjuvant therapy with ipilimumab, nivolumab, pembrolizumab, or dabrafenib plus trametinib results in substantial improvement in recurrence-free survival rates in patients with advanced-stage melanoma (stage III and IV) and is the new standard of treatment replacing adjuvant high-dose interferon $\alpha 2b$. For locoregional recurrence, consider re-excision

STAGE IV

- **SURGERY**—excision of solitary brain or lung metastasis is occasionally done, then treat as curable disease as above
- **MUTATION TESTING**—BRAF V600E/K. Mucosal and acral melanomas without a BRAF 600 mutation should be assessed for a KIT mutation

MANAGEMENT (CONT'D)

- **PALLIATIVE SYSTEMIC THERAPY**
 - **FIRST LINE**—consider nivolumab, pembrolizumab, or combined nivolumab and ipilimumab (preferred if BRAF mutant)
 - **SUBSEQUENT LINES**—BRAF and MEK inhibition (dabrafenib + trametinib, vemurafenib + cobimetinib) if BRAF mutant, imatinib if KIT mutant. Chemotherapeutic agents include dacarbazine, temozolomide, paclitaxel or carboplatin plus paclitaxel
- **PALLIATIVE RADIATION**—if localized pain
- **PALLIATIVE CARE**—referral for patients with supportive care needs

TREATMENT ISSUES

FOLLOW UP—should include a complete review of systems including headache, visual changes, cough, lymph node examination, and an LDH and imaging to rule out metastasis for patients with deep melanomas. Patients should continue skin examinations at least semi-annually for new lesions as patients have a 3–5% chance of developing another melanoma

SPECIFIC ENTITIES

DYSPLASTIC NEVI—acquired moles characterized by cytologic atypia and architectural disorder. They remain dynamic throughout life, constantly appearing, changing, or disappearing

DYSPLASTIC NEVUS SYNDROME—melanoma in ≥ 2 blood relatives and dysplastic nevi in other family members

BASAL CELL CARCINOMA

- **PATHOPHYSIOLOGY**—the most common form of skin cancer. Although they rarely metastasize, basal cell carcinomas are locally destructive and must be removed
- **CLINICAL FEATURES**
 - **NODULAR SUBTYPE** (50–80%)—pearly semi-translucent papules with telangiectasias and central depression; may ulcerate, crust, or bleed
 - **SUPERFICIAL SUBTYPE** ($> 15\%$)—psoriasiform scaly plaque; most common on trunk and extremities
 - **PIGMENTED SUBTYPE** (6%)—more common in Latin Americans and Asians
 - **MORPHEIFORM SUBTYPE** (2–6%)—white sclerotic plaque, can mimic a scar; predilection to recur
- **RISK FACTORS**—history of prior sunburns (especially in childhood), radiation therapy, family

SPECIFIC ENTITIES (CONT'D)

history, immunosuppression, fair complexion, and red hair

- **TREATMENTS**—usually treated by either excision or electrodesiccation and curettage. However, if superficial they may be treated with topical imiquimod or photodynamic therapy

ACTINIC KERATOSIS

- **PATHOPHYSIOLOGY**—form after chronic sun exposure in susceptible individuals usually on the face, scalp, forearms, and dorsal hands. Actinic keratoses are foci of superficial keratinocyte dysplasia capable of evolving into squamous cell carcinoma
- **CLINICAL FEATURES**—thin pink to red papules and plaques with overlying scale, may sometimes contain focal pigment. They are most common on people with fair skin (type I or II) and occur with increased frequency in patients who are immunosuppressed or have received phototherapy
- **TREATMENTS**—cryotherapy for focal lesions. If diffuse damage is present, one may use topical imiquimod, 5-fluorouracil, diclofenac, trichloroacetic acid peels, and photodynamic therapy. If there is a thick component below the skin surface, one should consider a skin biopsy to rule out underlying squamous cell carcinoma

SQUAMOUS CELL CARCINOMA

- **PATHOPHYSIOLOGY**—second most common form of skin cancer. On average 0.5–5.2% of squamous cell carcinomas metastasize, but they are much more aggressive on mucosal surfaces such as the lip and in areas of previous irradiation and scarring
- **RISK FACTORS**—same as risk factors for actinic keratoses, plus HPV infection for genital lesions
- **CLINICAL FEATURES**—typically firm red scaly plaques that frequently become ulcerated and occur in areas of heavy sun exposure in fair-skinned individuals. Subtypes include:
 - **BOWEN DISEASE**—squamous cell carcinoma in situ
 - **ERYTHROPLASIA OF QUEYRAT**—squamous cell carcinoma in situ of the penis
 - **KERATOACANTHOMA**—rapidly developing volcano-like nodule that may spontaneously involute
 - **VERRUCCOUS CARCINOMA**—clinically and histologically resembles a wart
- **TREATMENTS**—surgical excision is the treatment of choice

SPECIFIC ENTITIES (CONT'D)**SEBORRHEIC KERATOSIS**

- **PATHOPHYSIOLOGY**—benign tumor of keratinocytes. Generally familial in nature
- **CLINICAL FEATURES**—benign skin colored to black papules and plaques with well-defined borders. They often have a warty surface and a stuck-on appearance. Seborrheic keratoses are most commonly located on the back but can occur on the head, neck, and extremities. It is important to try to differentiate seborrheic keratoses clinically from melanoma. The Leser–Trelat sign denotes the sudden onset of numerous pruritic seborrheic keratosis along with skin tags and acanthosis nigricans and may indicate underlying malignancy (adenocarcinoma of the stomach and lung, leukemia, lymphoma, Sezary syndrome)
- **TREATMENTS**—liquid nitrogen cryotherapy, curettage, or shave removal

VERRUCA VULGARIS (COMMON WARTS)

- **PATHOPHYSIOLOGY**—a human papillomavirus (HPV) infection of keratinocytes. Lesions are benign but may cause cosmetic concern and are increased in immunocompromised individuals
- **CLINICAL FEATURES**—lesions are well-defined, firm papules or plaques with a hyperkeratotic cauliflower-like or flat surface. Lesions may have brown/black dots that represent thrombosed capillaries. Typically occur over extremities and genital area. Spontaneous resolution within 6 months for 30% of patients and 2 years for 65% of patients
- **TREATMENTS**—manual paring of the lesions, cryotherapy, topical salicylic acid (e.g. salicylate cream 40% daily with glutaraldehyde 10–25% daily), imiquimod, 5-fluorouracil, cantharidin, podophylin, laser therapy, and intralesional bleomycin

VITILIGO

- **PATHOPHYSIOLOGY**—autoimmune process against melanocytes. Differential diagnoses include tinea, leprosy, morphea, lichen sclerosus, post-inflammatory hypopigmentation, and chemicals
- **CLINICAL FEATURES**—hypopigmented patch(es)
- **TREATMENTS**—topical steroids, systemic corticosteroids, topical calcineurin inhibitors, phototherapy

Cutaneous Lupus Erythematosus

DIFFERENTIAL DIAGNOSIS OF PHOTSENSITIVITY

IATROGENIC (DRUGS)

- **AMIODARONE**
- **DIURETICS**—hydrochlorothiazide, loop diuretics
- **ANTIBIOTICS**—tetracycline
- **NSAIDS**
- **ANTINEOPLASTIC**—methotrexate, vincristine, 5-fluorouracil

INFLAMMATORY—SLE, dermatomyositis, rosacea

IDIOPATHIC—polymorphic light eruption, prurigo, actinic dermatitis, solar urticaria, chronic photosensitivity dermatitis

OTHERS—photocontact dermatitis, phytocontact dermatitis (celery, parsley, lime, lemon, yarrow), porphyria, xeroderma pigmentosum

CLINICAL FEATURES

CUTANEOUS MANIFESTATION OF SLE

- **MALAR RASH**—"butterfly rash" in up to 50% of lupus patients. Erythema in a malar distribution over the cheeks and bridge of the nose that spares nasolabial folds, especially after UV exposure
- **DISCOID LUPUS**—up to 50% of lupus patients. Discrete, erythematous, scaly plaques with follicular plugging over face, neck, and scalp, especially after UV exposure. May lead to central scars, atrophy, telangiectasias, and hyper-/hypopigmentation
- **SUBACUTE CUTANEOUS LUPUS**—up to 10% of lupus patients. Erythematous, slightly scaly papules that evolve into a papulosquamous or annular lesion over shoulders, forearms, neck, and upper torso. Usually no follicular plugging, hyperkeratosis, atrophy, pigment changes, and scarring
- **LUPUS PROFUNDUS**—firm, painful nodules over scalp, face, arms, chest, back, thighs, and buttocks
- **LUPUS TUMIDUS**—chronic violaceous papules and plaques or nodule lesions over areas exposed to the sun
- **BULLOUS LESIONS**—photosensitivity
- **LIVEDO RETICULARIS**—see SPECIFIC ENTITIES
- **NAIL LESIONS**—up to 25% of lupus patients. Changes include pitting, ridging, onycholysis and lunula (redness of half-moon), periungual erythema
- **MUCOUS MEMBRANE ULCERS**
- **LUPUS ALOPECIA**

INVESTIGATIONS

BASIC

- **BLOOD TESTS**—CBC, ANA, ENA, dsDNA

SPECIAL

- **SKIN BIOPSY**
- **PORPHYRIA WORKUP**—porphyrin, urine porphyrin

MANAGEMENT

TREATMENT UNDERLYING CAUSE—remove offending agent, sun protection. Topical steroid ointments and topical calcineurin inhibitors (tacrolimus) for localized cases. Antimalarials (hydroxychloroquine, chloroquine) for widespread cases. Systemic immunosuppressants or biologics for refractory cases

Borucki et al. *Expert Rev Clin Pharmacol* 2020;13(1)

Related Topics

Systemic Lupus Erythematosus (p. 304)
Porphyria (p. 484)

SPECIFIC ENTITIES

CENTRAL FACIAL TELANGIECTASIA OR ERYTHEMA—common causes include rosacea, dermatomyositis, SLE, dermatitis (seborrheic, atopic, contact), glucocorticoid-induced dermal atrophy, flushing

TELANGIECTASIA—common causes include sun damage, aging, hypertension, alcoholism, diabetes, rosacea, amyloidosis, lupus, other rheumatic diseases, and ataxia telangiectasia

LIVEDO RETICULARIS

- **CAUSES**—**vascular** (polyarteritis, SLE, livedo vasculitis, cryoglobulinemia, antiphospholipid antibody syndrome, atherosclerosis, syphilis, TB), **hyperviscosity** (polycythemia, thrombocytosis, macroglobulinemia), **congenital cerebrovascular disease** (Sneddon syndrome), **idiopathic**
- **CLINICAL FEATURES**—reddish-cyanotic, reticular patches over the arms, legs, and torso, particularly in cold environments. May progress to vascular occlusion with ischemia and tissue infarction (livedo vasculitis with triad of purpuric macules, cutaneous nodules, and painful ulcerations)

SPECIFIC ENTITIES (CONT'D)**PORPHYRIA CUTANEA TARDA**

- **PATHOPHYSIOLOGY**—heterozygous deficiency of uroporphyrinogen decarboxylase, important for heme synthesis
- **ASSOCIATIONS**—hemochromatosis, alcohol, HCV, HIV, estrogens, smoking, hemodialysis
- **CLINICAL FEATURES**—photodistributed blistering or superficial skin erosion (commonly on back of hands)

Drug Eruptions**DIFFERENTIAL DIAGNOSIS****EXANTHEMS**

- **ANTIBIOTICS**—penicillins, sulfonamides, erythromycin, gentamicin
- **ANTICONVULSANTS**
- **ALLOPURINOL**
- **GOLD**

URTICARIA, ANGIOEDEMA

- **IMMUNE IGE-MEDIATED**—penicillins, cephalosporins, sulfonamides, local anesthetic agents, radiocontrast, transfusion, latex
- **NON-IMMUNE BRADYKININ-MEDIATED**—radiocontrast, ACE inhibitors
- **MAST CELL DEGRANULATION**—narcotics, muscle relaxants (atracurium, vecuronium, succinylcholine, curare), vancomycin

FIXED DRUG ERUPTION

- **LAXATIVES**—phenolphthalein
- **ANTIBIOTICS**—tetracyclines, sulfonamides, quinolones, penicillins
- **ANTI-INFLAMMATORIES**—NSAIDs, ASA
- **DIURETICS**—hydrochlorothiazide, loop diuretics
- **ANTI-NEOPLASTIC AGENTS**—methotrexate, vincristine, 5-fluorouracil
- **OTHERS**—barbiturates, antimalarials

ERYTHEMA MULTIFORME, STEVENS-JOHNSON SYNDROME ★4A'S★

- **ALLOPURINOL**
- **ANTIBIOTICS**—sulfonamides, penicillins, cephalosporins
- **ANTICONVULSANTS**—phenytoin, carbamazepine, phenobarbital
- **ANTI-INFLAMMATORIES**—NSAIDs

CONTACT DERMATITIS—neomycin, benzocaine, paraben, ethylenediamine, formaldehyde, para-aminobenzoic acid

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—avoid exacerbating factors (alcohol, smoking, estrogens, iron supplements, drugs). Phlebotomy to reduce ferritin <20 ng/mL is first line. Chloroquine, hydroxychloroquine. Avoid sunlight exposure until porphyrin levels are normalized

DIFFERENTIAL DIAGNOSIS (CONT'D)**HYPERSENSITIVITY VASCULITIS**

- **ALLOPURINOL**
- **DIURETICS**—furosemide, thiazide
- **ANTIBIOTICS**—penicillins, sulfonamides
- **OTHERS**—cimetidine, hydantoin

PIGMENTARY CHANGES

- **AMIODARONE**
- **ANTIBIOTICS**—tetracycline, minocycline, antimalarials
- **METALS**—silver, mercury, gold
- **OTHERS**—TCA, quinine, oral contraceptives

INVESTIGATIONS**SPECIAL**

- **BLOOD TESTS**—CBC (eosinophils), quantitative Ig (IgE increased), tryptase (marker of mast cell degranulation)
- **ALLERGY TESTING**—radioallergosorbent test, patch testing
- **SKIN BIOPSY**

MANAGEMENT

DISCONTINUE OFFENDING DRUG—see SPECIFIC ENTITIES for further details

SPECIFIC ENTITIES**EXANTHEMATOUS DRUG REACTION**

- **PATHOPHYSIOLOGY**—the most common type of cutaneous drug reaction. Common offenders include penicillins, sulfonamides, carbamazepine, allopurinol and gold
- **CLINICAL FEATURES**—exanthematous rash usually appears within 14 days of drug initiation or 3 days of re-offending drug. The reaction is characterized by the development of symmetric, red, morbilliform rash almost always found on the trunk and extremities, which may be very pruritic. Usually lasts 1–2 weeks

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—identification and cessation of the offending drug. Oral antihistamines for relief of itching. Topical glucocorticoids may speed up recovery. Oral and IV steroids may be used for severe symptoms

URTICARIA AND ANGIOEDEMA

- **PATHOPHYSIOLOGY**—urticaria involves the development of highly pruritic pink wheals. Angioedema is subcutaneous tissue swelling, most prominent on the face (lips, eyelids) and tongue
- **TYPES**—**IgE-mediated type I hypersensitivity reactions** occur within minutes to hours in sensitized patients and are classically associated with penicillin as well as cephalosporins and sulfonamides. Hypotension, bronchospasm, and laryngeal edema may accompany the rash. **Immune-complex mediated reactions** usually occur within 12–36 h of drug exposure in a sensitized individual. Common offenders are penicillins and immunoglobulins. **Non-allergic forms** of urticaria and angioedema occur from drug-induced bradykinin release and/or mast cell degranulation. The reaction typically occurs within 20–30 min of drug administration. Common drugs include NSAIDs, opiates, ACE inhibitors, calcium channel blockers, and radioccontrast
- **TREATMENTS**—cessation of the offending drug. Antihistamines and oral steroids may be used. For acute, life-threatening reactions, ABCs, O₂, **epinephrine** 0.5 mL of 1:1,000 (1 mg/mL) IM, repeat q5min as needed (consider epinephrine 0.01–0.02 mg/h IV for severe/refractory anaphylaxis), NS 1–2 L IV bolus, **salbutamol** 2.5 mg NEB q5min PRN, **dimenhydrinate** 25–50 mg IV, **steroids** (*methylprednisolone* 125 mg IV or *dexamethasone* 20 mg IV). Consider vasopressors if severe shock. **Consult** anesthesia if anticipate difficult intubation or ENT if urgent tracheostomy required

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

- **PATHOPHYSIOLOGY**—an acute, pustular eruption that typically begins in the body folds and/or face and spreads over the trunk and extremities
- **CLINICAL FEATURES**—diffuse, sterile pustules with an edematous, erythematous background. Patients may appear ill with fever and leukocytosis. Most cases begin within 2–3 days of drug administration

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—typically resolves within 2 weeks after the drug is stopped

FIXED DRUG ERUPTION

- **PATHOPHYSIOLOGY**—the appearance of a solitary erythematous patch or plaque within 30 min to 8 h after ingestion of a drug. Offending agents include antibiotics (tetracyclines, sulfonamides), analgesics (NSAIDs, salicylates), and yellow dyes
- **CLINICAL FEATURES**—erythematous, edematous plaques with a grayish center or bullae over genitalia (most common), lips, tongue, face, and acral areas. Characterized by presence of post-inflammatory hyperpigmentation and the recurrence at exactly the same site with reexposure. Lesions may be accompanied by itching or burning
- **TREATMENTS**—cessation of the offending drug and application of topical steroid ointment

CONTACT DERMATITIS

- **PATHOPHYSIOLOGY**—due to topical agents or contact. Type IV delayed hypersensitivity reaction causes allergic contact dermatitis. Non-immunological chemical or physical irritation causes irritant contact dermatitis
- **CLINICAL FEATURES**—erythematous, papular, urticarial, or vesicular pruritic plaques over area of exposure. Well-defined shape correlates with the offending contactant (e.g. nickel, tape, antibiotic ointment). Lichenification with chronic exposure
- **TREATMENTS**—identify and avoid causative agent(s). Emollients (irritant contact dermatitis) and topical steroids (allergic contact dermatitis) may alleviate symptoms

HYPERSENSITIVITY VASCULITIS

- **CLINICAL FEATURES**—macules/papules on lower extremities or back evolving into palpable purpura, bullae, and/or necrosis. May also have fever, myalgia, and arthralgia
- **ACR CRITERIA**—age at disease onset >16 years, medication at disease onset, palpable purpura, morbilliform rash, biopsy including arteriole and venule. Need 3 of 5 criteria (sens 71%, spc 84%)
- **TREATMENTS**—discontinue offending drug

Related Topics

Antibiotics (p. 270)

Penicillin Allergy (p. 274)

Erythema Nodosum

DIFFERENTIAL DIAGNOSIS OF PAINFUL NODULES

PANNICULITIS—erythema nodosum, erythema induratum, Weber–Christian disease (relapsing febrile nodular panniculitis)

INFECTIONS—bacteria, fungi

CUTANEOUS VASCULITIS

SUPERFICIAL THROMBOPHLEBITIS

PATHOPHYSIOLOGY

CAUSES OF ERYTHEMA NODOSUM

- **INFECTIOUS**—bacterial (streptococcal, yersiniosis), atypical (*Chlamydia pneumoniae*), TB, fungal (coccidioidomycosis, histoplasmosis, blastomycosis), leprosy
- **INFLAMMATORY**—IBD, SLE, Behçet
- **INFILTRATIVE**—sarcoidosis, Hodgkin lymphoma
- **IATROGENIC**—oral contraceptive pills, omeprazole, montelukast
- **IDIOPATHIC**

CLINICAL FEATURES

TYPICAL PRESENTATION—painful, erythematous nodules on the anterior surfaces of bilateral shins and sometimes thighs, trunk, and upper extremities. May evolve into bruise-like lesions that resolve without scarring over a 2–8-week

CLINICAL FEATURES (CONT'D)

period. Other symptoms include polyarthralgia, fever, and malaise. Presence of GI symptoms and/or hilar adenopathy may help in narrowing differential

INVESTIGATIONS

BASIC

- **LABS**—CBC, antistreptolysin-O titer, ANA
- **MICROBIOLOGY**—wound C&S, throat C&S (for *Streptococcus*), TB skin test
- **IMAGING**—CXR

SPECIAL

- **DEEP INCISIONAL BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE

SYMPTOM CONTROL—NSAIDs, potassium iodide, glucocorticoids (beware of TB)

Related Topics

Tuberculosis (p. 267)

Fungal Infections (p. 286)

Sarcoidosis (p. 483)

Clubbing

DIFFERENTIAL DIAGNOSIS

RESPIRATORY—lung cancer, lung abscess, bronchiectasis, cystic fibrosis, empyema, mesothelioma, idiopathic pulmonary fibrosis, asbestosis

CARDIAC—cyanotic heart disease, subacute endocarditis

GI—colon cancer, esophageal cancer, inflammatory bowel disease, celiac disease, cirrhosis

OTHERS—hyperthyroidism (thyroid acropachy), hemoglobinopathies, local vascular disease, familial

PATHOPHYSIOLOGY

MECHANISM—proliferation of the connective tissue between the nail matrix and the distal phalanx

STAGES—periungual erythema → spongy nail bed → loss of Lovibond angle → increased phalangeal depth ratio → hypertrophic osteoarthropathy

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE CLUBBING?

INSPECTION—**nail fold profile angle** (angle that nail projects from nail fold, normal $\leq 176^\circ$, simplified to straight line of $< 180^\circ$ for clinical use),

hyponychial nail-fold angle (angle that nail directs toward the nail tip, normal $\leq 192^\circ$, simplified to $< 190^\circ$ for clinical use), **phalangeal depth ratio** (distal phalangeal finger depth/interphalangeal finger depth ratio normal ≤ 1),

Schamroth sign (normal = diamond)

PALPATION—floating nail bed elicited by rocking the distal and proximal nail back and forth

APPROACH—if profile angle $\leq 176^\circ$, hyponychial angle $\leq 192^\circ$ and phalangeal depth ratio ≤ 1 , clubbing is unlikely. Inter-observer agreement of clubbing is highly variable among clinicians (κ 0.39–0.90). “The accuracy of clubbing as a marker of specific underlying disease has been

CLINICAL FEATURES (CONT'D)

determined for lung cancer (likelihood ratio, 3.9 with phalangeal depth ratio in excess of 1.0) and for inflammatory bowel disease (likelihood ratio, 2.8 and 3.7 for active Crohn disease and ulcerative colitis, respectively, if clubbing is present)."

UPDATE—clubbing in cystic fibrosis predictive of hypoxemia (LR+ 3.2)

Myers et al. JAMA 2001;286(3)

Simel et al. The Rational Clinical Examination McGraw-Hill, 2009

INVESTIGATIONS**BASIC**

- **IMAGING**—CXR

SPECIAL

- **CARDIAC WORKUP**—ECG, echocardiogram
- **OTHER ETIOLOGY WORKUP**—CBC, TSH, AST, ALT, ALP, bili

MANAGEMENT**TREAT UNDERLYING CAUSE****SPECIFIC ENTITIES**

HYPERTROPHIC OSTEOARTHROPATHY—clubbing and periarticular pain and swelling, most often affecting the wrists, ankles, and knees. Associated with bronchogenic cancer, chronic pulmonary infections, cystic fibrosis, and cyanotic congenital heart disease

Related Topics

Celiac Disease (p. 142)

Inflammatory Bowel Disease (p. 140)

Lung Cancer (p. 205)

Dupuytren Contracture**DIFFERENTIAL DIAGNOSIS**

DIABETIC CHEIROARTHROPATHY (usually all four fingers)

INTRINSIC JOINT DISEASE

DUPUYTREN CONTRACTURE

VOLKMANN ISCHEMIC CONTRACTURE

TRAUMATIC SCARS

PALMAR FASCIITIS—malignancy (usually bilateral)

PATHOPHYSIOLOGY

RISK FACTORS—alcoholism, smoking, diabetes, repetitive hand motions/vibrations, reflex sympathetic dystrophy, positive family history, Scandinavian/Northern European descent. Most patients are over 50 years of age.

4 STAGES—progressive fibrosis of the palmar fascia → nodules form on the palmar fascia → flexion deformity → fibrosis of dermis leads to skin thickening

CLINICAL FEATURES

HISTORY—finger stiffness (duration, pain, function), past medical history (alcohol, diabetes, smoking, HIV), occupational history

PHYSICAL—most commonly involves the fourth and fifth digits. Triangular puckering of the dermal tissue over the flexor tendon just proximal to the flexor crease of the finger (earliest sign), skin blanching on active finger extension, palpable and visible nodules along flexor tendons, mild tenderness over nodules, fixed flexion contractures, reduced range of motion, tender knuckle pads over the dorsal aspect of the PIP joints

MANAGEMENT

SYMPTOM CONTROL—padded gloves, stretching exercises for mild disease. Triamcinolone or lidocaine injection for moderate disease. Radiation, needle aponeurotomy, collagenase injection or surgery (fasciotomy or fasciectomy) for severe disease



Geriatric-Specific Issues

THE FRAIL ELDERLY

THE CONCEPT OF FRAILTY—no single definition; frailty refers to a state of functional decline in which loss of physiologic reserve makes an individual susceptible to disability from minor stresses. Patients with frailty are at higher risk of complications, such as increased mortality, morbidity, and rates of institutionalization

PATHOPHYSIOLOGY—not well understood; but possibly related to dysregulated immune and endocrine systems, which negatively affect muscle, immune function, metabolism, clotting, and cognition

SCREENING—**Fried Physical Frailty Phenotype** is based on self-reported exhaustion, gait speed, weight loss (>10 lbs), grip strength, and activity level. This instrument requires additional measurement tools and does not take into account cognition. **Edmonton Frail Scale** is based on the comprehensive geriatric assessment, and assesses multiple domains, including cognition, function, social support, nutrition, and comorbidities. **Clinical Frailty Scale** is a graded scale, scored from very fit to severely frail, and based on comorbidities and the need for help with ADLs

TREATMENT—tailored for a patient's specific needs and goals, such as caregiver support, exercise/rehab intervention, medication adjustments, etc

Buta et al. *Ageing Res* 2016;26
Rolfson et al. *Age Ageing* 2006;35(5)

COMPREHENSIVE GERIATRICS ASSESSMENT

In addition to a focused history and physical, special attention should be paid to the following domains, which provide important information for the geriatric assessment:

COMPREHENSIVE GERIATRICS ASSESSMENT (CONT'D)

FUNCTIONAL HISTORY—ADLs (mobility, bathing, dressing, toileting, transferring, maintaining continence, and feeding) and IADLs (transportation, shopping, phoning, laundry, cooking, accounting, housekeeping, medications)

GERIATRIC SYNDROMES/GIANTS—falls (number and mechanism in last year) and mobility, presence of osteoporosis and previous fractures, chronic pain, pressure sores, sleep patterns, mood and behavioral problems, continence (urinary and fecal), nutrition (appetite and weight loss), hearing and visual impairment

COGNITIVE HISTORY—memory, language, executive function, praxis and visuospatial domains. Inquire about behavioral problems (anger, withdrawn, hoarding/sundowning) and safety concerns (driving, using appliances, potential of abuse)

COMORBID CONDITIONS—in addition to the geriatric syndromes, inquire about the number and severity of co-existing diseases that are either life threatening or function limiting

POLYPHARMACY—number of medications, potential medications that can cause delirium and other significant side effects, adherence, assistance with medications, drug interactions (p. 428)

SOCIAL HISTORY—living situation, education, work, family, caregivers at home (ask directly about caregiver stress or burn out), financial stability, access to transportation, personal directives

COGNITIVE EXAMINATION—screen for cognitive impairment with the Mini-Mental State (MMSE) exam or Montreal Cognitive Assessment (MoCA). MMSE is limited in assessing executive function, which can further be evaluated with clock drawing, Frontal Assessment Battery (FAB)

COMPREHENSIVE GERIATRICS ASSESSMENT (CONT'D)

and/or the EXIT test. Delirium can be assessed with the CAM score (see DELIRIUM p. 422)

COMPREHENSIVE GERIATRIC MANAGEMENT—systematic evaluation by a team of health professionals with the aim of identifying treatable health problems and developing a treatment plan that addresses physical health, functional status, psychological health, cognition, and socioenvironmental factors:

Discipline	Task(s)
Dieticians	Nutrition and diet
Nurses	Education and assistance with ADLs, IADLs
Occupational therapists	Cognitive and functional assessments, ADL training
Pharmacists	Medication use
Physicians	Disease management, symptom management, communication and decision making, care planning
Physiotherapists	Training to increase, strength, endurance, coordination, mobility, and balance
Recreational therapists	Maintenance of social roles
Social workers	Counseling, evaluation, and disposition
Speech language therapists	Training in communication and therapy for swallowing disorders

HEALTH CARE AND FINANCIAL PROXY

ADVANCE DIRECTIVE (living will)—a document created when the patient is competent. Allows direction of their care in future (e.g. regarding tube feeding, resuscitation status) if and when they are no longer capable of expressing their own wishes

PERSONAL DIRECTIVE—agent assigned, when patient competent, who can act on patient's behalf regarding decisions for personal care and accommodation when patient lacks capacity

POWER OF ATTORNEY—agent assigned, when patient competent, that can act on patient's behalf regarding finances when patient lacks capacity

HEALTH CARE AND FINANCIAL PROXY (CONT'D)

GUARDIANSHIP—created when patient is incompetent and personal directive not available. Guardian assists with decisions regarding personal care and accommodation

TRUSTEESHIP—created when patient is incompetent and power of attorney not available. Trustee assists with finances

COMPETENCY ASSESSMENT

ENSURE IT IS NECESSARY—usually requires a trigger (e.g. patient is no longer managing money wisely, needs long term care placement but not willing to go)

DIAGNOSED PHYSICAL/MENTAL ILLNESS—chronic vs. acute

OBTAIN RELEVANT COLLATERAL INFORMATION—reliable? Ask what concerns them (ADLs, financial)

PERFORM FORMAL TESTING—ask patient details about comorbidities, ADLs, finances, medical condition, living will. Are their details consistent with reality?

The four elements required for capacity are:

1. Understanding: the ability to comprehend, retain and recall information regarding nature of involvement, risks, alternatives, and effect on outcomes
2. Appreciation: the ability to relate the information above to the patient's own situation, including risks and benefits of proposed situation
3. Reasoning: the ability to weigh the risks and benefits, and to justify a treatment
4. Expression: the ability to articulate a choice with consistency

INFORM AND ACT

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE MEDICAL DECISION MAKING CAPACITY?

	LR+	LR-
Physician Clinical Judgment	7.9	0.61
Measures of Cognitive Ability		
MMSE <16	12	-
MMSE <20	6.3	-
MMSE 20–24	0.87	-
MMSE >24	0.14	-
Capacity Assessment Instruments		
Aid to Capacity Evaluation (ACE)	8.5	0.21

COMPETENCY ASSESSMENT (CONT'D)

	LR+	LR-
Hopkins Competency Assessment Test (HCAT)	54	0
Understanding Treatment Disclosure (UTD)	6.0	0.16

APPROACH—physicians frequently do not identify patients who lack capacity, although capacity is necessary for informed consent. Capacity can be optimized by treating

COMPETENCY ASSESSMENT (CONT'D)

reversible disorders. Measures of cognition (e.g. MMSE) correlate with capacity but are not the only criterion. Multiple instruments are available for capacity assessment; the ACE instrument (understanding the problem, treatment proposed and alternatives, option to refuse treatment, possible consequences of accepting and not accepting treatment, presence of depression and psychosis) has been validated

Sessums et al. JAMA 2011;306(4)

Mild Cognitive Impairment and Dementia

Livingston et al. *Lancet* 2020;396(10248)

Ismail et al. *Alzheimers Dement* 2020;16(8)

DIFFERENTIAL DIAGNOSIS**MILD COGNITIVE IMPAIRMENT AND DEMENTIA**

- **MILD COGNITIVE IMPAIRMENT (MCI)**—defined as some loss of cognition (ability to think, understand, and reason), but not interfering with function (ADLs and IADLs)
- **ALZHEIMER DEMENTIA**—general sequence of changes include mood alterations and slow progressive cognitive decline; primarily affecting memory, language and visuospatial domains early on; early motor symptoms rare but may have apraxia later; loss of functional autonomy, neuropsychiatric manifestations, and parkinsonism may be seen in more advanced disease. CT may show white matter change, mostly a diagnosis of exclusion, but accounting for 60% of dementias
- **VASCULAR DEMENTIA**—acute stepwise or slow progressive decline; may have focal neurological deficits; MMSE patchy; CT may show white matter change; pure vascular dementia uncommon; more frequently occurs with Alzheimer-like dementia (mixed dementia)
- **LEWY BODY DEMENTIA**—progressive memory decline, parkinsonism, visual hallucinations, fluctuating cognition (especially attention/alertness), visuospatial domain often markedly impaired, supportive features include adverse hypersensitivity to typical antipsychotic medications, syn-

DIFFERENTIAL DIAGNOSIS (CONT'D)

- cope, falls, delusions, and REM sleep disturbance
 - **FRONTO-TEMPORAL LOBE DEMENTIA**—age usually <60; behavioral symptoms noticeable before cognitive impairment disinhibited or passive presentation, impaired judgment, significant social indifference, declining hygiene, prominent language deficits but amnesia less noticeable early on; early primitive reflexes/incontinence, late akinesia/rigidity/tremor, impaired executive function, MMSE may be normal; CT shows frontal temporal atrophy
 - **PARKINSON DISEASE DEMENTIA**—Parkinson disease diagnosed for more than one year prior to cognitive onset; slow decline; Parkinson patients have 6 × increased risk for dementia
 - **PRION DISEASE**—Creutzfeldt–Jakob disease
- POTENTIALLY REVERSIBLE DEMENTIA (<1%)**
- **METABOLIC**—alcoholism, vitamin B12, thiamine deficiency, hypothyroidism, heavy metal toxicity, hepatic encephalopathy, uremia, Wilson disease
 - **STRUCTURAL**—normal pressure hydrocephalus (NPH), subdural hemorrhage, neoplastic, vascular, stroke
 - **INFECTIONS**—chronic meningitis, HIV, neurosyphilis, Whipple, Lyme disease
 - **INFLAMMATORY**—vasculitis, multiple sclerosis
- DEMENTIA MIMICS**—depression, delirium, developmental disorder, Parkinson plus syndromes

CLINICAL FEATURES

DISTINGUISHING FEATURES OF COMMON DEMENTIAS

	Alzheimer	Vascular	Frontal-temporal lobe	Lewy body
Affected Cognitive Domains	Memory affected early on; global cognitive impairment over time	Patchy changes; often impaired executive function	Executive function impaired early on; behavioral symptoms prominent; compulsive and bizarre behavior	Visuospatial domains may be affected early on
Signs and Symptoms	Physical function often normal early on; apraxia occurs later on	Focal neurological signs (e.g. upgoing Babinski)	Positive primitive reflexes; apathy	REM sleep disorders, visual hallucinations, parkinsonian motor features, frequent falls, neuroleptic sensitivity
Screening	Tests for poor recall memory very sensitive, especially MoCA	Patchy deficits; greater executive dysfunction and less prominent memory dysfunction	Cognitive screens often normal	Visuospatial / constructional impairment
Imaging Findings	Hippocampal and medial temporal lobe atrophy	Previous strokes or small vessel ischemic changes	Often normal early on; progresses to variable frontal temporal atrophy	Generalized nonspecific cortical atrophy, PET shows hypometabolism, especially in occipital regions
Course	Gradual cognitive decline	Sudden stepwise regression	Insidious, early onset	Fluctuating with progressive decline

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, creatinine, HbA1c, Ca, TSH, vitamin B12
- **IMAGING**—CT head

SPECIAL

- **LABS**—ALT, ALP, bilirubin, RBC folate, VDRL, HIV serology, urine collection for heavy metals
- **CEREBROSPINAL FLUID**—not routinely recommended, but sometimes used if early onset (<65 years) dementia

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE DEMENTIA?

INVESTIGATIONS (CONT'D)

MINI-MENTAL STATE EXAMINATION

(MMSE)—orientation to place (5), time (5), immediate and delayed recall (6), spell “WORLD” backward (5), 3 step command (3), name two objects (2), close your eyes (1), repeat sentence “No ifs, ands, or buts” (1), write a sentence (1), intersecting pentagons (1). Maximum score is 30, generally <24 is impaired but varies with education and age

MEMORY IMPAIRMENT SCREEN—recall four objects (an animal, a city, a vegetable, and a musical instrument). Two points for free recall of each object and one point if prompting needed (“Tell me the name of the city”). Maximum score is 8. Takes 4 min

INVESTIGATIONS (CONT'D)**SELECTED TOOLS**

	LR+	LR-
MMSE	6.3	0.19
Reports from an informant that the patient has memory loss	6.5	
Memory impairment screen	33	0.08
Clock drawings	1.2–7.7	0.13–0.71

APPROACH—to detect cognitive impairment of at least moderate severity, consider the Mini-Mental State Examination. If very little time is available, consider the Memory Impairment Screen or the Clock Drawing Test. If plenty of time is available, consider the Cambridge Cognitive Examination, Modified Mini-Mental State Examination, Community Screening Interview for Dementia, or the Montreal Cognitive Assessment

Holsinger et al. JAMA 2007;297(21)

DIAGNOSTIC ISSUES

DSM-5 CRITERIA FOR MAJOR NEUROCOGNITIVE DISORDER—most commonly used criteria in clinical practice. The term “major neurocognitive disorder” is used interchangeably with dementia:

1. A decline in one or more cognitive domains: learning and memory, language, executive function, complex attention, perceptual-motor or social cognition
2. Cognitive deficits must impair at least one IADL
3. Cognitive deficits do not occur during delirium and are not better explained by another psychiatric disorder

While declining memory was historically a central component of dementia, the DSM-5 places equal weight on all six cognitive domains. Note: vascular dementia, fronto-temporal lobe dementia, and Lewy body dementia have their own distinct criteria

BRIEF COGNITIVE TESTING BATTERIES—used to quantify the severity of disease and brief enough to be done in a clinical setting. Cognitive screens cannot replace history obtained from family, and cannot assess mood and thoughts

- **MMSE**—30 point screening test. Traditional threshold ≤ 23 suggests dementia (LR+ 6–8) in the absence of delirium. Newer thresholds: ≤ 20 rules in dementia (LR+ 14.5), ≥ 26 rules

DIAGNOSTIC ISSUES (CONT'D)

out dementia (LR+ 0.1), 21–25 inconclusive. The scale is most sensitive for patients with mild to moderate dementia. Drawbacks are that it is poor at detecting MCI as well as frontal and executive deficits. It is confounded by age, education, and ethnicity. Use is limited by copyright, but the “standardized” MMSE is still free

- **MoCA**—also a 30 point test, but more sensitive for detecting MCI compared to MMSE, as it assesses executive function. MoCA scores are consistently lower than the MMSE; < 25 is considered abnormal in patents with less than 12 years of education. Use of MoCA requires training course
- **CLOCK DRAWING**—a test of constructional apraxia that covers several cognitive domains. Several scoring methods: the Wolf–Klein method provides patient with paper and pre-printed circle (4 in. in diameter) and instructions to “draw a clock.” The time must always be stated as “10 after 11.” “Normal” clock has numbers clockwise in correct order and near the rim, even without hands on clock. Abnormal clock drawing argues for dementia (LR+ 5.3). Normal clock drawing not useful (as half of demented patients can produce normal clock)

CRITERIA FOR PERFORMING NEUROIMAGING—age < 60 , rapid (1–2 months) unexplained decline in cognition or function, dementia of short duration (< 2 years), unexplained neurological symptoms (e.g. new onset headache or seizures), early incontinence/gait disorder (NPH), recent head trauma, history of cancer, use of anticoagulants or history of bleeding disorder, new localizing signs, unusual or atypical cognitive symptoms or presentation (e.g. progressive aphasia), significant vascular risk factors

- **ANATOMICAL**—MRI generally preferred over CT, due to higher sensitivity for vascular lesions. If CT performed, non-contrast study assessing hippocampal volume preferred
- **FUNCTIONAL**—PET amyloid imaging helpful for diagnosing Lewy body dementia, but limited by costs

MANAGEMENT

RISK REDUCTION—strongest evidence is for physical activity and treatment of hypertension (see HYPERTENSION p. 70). Also consider consuming Mediterranean diet, treating hearing impairment, avoiding sleep deprivation (< 5 hrs), treating

MANAGEMENT (CONT'D)

obstructive sleep apnea, cognitive training, social engagement, and avoiding air pollutants, but no RCT evidence for these latter interventions

DISEASE MANAGEMENT—acetylcholinesterase inhibitors may be considered for Alzheimer and mixed dementias, including *donepezil* 5–10 mg PO nightly, *rivastigmine* 1.5–6 mg PO BID, and *galantamine ER* 8–24 mg daily. Avoid if seizures, cardiac conduction abnormalities, significant asthma, CHF, COPD, or recent GI bleed.

N-methyl-D-aspartate receptor antagonist, memantine 5–10 mg PO BID, may be used for moderate-to-severe dementia as a single agent or as add-on therapy to an acetylcholinesterase inhibitor, and can be especially helpful for ameliorating behavioral symptoms

SYMPTOM MANAGEMENT—treat problem behaviors with non-pharmacological and pharmacological approaches (trazodone, atypical antipsychotics). Treat co-existing depression

TUBE FEEDING—generally not recommended for advanced dementia because of increased complications without evidence of clinical benefit (e.g. survival, quality of life, prevention of aspiration pneumonia, reduction of pressure sores or infections, functional improvement)

SPECIFIC ENTITIES**LESS COMMON CAUSES OF DEMENTIA**

- **NORMAL PRESSURE HYDROCEPHALUS (NPH)**
 - **PATHOPHYSIOLOGY**—inflammation and fibrosis of the arachnoid granulations → decreased absorption of CSF → hydrocephalus → nor-

SPECIFIC ENTITIES (CONT'D)

mal opening pressure but elevated pressure over periventricular white matter tracts

- **CAUSES**—idiopathic or secondary (e.g. subarachnoid hemorrhage, chronic meningitis)
- **CLINICAL FEATURES**—classic triad of gait apraxia (magnetic gait as feet are stuck to floor), urge incontinence, and cognitive decline. Also may have postural instability, lower extremity spasticity, hyperreflexia, and extensor plantar responses
- **DIAGNOSIS**—clinical diagnosis and MRI. Improvement of gait or cognition 1 h after removal of 30–50 mL of CSF can be helpful for diagnosis (Fisher test, PPV 90–100%, NPV 30–50%). An improvement also predicts responsiveness to shunting
- **TREATMENTS**—lumbar puncture, shunts (ventriculoperitoneal, ventriculoatrial, lumboperitoneal)
- **PARKINSON-PLUS SYNDROMES**—include progressive supranuclear palsy, multiple system atrophy and corticobasal ganglionic degeneration
- **CREUTZFELDT-JAKOB DISEASE**—rapid progression, characteristic EEG, myoclonic jerks, and expected death in 6–12 months
- **HUNTINGTON DEMENTIA**—autosomal dominant with incomplete penetrance; premorbid DNA testing quantifies risk, severity, and age of onset

CORTICONUCLEAR DEGENERATION—marked visual-spatial impairment, substantial apraxia, but memory impairment less noticeable

DeliriumInouye *NEJM* 2006;354(11)**DIFFERENTIAL DIAGNOSIS****★DIMS★****DRUGS ★ABCD★**

- **ALCOHOL**—intoxication, withdrawal, Wernicke–Korsakoff syndrome
- **ANTICHOLINERGICS**—atropine, benztropine, scopolamine
- **ANTIDEPRESSANTS**—SSRIs, TCAs
- **ANTICONSULSANTS**—carbamazepine, phenytoin, valproate, phenobarbital
- **ANALGESICS**—opioids, NSAIDs, steroids
- **ANTIBIOTICS**—penicillins, quinolones, sulfonamides, isoniazid, rifampin, streptomycin, chloroquine, acyclovir
- **ANTI-HISTAMINES**—cimetidine, famotidine, ranitidine

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **BENZODIAZEPINES AND BARBITURATES**—intoxication, withdrawal
- **CARDIAC**—amiodarone, β -blockers, digoxin, diuretics
- **DOPAMINE AGENTS**—amantadine, bromocriptine, levodopa

INFECTIOUS—pneumonia, UTI, meningitis, encephalitis, abscess, sepsis

METABOLIC

- **ORGAN FAILURE**—hepatic, azotemia, hypothyroidism or thyrotoxicosis, hypoxia, hypercapnia, hypothermia, hypertensive
- **ELECTROLYTE IMBALANCE**—ketoacidosis, glucose (hypo, hyper), hyponatremia, hypernatremia, hypomagnesemia, hypercalcemia

DIFFERENTIAL DIAGNOSIS (CONT'D)**STRUCTURAL**

- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral
- **STROKE**—basilar
- **TUMOR**
- **ABSCESS**

SEIZURES—non-convulsive status epilepticus, post-ictal

PATHOPHYSIOLOGY

HOSPITALIZATION—elderly hospitalized patients are at high risk of developing delirium; 15% of all medical and surgical inpatients become delirious (with up to 30% of those on geriatric wards and 50% of patients after hip fracture)

DISTINGUISHING FEATURES BETWEEN DELIRIUM AND DEMENTIA

	Delirium	Dementia
Onset	Abrupt	Insidious
Course	Fluctuating, usually reversible	Slowly progressive and usually irreversible
Duration	Days to weeks	Years
Level of consciousness	Hyperactive or hypoactive	Affected in late stages
Attention span	Often affected	Affected in late stages
Orientation	Usually affected	Usually affected
Memory	May be affected	Usually affected
CT head	May be normal; structural changes	White matter changes, atrophy

PATHOPHYSIOLOGY (CONT'D)**DELIRIUM SUBTYPES**

- **HYPERACTIVE DELIRIUM**—characterized by agitation and/or hallucinatory symptoms
- **MIXED DELIRIUM**—variable course with alternating hyperactive and hypoactive features. The majority of patients with delirium fall under this category
- **HYPOLACTIVE DELIRIUM**—characterized by excessive drowsiness and decreased level of consciousness. May mimic depression

COMPLICATIONS—delirium can have a negative impact on patients' quality of life, symptom expression, emotions, and decision-making ability. Delirium is associated with a 25–30% mortality, increased morbidity, increased length of stay, and need for a higher level of care

CLINICAL FEATURES

CONFUSION ASSESSMENT METHOD (CAM)—positive test argues strongly for delirium (LR + 10.3) and negative test argues against delirium (LR – 0.2). Positive test requires both major criteria 1+2 and either of the minor criteria 3 or 4 ★AIDS★

CLINICAL FEATURES (CONT'D)

1. **ACUTE ONSET AND FLUCTUATING CONFUSION**—abnormal behaviors come and go, ↑/↓ severity
2. **INATTENTION**—difficulty focusing/difficulty following conversation (serial subtraction with distraction)
3. **DISORGANIZED THINKING**—rambling, irrelevant, illogical conversation
4. **SENSORIUM CHANGE (ALTERED LOC)**—agitated, hyperalert, lethargic, stuporous, or comatose

EXAMINATION OF THE DELIRIOUS PATIENT—in addition to general physical and neurological examinations, obtain a baseline MMSE (useful for monitoring)

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, Cr, glucose, Ca, thiamine
- **URINE**—urinalysis
- **IMAGING**—CXR, CT head
- **MICROBIOLOGY**—urine C&S, blood C&S (if any fever)

INVESTIGATIONS (CONT'D)**SPECIAL**

- **METABOLIC WORKUP**—TSH if suspect thyroid disease, ALT, ALP, bilirubin, INR, ammonia if suspect liver disease, Mg, PO₄
- **CARDIAC WORKUP**—ECG, CK, troponin if suspect ACS
- **SEIZURES WORKUP**—EEG
- **DRUG OVERDOSE WORKUP**—urine drug screen, medication serum levels (e.g. digoxin, phenytoin, salicylate, acetaminophen), alcohol level, serum osmolality (osmolar gap)
- **MENINGITIS WORKUP**—lumbar puncture

DIAGNOSTIC ISSUES

PERSISTENT DELIRIUM—if delirium persists despite basic workup, think through differential diagnosis again (**very carefully**). A sudden-onset of delirium after initial improvement is usually due to underlying infection. Severe hyperactive delirium is usually drug-related, or due to alcohol or benzodiazepine withdrawal. Ask caregivers/family about baseline cognitive changes or pre-existing sundowning. Also consider dehydration, depression, urinary/fecal retention, abscess, sleep deprivation, environmental factors (i.e. hospitalization) as potential contributors. Inadequate pain control has also been proposed as a precipitant of delirium

MANAGEMENT

PREVENTION—ensure adequate O₂, fluid and electrolyte balance, pain management, reduction in use of psychoactive drugs, bowel and bladder function, nutrition, early mobilization, prevention of postop complications, stable orientating environment, treatment of symptoms of delirium, and optimizing sleep

TREAT UNDERLYING CAUSE—discontinue offending medications. Delirium may take days/weeks to resolve even after the precipitating cause is removed and treated

NON-PHARMACOLOGICAL MEASURES—reduce noise, orient patient frequently, early mobilization, provide proper hearing and visual

MANAGEMENT (CONT'D)

aids, provide clock/calendar and familiar objects (personal photos) and people (family), supervision for meals, restoration of day–night cycle (optimal lighting during day, promote sleep hygiene at night), avoidance of unnecessary interventions (physical or chemical restraints, urinary catheters, central lines)

PHARMACOLOGICAL MEASURES—**neuroleptics** are often used for restlessness/agitation, visual hallucinations or unsafe behavior. Indications for antipsychotics need to be reassessed on a daily basis. High potency antipsychotics are generally preferred because of their low anticholinergic activity and minimal effect on blood pressure. First generation antipsychotics (*haloperidol* 0.25–2 mg PO/IV/SC q4–6h, *chlorpromazine* 12.5–25 mg IV q4–6h) have been extensively studied but are associated with extra-pyramidal side effects. Second generation antipsychotics have been shown to be equivalent in efficacy (*olanzapine* 2.5–10 mg PO daily PRN, *quetiapine* 25 mg PO BID PRN). In patients with Parkinson or Lewy body dementia, quetiapine is preferred due to its lower risk of extrapyramidal symptoms.

Benzodiazepines may precipitate or worsen delirium and should generally be avoided except for patients with terminal agitated delirium, alcohol or benzodiazepine withdrawal

TREATMENT ISSUES

CONSENT FOR TREATMENT—if patient delirious and need to clarify direction of care, try to find agent for personal directive and/or proxy. If not available, consider calling closest family to discuss treatment options

Related Topics

Alcohol Withdrawal (p. 478)
 Hypercalcemia (p. 388)
 Meningitis (p. 257)
 Metabolic Acidosis (p. 94)
 Overdose (p. 120)

Falls

Gregg et al. *J Am Geriatr Soc* 2000; 48(8)
Tinetti *NEJM* 2003;348(1)

DIFFERENTIAL DIAGNOSIS

SYNCOPE—neurogenic, cardiogenic, neurocardiogenic

DROP ATTACKS—transient vertebrobasilar insufficiency

POSTURAL HYPOTENSION

CONFUSION—delirium

DIZZINESS—vertigo, disequilibrium

FALLS—accidental, imbalance

PATHOPHYSIOLOGY

PREDISPOSITION TO FALLS IN ELDERLY—multi-factorial in nature; 50% of patients who fall do so repeatedly. Multiple falls are a marker for other underlying factors, including chronic diseases and functional disability

- **HIGHER CORTICAL/CNS**—decreased reaction time
- **VESTIBULAR SYSTEM**—decreased balance
- **VISUAL SYSTEM**—presbyopia, decreased peripheral vision, and accommodation
- **AUTONOMIC SYSTEM**—postural hypotension
- **SOMATOSENSORY SYSTEM**—decreased sensation, proprioception, vibration perception
- **MUSCULOSKELETAL SYSTEM**—weakness
- **GAIT INCOORDINATION**—Parkinson, cerebellar ataxia, stroke, NPH
- **MEDICATIONS** (strongest risk factor for falls)—SSRIs, TCAs, neuroleptics, anticonvulsants, benzodiazepines, class IA antiarrhythmics, narcotics
- **ENVIRONMENT**
- **PRECIPITANTS**—infection, infarction, medications, social stress

COMMUNITY DWELLING—41% of falls secondary to environment (trips, slips), 13% weakness or gait/balance disorder

NURSING HOME DWELLING—26% of falls secondary to weakness, gait/balance disorder, 16% environment related

COMPLICATIONS—institutionalization, fear of recurrent falls, prolonged immobility (risk for dehydration, pressure sores, pneumonia, rhabdomyolysis), and death

CLINICAL FEATURES

HISTORY—★**SPLAT**★ Symptoms associated with fall (circumstances, onset, frequency), Previous falls, Past medical history, Location, Activity preceding fall, Toxins (meds), and Trauma
PHYSICAL—vitals (postural HR and BP, temperature), cardiovascular (murmurs, rhythm, volume status), respiratory (adventitious sounds),

CLINICAL FEATURES (CONT'D)

musculoskeletal (strength in knee/hip extensors, joint stability and range of motion, pain, feet, footwear, walking aids), neurologic (focal signs, vision/hearing, cerebellar, sensory), cognitive exam (MMSE, CAM)

EVALUATION OF GAIT AND BALANCE

- **TIMED UP AND GO TEST**—rise from chair, walk 10 ft (3 m), turn, and return to chair. Should finish in less than 10 s. If takes >20 s, further evaluation required
- **TINETTI PERFORMANCE-ORIENTED MOBILITY ASSESSMENT (POMA)**—easy to administer, incorporates gait and balance scales to identify high risk of falls, score $\leq 20/28$ predictive of recurrent falls
- **SELF-REPORTED HISTORY**—(1) Have you fallen two or more times? (2) Have you presented to the emergency department with a fall? (3) Do you have problems with walking or balance? A positive answer to any of these questions indicates a high-risk for falls

RATIONAL CLINICAL EXAMINATION SERIES: WILL MY PATIENT FALL?

	LR+
Fallen in the past year	2.3–2.8
Clinically detected abnormalities of gait or balance	1.7–2.4
Age, visual impairment, medication variables, decreased activities of daily living, and impaired cognition did not consistently predict falls across studies. Orthostatic hypotension did not predict falls after controlling for other factors	

APPROACH—“Screening for risk of falling during the clinical examination begins with determining if the patient has fallen in the past year. For patients who have not previously fallen, screening consists of an assessment of gait and balance. Patients who have fallen or who have a gait or balance problem are at higher risk of future falls.”

Ganz et al. *JAMA* 2007;297(1)

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, Cr, glucose, TSH, CK, urinalysis
- **IMAGING**—CT head

INVESTIGATIONS (CONT'D)**SPECIAL**

- **CARDIAC WORKUP**—orthostatic vitals, ECG, Holter monitor if suspect arrhythmia
- **SEIZURES WORKUP**—EEG
- **NEUROLOGIC WORKUP**—EMG/NCS if significant weakness thought to be related to peripheral lesion

MANAGEMENT

PREVENTION—education (shoes with thin soles, avoid hot tubs, drink 1.5–2 L/day, getting up slowly). **Exercise** (balance and gait training,

MANAGEMENT (CONT'D)

muscle strengthening, day programs). **Environmental assessment** (remove loose rugs, non-slip bath mats, lighting, stair rails). **Tapering and discontinuation of medications**, if appropriate. **Referral** (physiotherapy, occupational therapy, ophthalmology, geriatrics, cardiology if appropriate). **Treatment and prevention of osteoporosis** (see OSTEOPOROSIS p. 389)

Osteoporosis

See OSTEOPOROSIS (p. 389)

Urinary IncontinenceHogan *CMAJ* 1997;157(8)
Rogers *NEJM* 2008;358(10)**DIFFERENTIAL DIAGNOSIS OF CHRONIC URINARY INCONTINENCE**

URGE (most common. Sudden, uncontrollable. Associated with urinary frequency and nocturia)

- **IDIOPATHIC**
- **NEUROLOGIC/DETRUSOR HYPERREFLEXIA**—normal pressure hydrocephalus, dementia, stroke
- **GU BLADDER/DETRUSOR INSTABILITY**—infection, stone, tumor, inflammation

STRESS (small volumes with ↑ abdominal pressure, e.g. coughing, sneezing, laughing)

- **URETHRAL HYPERMOBILITY**—childbirth, menopausal
- **SPHINCTER WEAKNESS**—post-TURP

OVERFLOW (over-distended bladder, small volumes but continuous leakage, incomplete emptying)

- **BLADDER OUTLET OBSTRUCTION**—BPH, prostate cancer
- **URETHRAL/BLADDER NECK STRICTURE**
- **DETRUSOR HYPOCONTRACTILITY**—peripheral neuropathy, alcohol, herniated disc, spinal stenosis, fibrotic detrusor

MIXED/DETRUSOR HYPERACTIVITY WITH IMPAIRED CONTRACTILITY (DHIC)—combines symptoms of urge and overflow incontinence with frequency and large volume, usually late stages of above (e.g. BPH or diabetes mellitus)

DIFFERENTIAL DIAGNOSIS OF CHRONIC URINARY INCONTINENCE (CONT'D)

FUNCTIONAL (reduced mobility, inability to ambulate to toilet)

DIFFERENTIAL DIAGNOSIS OF TRANSIENT URINARY INCONTINENCE★ **DIAPERS** ★**DELIRIUM**

INFECTION—symptomatic UTI

ATROPHIC VAGINITIS/URETHRITIS

PROSTATE

PHARMACY—diuretics, benzodiazepines, alcohol

PSYCHOLOGICAL

ENDOCRINE—hypercalcemia, diabetes mellitus, diabetes insipidus

RESTRICTED MOBILITY**STOOL IMPACTION****PATHOPHYSIOLOGY****PHYSIOLOGY OF URINATION**

- **DETRUSOR MUSCLES**—parasympathetic S234 (contract), β2 sympathetic T10-L2 (relax)
- **INTERNAL SPHINCTER**—α1 sympathetic T10-L2 (contract)
- **EXTERNAL SPHINCTER**—somatic S234 (contract)

PATHOPHYSIOLOGY (CONT'D)**RATIONAL CLINICAL EXAMINATION SERIES: WHAT TYPE OF URINARY INCONTINENCE DOES THIS WOMAN HAVE?**

	LR+	LR-
STRESS INCONTINENCE		
Simple question: "Do you lose urine during sudden physical exertion, lifting, coughing or sneezing?"	2.2	0.39
Filled bladder stress test (fill bladder with 200 cc of saline, supine, and observe while cough)	9.4	0.07
Systematic assessment	3.7	0.20
URGE INCONTINENCE		
"Do you experience such a strong and sudden urge to void that you leak before reaching the toilet?"	4.2	0.48

APPROACH—"... a systematic approach that includes a history, physical examination, and stress test increases the likelihood of correctly classifying the type of incontinence... The most helpful component of the assessment for determining the presence of urge incontinence is a history of urine loss associated with urinary urgency..." A filled bladder stress test "may be helpful for diagnosing stress incontinence... For primary care physicians unable to perform stress tests in their office, it would be reasonable to refer patients for further evaluation when a diagnosis is needed with more certainty. Measurement of the post-void residual urine volume detects incomplete bladder emptying, but no data support using this in women for separating out incontinence type."

Holroyd-Leduc et al. JAMA 2008;299(12)

INVESTIGATIONS**BASIC**

- **VOIDING DIARY**—with frequency and volume
- **LABS**—lytes, Cr, glucose, Ca, urinalysis
- **MICROBIOLOGY**—urine C&S

INVESTIGATIONS (CONT'D)

- **POST-VOID RESIDUAL VOLUME**—to determine if bladder outlet obstruction or reduced detrusor contractility

SPECIAL

- **URODYNAMIC STUDIES**—cystometry, urinary flow measures, and urethral pressure profiles

MANAGEMENT OF CHRONIC URINARY INCONTINENCE

GENERAL MEASURES—avoid alcohol and caffeine, weight loss (if overweight/obese), minimize anticholinergics, sedatives, and diuretics (if possible), supervised pelvic floor physiotherapy several times a day (but not appropriate for cognitively impaired or those with significant frailty), prompted or scheduled voids (including double voiding), bedside urinal/commode (if restricted mobility)

- **ABSORPTIVE PADS**—incontinence pad or adult diapers
- **CATHETERIZATION**—indwelling catheter, condom catheter, timed collection, intermittent self-catheterization

MEDICATIONS

- **URGE OR MIXED INCONTINENCE**—**antimuscarinics** (*tolterodine* 1–2 mg PO BID, *solifenacin* 5–10 mg PO daily, or *darifenacin* 7.5–15 mg PO daily) are generally well-tolerated in older females and those with frailty. Should be reviewed after 8 weeks, and discontinued if no improvement. Common side effects include dry mouth, constipation and dizziness. Renal dosing advised. **β3 adrenoreceptor agonist** (*mirabegron* 25 mg PO daily, increased to 50 mg PO daily after 8 weeks if needed), as an alternative if antimuscarinics not tolerated. Risk of urinary retention if combined with antimuscarinic. Renal dosing advised
- **OVERFLOW INCONTINENCE**—**α1-adrenoreceptor antagonists** (*tamsulosin* 0.4–0.8 mg PO nightly, *terazosin* 1–5 mg PO nightly, or *doxazosin* 1–4 mg PO nightly) for symptomatic benign prostatic hypertrophy. **5-α reductase inhibitors** (finasteride or dutasteride) if prostate volume >40 mL

Pharmacological Issues in the Elderly

Beers Expert Panel. *J Am Geriatr Soc* 2019;67

Thevelin et al. *Drugs Aging* 2019;36(5)

PRINCIPLES OF DRUG USE IN THE ELDERLY

PRINCIPLES OF PHARMACOLOGY—elderly are at increased risk of adverse drug reactions because of altered physiology of aging, multiple co-existing illnesses, reduced homeostatic reserve, polypharmacy, and medical error. Of the 4 key components of pharmacokinetics (absorption, distribution, metabolism, excretion), only the last 3 are meaningfully affected by age. Pharmacokinetic changes are related to decreased renal (most important) and hepatic function (phase I reactions ↓, phase II reactions unaffected), decreased lean body mass (↑ fat), decreased total body water, and increased total body fat

COMPLICATIONS—falls, delirium, incontinence, renal impairment, heart failure, gastrointestinal hemorrhage, hypoglycemia, drug–drug interactions

PRESCRIBING PRINCIPLES—initiate most medications at half usual starting dose, increase dose slowly. Carry out regular medication reviews and stop any unnecessary medications. Avoid medications with known significant side effects in the elderly. Avoid treating adverse drug reactions with further drugs

UNDER-PRESCRIBING IN THE ELDERLY

REASONS FOR UNDER-PRESCRIBING—under-recognition of medication benefit in older patients, affordability, and dose availability (i.e. requiring a dose of medication that is smaller than supplied by the manufacturer, resulting in more complicated dosing strategies such as once every other day)

OVER-PRESCRIBING IN THE ELDERLY

POLYPHARMACY AND DRUG INTERACTIONS—57% of elderly use >5 drugs per week, 19% use >10 drugs per week; 1 in 25 are at risk for major drug–drug interaction, nearly half involve use of anticoagulants or antiplatelet agents

BEERS LIST 2019—list of designated drugs that fall in one of three categories: 1) should **always** be avoided (e.g. barbiturates); 2) drugs that are potentially inappropriate (e.g. glyburide), and 3) drugs

OVER-PRESCRIBING IN THE ELDERLY (CONT'D)

that should be used with caution (e.g. SSRIs). Several deficiencies in the Beers criteria have been noted including potential drug–drug interactions and prescribing-omission errors. The STOPP (Screening Tool of Older Persons' Prescriptions) and START (Screening Tool to Alert to Right Treatment) were consequently developed. These criteria are organized by physiological systems

SUPPLEMENTS—49% of elderly use herbal or dietary supplements and are at increased risk of herb–drug interaction (e.g. ginkgo biloba and warfarin resulting in increased bleeding risk)

AVOID TREATING ADVERSE DRUG REACTIONS WITH FURTHER DRUGS—medications are often inappropriately prescribed to symptomatically treat side effect of another medication. For example, metoclopramide → extrapyramidal effects → levodopa. Metoclopramide users are >3 times more likely to be prescribed levodopa compared to non-users, a treatment generally reserved for management of idiopathic Parkinson disease

COMMON ADVERSE DRUG REACTIONS AND DRUG–DRUG INTERACTIONS

CHARACTERISTIC SIDE EFFECTS OF DRUGS FREQUENTLY USED IN THE ELDERLY

Drugs	Adverse effects
α1 blockers (e.g. doxazosin)	Falls, orthostatic hypotension, dry mouth
Anticholinergics (e.g. diphenhydramine)	Delirium, urinary retention, constipation, dry mouth, blurred vision, postural hypotension
Benzodiazepines (e.g. lorazepam)	Falls, confusion
NSAIDs (e.g. indomethacin)	Gastrointestinal irritation and hemorrhage, renal impairment, hypertension, heart failure

COMMON ADVERSE DRUG REACTIONS AND DRUG-DRUG INTERACTIONS (CONT'D)

Drugs	Adverse effects
Sulfonylureas (chlorpropamide)	Hypoglycemia
Tricyclic antidepressants (e.g. amitriptyline)	Falls, orthostatic hypotension, sedation, delirium, arrhythmias

WARFARIN INTERACTIONS—many medications implicated in increasing bleeding risk (↑ INR) with warfarin. Most severe interactions described with trimethoprim-sulfamethoxazole, erythro-

COMMON ADVERSE DRUG REACTIONS AND DRUG-DRUG INTERACTIONS (CONT'D)

mycin, amiodarone, propafenone, ketoconazole, fluconazole, itraconazole, metronidazole. Antibiotics, acetaminophen, steroids, and ginkgo biloba may also increase bleeding risk

GRAPEFRUIT JUICE INTERACTIONS—grapefruit interferes with drugs that are metabolized by CYP3A4, including statins (simvastatin/lovastatin > atorvastatin), calcium channel blockers, and benzodiazepines

HEART FAILURE PRECIPITANTS AND EXACERBANTS—NSAIDs (>2 times risk for admission for HF, correlating with dose of drug), thiazolidinediones, sodium polystyrene sulfonate



Palliative Care-Specific Issues

Hui et al. *CA Cancer J Clin* 2018;68(5)

INTRODUCTION

DEFINITION OF PALLIATIVE CARE—according to the World Health Organization, palliative care is “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual... Palliative care is applicable *early* in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications”

DEFINITION OF END OF LIFE—6 months or less of life expectancy

DEFINITION OF TERMINALLY ILL—6 months or less of life expectancy

RELIEF OF SUFFERING—suffering is defined as “the state of severe distress associated with events that threaten the intactness of the person.” Living with advanced disease inevitably involves variable degrees of physical, psychosocial, and existential suffering. Palliative care aims at alleviating this suffering through the provision of interdisciplinary comprehensive care from the time of diagnosis to death

INTRODUCTION (CONT'D)

TIMELY REFERRAL TO PALLIATIVE CARE—palliative care teams have significant expertise in managing symptoms, providing psychosocial and spiritual care, facilitating complex communication and decision making and supporting caregivers. Because patients with life-limiting diseases such as advanced stage cancer, COPD, heart failure, chronic kidney disease, and liver failure often have significant symptom burden and other supportive care needs throughout the disease trajectory, these patients should be referred to palliative care from the *time of diagnosis* rather than only in the last weeks or months of life. In randomized controlled trials, timely outpatient palliative care referral can significantly improve quality of life, increase patient and caregiver satisfaction, reduce psychological distress, facilitate care planning and enhance the overall quality of care

SYMPTOM COMPLEX AND ASSESSMENT

SYMPTOM COMPLEX—patients with advanced disease typically experience multiple symptoms at the same time. In addition to underlying disease and associated symptom burden, expression of symptoms is modulated by patients’ psychosocial and existential distress, cultural background, personality, past experiences, and comorbidities

SYMPTOM PREVALENCE IN TERMINALLY ILL PATIENTS

Symptom	Cancer (%)	AIDS (%)	Heart failure (%)	COPD (%)	CKD (%)
Pain	35–96	63–80	41–77	34–77	47–50
Depression	3–77	10–82	9–36	37–71	5–61
Delirium	6–93	30–65	30–65	18–32	18–33
Fatigue	32–90	54–85	69–82	68–80	73–87
Dyspnea	10–70	11–62	60–88	90–95	11–62
Anorexia	30–92	57	21–41	35–67	25–64

Solano et al. *J Pain Symp Manage* 2006;31(1)

SYMPTOM COMPLEX AND ASSESSMENT (CONT'D)

COMPREHENSIVE PALLIATIVE CARE ASSESSMENT—given the intricate nature of interaction between the physical, psychosocial, and existential, it is important to perform regular screening to accurately assess and manage symptoms

- **SYMPTOM BATTERY**—Edmonton Symptom Assessment Scale (ESAS, numeric rating scale of 0–10 for 10 symptoms including pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, and sleep), Memorial Symptom Assessment Scale (MSAS), Palliative Care Outcome Scale (POS)
- **DELIRIUM**—Memorial Delirium Assessment Scale, Confusion Assessment Method
- **CAGE**—history of substance use (ever) may guide opioid therapy, potential marker of psychosocial distress
- **FUNCTION**—ECOG performance status, Karnofsky performance scale (KPS), and palliative performance scale (PPS). Performance status has prognostic utility and is one of the key factors in care planning (e.g. discharge location, initiation or termination of treatment, need for home care)
- **OTHERS**—falls, suicidal ideation, spirituality, caregiver distress, illness understanding, prognostic awareness, care planning

DEPRESSION IN THE PALLIATIVE SETTING

DIAGNOSIS—**somatic symptoms** (anorexia, fatigue, insomnia, weight loss) are less useful for diagnosis of depression since they are common in patients with advanced cancer. The diagnosis of depression depends on **psychological symptoms** (worthlessness, guilt, anhedonia, hopelessness, decreased will to live and suicidal ideation) for at least 2 weeks. Rule out hypothyroidism, hypercalcemia, hypoactive delirium, and medication side effects

SCREENING—given the high prevalence of depression, it is important to conduct routine screening. The Patient Health Questionnaire-2 (PHQ-2) has two questions (“Over the last 2 weeks, how often have you been bothered by the following problems?” (1) Little interest or pleasure in doing things; (2) feeling down, depressed or hopeless? Answers include “not at all” [0 points], “several days” [1 point], “more than half the days” [2 points], and “nearly every day” [3 points]).

DEPRESSION IN THE PALLIATIVE SETTING (CONT'D)

Patients who score 3 or more points on PHQ-2 should be further evaluated by PHQ-9 or an in-depth interview

TREATMENTS—**expressive/supportive counseling, cognitive behavioral therapy, antidepressants** (*mirtazapine* 15–45 mg PO nightly, *paroxetine* 10–20 mg PO daily, *fluoxetine* 10–20 mg PO daily, *sertraline* 25–100 mg PO daily, *fluvoxamine* 50–200 mg PO daily, *escitalopram* 10 mg PO daily), **psychostimulants** (*methylphenidate* 5–10 mg PO daily, dextroamphetamine, pemoline)

CARE FOR CAREGIVERS

EMPHASIS ON CAREGIVERS—palliative care is unique among medical disciplines in placing a particular emphasis on the well-being of family caregivers. This is because caregivers play a crucial role caring for their loved ones both physically and emotionally, and their well-being is often one of the key concerns for patients. Caregivers are at risk of developing psychosocial distress themselves, given the physical burden of providing care, the emotional burden of seeing their loved ones suffer, and the financial burden of costly treatments. Moreover, many patients develop delirium close to the end of life, necessitating substitute decision making

INTERVENTIONS FOR CAREGIVERS—specific interventions may include (1) information sharing to facilitate care planning, (2) psychological interventions and self-management strategies for family members, (3) family meetings to help update all parties involved and to define goals of care, and (4) support groups and bereavement counseling

COMMUNICATION IN THE PALLIATIVE SETTING

Patients and their families need to have a sound understanding of their disease, treatment options, and prognosis to make decisions. The section on “Communication Issues” (p. 443) covers a number of basic techniques in breaking bad news. For further information, readers are referred to a review that covers various communication topics related to the end of life, including discussion of diagnosis, prognosis, treatment decisions, advance care planning, transition of care, and preparing for death and dying

Back et al. *Cancer* 2008;113(7 Suppl)

DECISION MAKING IN THE PALLIATIVE SETTING

Patients with advanced disease have to face many difficult decisions that are not only highly complex but also emotionally charged. One of the key roles of palliative care is to guide patients through the maze of difficult choices by providing individualized recommendations, taking into account the patient's preferences, health state, treatment options, and resources

MEDICAL DECISIONS AT THE END OF LIFE—initiation or discontinuation of treatments (e.g. chemotherapy, supplemental nutrition, life support), resuscitation orders (in-hospital, out-of-hospital), hospice referral (prognosis of 6 months or less and willingness to forgo life-sustaining treatments)

PERSONAL DECISIONS AT THE END-OF-LIFE—living arrangements as disease progresses (e.g. home, hospital, hospice; if home, may need to consider family support, hired help, and/or home care, to arrange hospital bed at home and to ensure bathroom safety), personal directive, power of attorney, saying "good bye" to loved ones, completing specific tasks, will, funeral arrangements, care of family after death (especially children)

SPIRITUALITY IN THE PALLIATIVE SETTING

DEFINITION—relationship with oneself, with others (family, friends), and with God (or other supreme being/deity)

SPIRITUAL NEEDS OF THE DYING

- **SEARCH FOR MEANING OF LIFE AND HOPE**—provide time for personal reflection, spending quality time with family, reminiscing, legacy projects (e.g. dignity therapy), and life review
- **TO DIE APPROPRIATELY**—minimize pain and suffering, not to prolong death, not to be a burden on family
- **LEGACY AND IMMORTALITY**—ensure family are cared for, explore religious or other belief systems in order to give the reassurance of immortality, religious rituals (i.e. chaplains)

FACILITATION—listen, acknowledge, explore, reflect, integrate

SPIRITUAL HISTORY ★ SPIRIT ★

- **SPIRITUAL BELIEF SYSTEM**
- **PERSONAL SPIRITUALITY**
- **INTEGRATION WITH A SPIRITUAL COMMUNITY**
- **RITUALIZED PRACTICES/RESTRICTIONS**

SPIRITUALITY IN THE PALLIATIVE SETTING (CONT'D)

- **IMPLICATIONS FOR MEDICAL CARE**
- **TERMINAL EVENTS PLANNING**

PITFALLS—AVOID trying to solve patient's problems or resolving unanswerable questions, going beyond a physician's expertise and role, imposing own religious beliefs, or providing premature reassurance

RESOURCES—caregivers, spiritual counselors, chaplains, faith community

Sulmasy JAMA 2006;296(11)

DIAGNOSIS OF IMPENDING DEATH

DEFINITION OF IMPENDING DEATH—irreversible physiologic changes in a context of far advanced disease, suggesting the patient is in the last days of life (typically 3 days or less)

CHALLENGE—clinicians are usually reluctant to make the diagnosis if any hope of improvement exists, particularly if no definitive diagnosis has been established. When recovery is uncertain, it is better to discuss this with patient and family. It is important to understand that the diagnosis of impending death can be made, knowing that there may still be a small chance of prolonged survival in some patients

TELL-TALE SIGNS OF IMPENDING DEATH

- **EARLY SIGNS**—these signs are more commonly observed compared to late signs, typically start days to weeks before death, and have only have a moderate sensitivity/specificity for impending death. They include poor performance status (being bed bound), decreased level of consciousness, delirium, and dysphagia/anorexia/cachexia
- **LATE SIGNS**—these signs are less common compared to early signs, mostly occur within the last 3 days of life, and have a very high specificity (>95%) and positive likelihood ratio (~10) for impending death within 3 days. They include the following:
 - **NEUROMUSCULAR CHANGES**—inability to close eyelids, non-reactive pupils, drooping of nasolabial fold, hyperextension of neck, death rattle, grunting of vocal cords
 - **NEUROCOGNITIVE CHANGES**—decreased response to verbal/visual stimuli, respiration with mandibular movement, Cheyne-Stokes breathing

DIAGNOSIS OF IMPENDING DEATH (CONT'D)

- **CARDIOVASCULAR CHANGES**—pulselessness of radial artery, peripheral cyanosis, and decreased urine output
- **APPLICATION**—absence of early signs is useful to rule out impending death, while presence of late signs is useful to rule in impending death

Hui et al. *Oncologist* 2014;19(6)

Hui et al. *Cancer* 2015;121(6)

MEDICATION ADMINISTRATION IN THE PALLIATIVE SETTING

SUBCUTANEOUS ROUTE—preferred over intravenous route because it is associated with greater comfort, fewer complications, less

MEDICATION ADMINISTRATION IN THE PALLIATIVE SETTING (CONT'D)

maintenance, and medications can be given at home. Indwelling subcutaneous catheter may be used for convenience and patient comfort. Disadvantages include less rapid onset of medication effects. This route is only suitable for some medications (need to check before administration)

HYDRATION—hypodermoclysis rate is typically 1–2 mL/min per needle site. Contraindicated if severe edema, severe bleeding disorder, or severe thrombocytopenia

Principles of Pain Control**TYPES OF PAIN**

NOCICEPTIVE PAIN—**somatic** (musculoskeletal pain, fractures, arthritis, bone metastases), **visceral** (obstruction, liver metastases)

NEUROPATHIC PAIN—**dysesthetic (constant burning), neuralgic/lancinating (paroxysms of shooting pain)**

PSYCHOGENIC PAIN

PATHOPHYSIOLOGY

DEFINITION OF PAIN—an unpleasant sensory and emotional experience associated with actual or potential tissue injury or described in terms of such damage. The concept of total pain is the sum of all physical, emotional, psychosocial, and spiritual pain

PREVALENCE OF CANCER PAIN—approximately 80% of cancer patients experience some form of pain during their course of illness; the causes of pain vary and may include cancer (~70%), cancer treatments (~25%) and chronic non-malignant pain (~35%). Many patients have more than one type of pain

TOLERANCE—normal pharmacophysiological effect in which increasing doses of opioids are required to provide the same analgesic effect over time

DEPENDENCE—normal pharmacophysiological effect with the development of withdrawal symptoms (e.g. agitation, pain, fever, sweats, tremor, tachycardia) if opioid is stopped abruptly after a prolonged period of use. In general, a minimum of one-third of total daily

PATHOPHYSIOLOGY (CONT'D)

opioid dose is required to prevent withdrawal symptoms

NON-MEDICAL OPIOID USE—use of opioid “without a prescription or in greater amounts, more often, or longer than prescribed, or for a reason other than (prescribed).” Behaviours that may indicate aberrant use include excessive self increase, inappropriate early opioid refills, illicit drug use, preference for specific opioids, obtaining opioids from unauthorized sources, opioid sharing, stolen opioids, doctor shopping, pharmacy shopping, and diversion. Although the majority of patients using analgesics as prescribed will not get addicted and should be reassured, approximately 10–20% of patients (with a history of substance use, CAGE positive) are at risk of developing non-medical opioid use. These individuals may be prescribed an ever escalating dose of opioid without adequate pain control

CHEMICAL COPING—the use of opioids or other psychotropic medications (e.g. benzodiazepines) to cope with emotional distress and is characterized by inappropriate and/or excessive use. Chemical coping is one form of non-medical opioid use

SUBSTANCE USE DISORDER—abnormal psychopathological compulsion to use a substance affecting daily function. In addition to education on safe opioid use, these patients need to be monitored frequently (e.g. weekly or every 2 weeks if necessary), have routine and/or random urine drug screening, and careful titration of analgesics to optimize their function

PATHOPHYSIOLOGY (CONT'D)**DISTINGUISHING FEATURES OF PAIN**

	Somatic	Visceral	Neuropathic
Location	Localized	Poorly localized, referred	Radiation, dermatome
Nature	Aches	Squeezing, cramping	Shooting, burning
Analgesics	Opioids, NSAIDs	Opioids	Opioids, gabapentinoids, TCAs, antiepileptics, venlafaxine

PATHOPHYSIOLOGY (CONT'D)

CAUSES OF INTRACTABLE CANCER PAIN—disease progression, neuropathic pain, bone pain, breakthrough pain, delirium, substance use, depression/anxiety, and somatization (i.e., psychosocial/existential distress)

MANAGEMENT

IMPORTANT NOTE—it is critical to make the proper diagnosis of pain based on presentation. The management of cancer-related pain is very different from non-malignant pain

NON-OPIOIDS (first line for non-malignant pain or mild cancer pain)—*acetaminophen* 650 mg PO q4h, NSAIDs (*ibuprofen* 300–800 mg PO TID–QID) may be particularly useful for bone metastases, hypertrophic pulmonary osteoarthropathy, soft tissue infiltration, arthritis, serositis, and post-operative pain. Consider ceiling dose effect. Common side effects include gastritis, peptic ulceration, hypertension, fluid retention, renal dysfunction (pre-renal, AIN), impaired platelet function. COX-2 inhibitors are associated with decreased risk of gastric ulceration and platelet dysfunction, but potentially higher risk of cardiovascular events

WEAK OPIOIDS (mild-moderate cancer pain)—in opioid naïve patients, consider *codeine* 30–60 mg PO q4h, *acetaminophen/codeine* 325 mg/30 mg 1–2 tabs PO q4h, *acetaminophen/hydrocodone* 325 mg/5–10 mg PO q4h, *tramadol* 50–100 mg PO q4–6h

STRONG OPIOIDS (moderate/severe cancer pain)—in opioid naïve patients, consider *morphine sulfate contin* 15 mg PO q12h and 7.5 mg PO q2–4h PRN (max 6 doses a day). Other options include *oxycontin* 10 mg PO q12h and 5 mg PO q2–4h PRN, *hydromorphone extended release* 8 mg PO daily and 2 mg PO q2–4h PRN (max 6 doses a day), oxymorphone, fentanyl, or methadone. Patients with severe cancer pain may be started with strong opioids up front instead of non-opioids or weak opioids

PROCEDURES—surgical interventions (celiac plexus/splanchnic block, subarachnoid block, cor-

MANAGEMENT (CONT'D)

dotomy, epidural/intrathecal infusion, vertebroplasty) may be added to any line as needed

ADJUVANT THERAPIES

- **MEDICATIONS MITIGATING ADVERSE EFFECTS OF OPIOIDS**—start bowel protocol (*senna* 1–4 tabs PO BID) and consider anti-nausea (*metoclopramide* 10 mg PO q4h) at the same time of opioids. *Methylphenidate* 5–10 mg PO qAM and 5–10 mg q noon may be used for opioid sedation
- **TRICYCLIC ANTIDEPRESSANTS** (neuropathic pain)—*nortriptyline* 25 mg PO nightly initially, increase by 25 mg/day every week if tolerated, target 75 mg PO nightly-BID
- **ANTICONSULSANTS** (neuropathic pain, opioid-induced myoclonus)—*gabapentin* 100–300 mg PO TID, *pregabalin* 100 mg PO TID, *carbamazepine* 100 mg PO BID, *phenytoin* 100 mg POTID
- **ANTISPASMODICS**—*baclofen* 10 mg PO TID for muscle spasms
- **ANTINEOPLASTIC TREATMENTS** (cancer pain)—chemotherapy, radiation (external beam radiation for focal tumor infiltration, Strontium⁸⁹, or Samarium¹⁵³ for multifocal osteoblastic bone metastases), hormonal agents
- **BISPHOSPHONATES** (bone metastases, hypercalcemia)—*pamidronate* 60–90 mg in 500 mL NS IV over 4–6 h, *zoledronate* 4 mg IV
- **CORTICOSTEROIDS** (acute nerve/spinal cord compression, visceral distension, increased intracranial pressure, and soft tissue infiltration)—*dexamethasone* 8–10 mg PO BID

OTHERS—physical therapy (massage, acupuncture, trigger point injection), psychological therapy (relaxation, imagery, biofeedback)

TREATMENT ISSUES**OPIOID USE**

- **STARTING DOSE**—start with short-acting opioids, which are usually given q4h around the clock, with breakthroughs (10–20% of total daily dose) given q1–2 h (see table below). May need to increase scheduled dose if ≥ 3 breakthroughs/day

TREATMENT ISSUES (CONT'D)

- **ROUTE**—for regular opioids, PO is preferred over SC/IV. IV/SC dose = ½ of PO dose for most opioids
- **MAXIMUM DOSE**—there is no absolute number for the ceiling dose of opioids that can be given. This is only limited by opioid toxicity. Any patient on morphine equivalent dose of 100 mg/day or more should be monitored closely and provided with naloxone prescription
- **MAINTENANCE**—if patient on stable dose of opioids, may consider switching to slow release (SR) formulations or fentanyl patch for convenience and improved compliance. Long-acting opioids provide similar pain control as short-acting opioids
- **TITRATING DOWN**—if patient did not require any rescue opioids and pain is well controlled, consider decreasing regular dose by 25–50% every 1–7 days to optimally control pain with minimum opioid dose
- **CAUTIONS**—avoid meperidine because of high toxicity from metabolites. Avoid fentanyl patch for unstable pain (although fentanyl infusion can be useful)

OPIOID TOXICITY

- **ADVERSE EFFECTS**—common side effects include constipation, nausea, fatigue and somnolence. While somnolence may resolve within a few days, patients do not develop tolerance to constipation and would require laxatives throughout opioid treatment. Patients receiving high doses of opioids may develop neurotoxicity, which include myoclonus, hyperalgesia, delirium, hallucinations, and cognitive impairment. Respiratory depression is **not** an expected side effect of opioids, except in cases of opioid overdose. Long-term side effects include secondary adrenal insufficiency, hypogonadism, sexual

TREATMENT ISSUES (CONT'D)

- dysfunction, osteoporosis, immunosuppression and peripheral edema. Methadone may also cause QT prolongation and ECG monitoring is recommended
- **TREATMENT OF OPIOID TOXICITIES**—ensure adequate hydration, opioid rotation, exclude underlying aggravating metabolic factors (uremia, liver failure, hypercalcemia), and symptom management (e.g. prevent and treat nausea and constipation)

OPIOID ROTATION—common reasons for rotation include opioid-induced neurotoxicities (sedation, nightmares, hallucinations, myoclonus), poor analgesic response despite high opioid doses, and logistical factors (e.g. loss of oral route, cost considerations). Remember to dose reduce by 25–50% to account for cross-tolerance

MITIGATING NON-MEDICAL OPIOID USE (NMOU)

—all patients on opioids should be educated on safe opioid use, storage and disposal. They should be monitored longitudinally (e.g. monthly visits) to titrate opioids based on symptom control, function and the overall risk: benefit ratio. Validated tools such as the Screener and Opioid Assessment for Patients with Pain (SOAPP) and Opioid Risk Tool (ORT) may be used at baseline for risk-stratification and to determine the intensity of monitoring. In addition to history and physical, random urine drug screens, pill counts, and prescription monitoring programs can provide objective information during monitoring visits. The decision to continue/discontinue opioids in patients with demonstrated NMOU needs to be personalized. If the decision is to continue opioids, more frequent visits (with smaller prescriptions) and referral to psychology, psychiatry, palliative care and/or addiction medicine is warranted

EQUIANALGESIC TABLE

	Ratio ^a	Starting	q1–2 h PRN	Route
Codeine ^b	0.1	30–60 mg q4h PRN	–	PO/PR
Hydrocodone ^c	1	5–10 mg q4h PRN	–	PO
Morphine	1	5 mg q4h	2.5–5 mg	PO/PR/SC/IV
Hydromorphone	5	1–2 mg q4h	0.5–1 mg	PO/PR/SC/IV
Oxymorphone	3	5 mg q8h	2.5 mg	PO
Oxycodone ^d	1.5	5 mg q4h	2.5 mg	PO/PR/SC
Fentanyl drip	100	10–50 µg/h	25 µg	IV
Methadone	2–20 ^e	5 mg q8–12 h	–	PO/PR/IV

^aHigher number indicates greater potency

^bTylenol #1–3 = acetaminophen plus codeine with or without caffeine

^cVicodin, Lortab, Norco = acetaminophen plus hydrocodone

^dPercocet = acetaminophen plus oxycodone

^eSee methadone conversion table below

TREATMENT ISSUES (CONT'D)**FENTANYL DURAGESIC CONVERSION**

Fentanyl TD ($\mu\text{g}/\text{h}$)	Morphine PO (mg)
25	45–134
50	135–224
75	225–314
100	315–404
125	405–494
150	495–584

TREATMENT ISSUES (CONT'D)

- **CONVERSION BETWEEN FENTANYL PATCH (IN $\mu\text{G}/\text{H}$) AND ORAL MORPHINE (IN MG/DAY)**—consider using a ratio of 3.6, e.g. fentanyl patch of 25 $\mu\text{g}/\text{h}$ is equivalent to $25 \times 3.6 = 90$ mg of oral morphine/day
- **CONVERSION BETWEEN INTRAVENOUS FENTANYL AND INTRAVENOUS MORPHINE**—consider using a ratio of 10 μg : 1 mg
- **BIOAVAILABILITY OF FENTANYL IS HIGHLY VARIABLE**—transdermal 90%, sublingual 65%, and transmucosal (lozenge) 50%

METHADONE CONVERSION**1. DETERMINE THE DOSE EQUIVALENT**

Oral morphine equivalent daily dose (mg/day)	Initial dose ratio (morphine: methadone)
<30	2:1
30–99	4:1
100–299	8:1
300–499	12:1
500–999	15:1
>1000	20:1 or greater

2. DETERMINE THE SCHEDULE

	Day 1	Day 2	Day 3	Day 4
Morphine (MS)	66%	33%	0%	0%
or other opioids	TDD	TDD	TDD	TDD
Methadone (ME)	33%	66%	100%	100%
	TDD	TDD	TDD	TDD
Breakthrough	10%	10%	10%	10%
	w/ morphine	w/ morphine	w/ morphine	w/ morphine

TDD total daily dose, breakthrough dose is 10% of TDD. Methadone is usually given q12h, sometimes q8h. Start low and go slow is the key for using methadone. Pay close attention to sedation during methadone conversion and be prepared to reduce dose if necessary. To improve tolerability with conversion, consider spreading out to a dose change every 3 days instead of every day. Due to its complex pharmacology, methadone should only be prescribed by clinicians familiar with this drug

TREATMENT ISSUES (CONT'D)

PROGNOSTIC FACTORS FOR POOR PAIN CONTROL—somatization, substance use, cognitive impairment, neuropathic pain

SPECIFIC SITUATIONS

- **RENAL FAILURE**—methadone is hepatically excreted and not dialyzable. Thus, methadone is

TREATMENT ISSUES (CONT'D)

the drug of choice for patients with renal failure and/or on dialysis. Other opioids for patients with renal failure include fentanyl (excreted unchanged by the kidneys with no intermediate metabolites) and hydromorphone (more potent and thus fewer toxic metabolites)

TREATMENT ISSUES (CONT'D)

- **NEUROPATHIC PAIN**—opioids are effective against neuropathic pain. Methadone is theoretically more useful because of its NMDA antagonist

TREATMENT ISSUES (CONT'D)

activity. Also consider use of non-opioids such as gabapentin, pregabalin, carbamazepine, venlafaxine, and TCAs

Delirium

See DELIRIUM (p. 422)

Cancer-Related Fatigue**CAUSES**

ALTERED PHYSIOLOGY—cytokine dysregulation, serotonin neurotransmitter dysregulation, HPA axis dysfunction, circadian rhythm disruption, vagal afferent activation, alterations in muscle ATP metabolism

CONTRIBUTING FACTORS ★ASTHENIC★

- **ANEMIA, ANOREXIA**
- **SLEEP DISTURBANCES, SHORTNESS OF BREATH**
- **THROBING PAIN**
- **HEAD**—depression, anxiety
- **ELECTROLYTES**—Na, K, Mg, Ca
- **NUTRITIONAL FAILURE**—anorexia—cachexia
- **INACTIVITY**
- **COMORBIDITIES**—cardiac/pulmonary failure, hepatic/renal failure, neurologic/endocrine failure (hypothyroidism, hypogonadism, adrenal insufficiency), infections

PATHOPHYSIOLOGY

DEFINITION—a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that interferes with usual functioning. Cancer-related fatigue is distinct from everyday tiredness as it does not correspond to the patient's level of exertion and is not typically relieved by rest or sleep. Although fatigue has not been as well studied in other palliative care settings, the underlying pathophysiology and treatments are believed to be similar to cancer-related fatigue

PREVALENCE—cancer-related fatigue is essentially present throughout the cancer journey, including 40% at diagnosis, 80–90% during cancer treatment, 30% 1-year post-treatment,

PATHOPHYSIOLOGY (CONT'D)

75% with metastatic disease, and >90% at the end of life. It is often under-diagnosed and under-treated

CLINICAL FEATURES

SCREENING—“How would you rate your fatigue on a scale of 0–10 over the past 7 days?”

0	Absence of fatigue
1–3	Mild fatigue
4–6	Moderate fatigue
7–10	Severe fatigue

INVESTIGATIONS**BASIC**

- **LABS**—CBC, lytes, urea, Cr, glucose, TSH, Mg, Ca, albumin, 25-hydroxyvitamin D

MANAGEMENT

TREAT UNDERLYING CAUSE—provide proper management of pain, depression, sleep disturbance (sleep hygiene, cognitive behavioral therapy), anemia, electrolyte imbalance, nutritional concerns, vitamin deficiency, polypharmacy, organ dysfunction and other comorbidities, if applicable

NON-PHARMACOLOGIC—aerobic or resistive exercise for at least 30 min/day for 5 days a week (strongest evidence); yoga; psychosocial interventions (self-management, activity pacing)

PHARMACOLOGIC—*methylphenidate* 5–10 mg PO qAM and noon; corticosteroids (*dexamethasone* 4 mg PO BID for 2 weeks)

Dyspnea in the Palliative Setting

DIFFERENTIAL DIAGNOSIS OF ACUTE DYSPNEA

RESPIRATORY

- **PARENCHYMA**—pneumonia, ARDS, lymphangitic carcinomatosis, lung cancer
- **AIRWAY**—COPD exacerbation, asthma exacerbation, acute bronchitis, bronchiectasis, obstruction (cancer)
- **VASCULAR**—pulmonary embolism, pulmonary hypertension, SVC obstruction
- **PLEURAL**—pleural effusion, pneumothorax

CARDIAC

- **MYOCARDIAL**—HF exacerbation, myocardial infarction
- **VALVULAR**—aortic stenosis, acute aortic regurgitation, endocarditis
- **PERICARDIAL**—pericardial effusion, tamponade

SYSTEMIC—sepsis, metabolic acidosis, anemia

OTHERS—neuromuscular (cachexia), anxiety, tense ascites

PATHOPHYSIOLOGY

DEFINITION—a subjective experience of breathlessness related to patient's physical, mental, emotional, and social circumstances. Degree of dyspnea has only a low correlation with physical findings, such as tachypnea, wheezing, cyanosis, and O₂ saturation

HISTORY—remember to ask if dyspnea is episodic or continuous (at rest). If episodic, what are the triggers and how long do they last? Assess the level of distress and functional limitation associated with dyspnea

INVESTIGATIONS (IF APPROPRIATE)

BASIC

- **LABS**—CBC, lytes, urea, Cr, D-dimer
- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S
- **IMAGING**—CXR, CT angiogram, V/Q scan

SPECIAL

- **ECG**—if suspect ACS
- **ABG**—judicious use in the palliative care setting

MANAGEMENT

TREAT UNDERLYING CAUSE—palliative radiation and/or chemotherapy may be used in specific cases

NON-PHARMACOLOGICAL—fan blowing in face (may add cool cloth to fan), self-management strategies, positions (e.g. leaning forward, standing against wall), breathing techniques (e.g. abdominal

MANAGEMENT (CONT'D)

breathing, purse-lip breathing), relaxation techniques, distraction therapy

PHARMACOLOGICAL—supplemental O₂ if hypoxicemic, **opioids** (similar for pain control, although the starting doses may be lower. If already on opioids, may increase dose by 25%. No difference shown between q4h dose and infusion), **corticosteroids** (*dexamethasone* 4–8 mg PO BID if structural causes), **bronchodilators** (if bronchoconstriction), **non-invasive ventilation** may be beneficial for patients with hypercapnia and/or significant respiratory muscle weakness, **high flow oxygen** (up to 80 L/min of humidified oxygen via nasal prongs) for patients with severe hypoxemia. **Palliative sedation** as a last resort

PROCEDURES—if significant pleural effusion, consider thoracentesis, pleurodesis, or indwelling pleural catheters

TREATMENT ISSUES

PALLIATIVE SEDATION

- **DEFINITION**—the use of medications to relieve intolerable suffering from refractory symptoms through sedation. Refractory symptoms are defined as those for which all possible treatment has failed or it is estimated that no methods are available for palliation within the time frame and the risk–benefit ratio that the patient can tolerate
- **INDICATIONS**—when suffering (delirium/agitation, dyspnea, pain) persists despite all other means; not to be confused with euthanasia. **Must** ensure detailed discussion with patient (if possible), family, and the interprofessional palliative care team prior to initiation of treatment with clear documentation
- **MEDICATIONS**—**benzodiazepines** (*midazolam* start at 1 mg/h IV/SC, titrate to achieve sedation, lorazepam), **neuroleptics** (e.g. haloperidol, chlorpromazine, methotrimeprazine [good for delirium and may be combined with midazolam]), **propofol** (intravenous access required, may be used temporarily)
- **ETHICS**—palliative sedation is permissible when the primary intention is relief of suffering, even if survival may be shortened (i.e., the doctrine of double effect). However, systematic reviews showed that palliative sedation is not associated with shortened survival

SPECIFIC ENTITIES

DEATH RATTLE—due to patient's inability to clear upper respiratory secretions. Patient's family should be reassured that this does not indicate that the patient is dyspneic or in distress. Treatments to decrease respiratory secretions include re-positioning, Trendelenburg for a minute then general oropharyngeal suction, *glycopyrrolate* 0.2 mg SC q4–6 h or 0.4–1.2 mg/day SC/IV, *hyoscine hydrobromide/scopolamine* 0.8 mg SC initially, then 0.2–0.6 mg SC q1h PRN, total 0.8–2 mg/day, or *hyoscine butylbromide/buscopan* 10–20 mg SC/IV/IM q4h, max 100 mg/day

SPECIFIC ENTITIES (CONT'D)

BREATHING PATTERN CHANGES IN DYING PATIENTS—reassurance should be provided to the patient's family that breathing pattern changes described below are not associated with dyspnea, as the patient is unconscious

- **CHEYNE–STOKES BREATHING**—cyclic variation in rate and depth of breathing with apneic spells. Causes include bilateral cerebral damage, HF, uremia, drug-induced respiratory depression
- **KUSSMAUL BREATHING**—rapid, deep, and regular breathing. Causes include mid-brain and pontine infarction/hypoxia, exercise, anxiety, metabolic acidosis
- **ATAXIC BREATHING**—irregular breaths with long apneic periods caused by medullary damage

Nausea and Vomiting in the Palliative Setting**INVESTIGATIONS (IF APPROPRIATE)**

BLOOD TESTS—CBC, lytes, urea, Cr, glucose, Ca, Mg, PO₄, cortisol

URINE TESTS—urinalysis

MICROBIOLOGY—urine C&S

IMAGING—CXR, AXR (rule out bowel obstruction and constipation)

Related Topic

Nausea and Vomiting (p. 127)

MANAGEMENT (CONT'D)

- **NEUROLEPTICS**—*methotrimeprazine* 5–25 mg PO TID, *chlorpromazine* 10–25 mg PO q4h
- **STEROIDS**—*dexamethasone* 4–10 mg PO/SC/IV BID
- **CANNABINOID AGONISTS**—*nabilone* 1 mg PO daily may also be considered
- **PROMOTILITY AGENTS**—*domperidone* 10 mg PO TID–QID
- **THIRD LINE** (more D2 blockade)—switch *metoclopramide* to IV/SC infusion 60–120 mg/day. Also consider adding *haloperidol* 1–2 mg IV/SC q8–12 h and q1h PRN

MANAGEMENT

TREAT UNDERLYING CAUSE—bowel obstruction (decompression, octreotide), constipation (bowel regimen), opioid use (opioid rotation), hypercalcemia (hydration, bisphosphonates)

NAUSEA CONTROL

- **FIRST LINE** (D2 blockade)—*metoclopramide* 10 mg PO/SC/IV q4h and q1h PRN or *prochlorperazine* 10 mg PO/IV q4h and q1h PRN. Avoid if complete bowel obstruction
- **SECOND LINE**
 - **H1 BLOCKADE**—*dimenhydrinate* 50 mg PO/SC/IV q4h or *diphenhydramine* 50 mg PO/SC/IV q4h
 - **5HT₃ ANTAGONISTS**—*ondansetron* 8 mg PO daily-TID for chemotherapy-induced nausea and vomiting

SPECIFIC ENTITIES**BOWEL OBSTRUCTION IN THE PALLIATIVE SETTING**

- **PATHOPHYSIOLOGY OF MALIGNANT BOWEL OBSTRUCTION**—3% of all advanced cancers, particularly ovarian (11–42%), colorectal (5–24%), gastric, endometrial, prostate, and bladder. If inoperable, survival is typically only a few months
- **CAUSES**—**intraluminal** (mass, constipation, intussusception), **luminal** (carcinomatous causing dysmotility, bowel infarction), and **extraluminal** (compression, adhesions)
- **CLINICAL FEATURES**—nausea and vomiting, abdominal distension and pain, obstipation, absent bowel sounds
- **DIAGNOSIS**—AXR or CT abdomen

SPECIFIC ENTITIES (CONT'D)• **MANAGEMENT**

- **SUPPORTIVE MEASURES**—intravenous fluids, bowel rest, pain control (opioids), corticosteroids (*dexamethasone* 4–8 mg IV q12h), antiemetics (*metoclopramide* 10 mg IV q4h if no complete obstruction, *haloperidol* 1–2 mg IV q4h), antimuscarinic agents (*hyoscine butylbromide/buscopan*

SPECIFIC ENTITIES (CONT'D)

- 10–20 mg PO/IV/IM TID, atropine), somatostatin analogues (*octreotide* 10 µg/h IV or 50 µg SC q8h), NG suction (clump when output <100 cc/day and ensure no further N&V before removal). Consider venting PEG tube insertion
- **BYPASS OBSTRUCTION**—surgery, colonic stent placement

Constipation in the Palliative Setting**DIFFERENTIAL DIAGNOSIS**★ **DUODENUM** ★**DIET**—low fiber, dehydration**PSYCHIATRY**—depression, somatization, obsessive compulsive disorder**OBSTRUCTION**—cancer, strictures, adhesions**DRUGS**—opioids, TCAs, neuroleptics, antihistamines, calcium channel blockers, iron, antacids**ENDOCRINE**—diabetes, hypothyroidism, hypercalcemia, hypokalemia, hypomagnesemia, uremia**NEUROLOGIC**—spinal cord compression/injury, Parkinson disease, multiple sclerosis, stroke, autonomic neuropathy (cachexia–anorexia syndrome)**UNKNOWN/MISCELLANEOUS**—immobility, irritable bowel syndrome (IBS), amyloidosis, scleroderma**PATHOPHYSIOLOGY**

CONSTIPATION IN THE PALLIATIVE CARE SETTING—the most common causes are opioids, other medications, dehydration, and immobility. Even if there is no food intake, a small amount of stool is produced everyday due to shedding of intestinal epithelium. It is important to rule out bowel obstruction

RISK FACTORS FOR CONSTIPATION—old age, female sex, intraabdominal malignancies, opioids use

COMPLICATIONS OF CONSTIPATION—abdominal pain, distension, nausea and vomiting, overflow diarrhea, hemorrhoids, anal fissures, confusion/delirium, fear of opioid use

INVESTIGATIONS**BASIC**

- **IMAGING**—AXR

SPECIAL

- **WORKUP**—lytes, urea, Cr, glucose, Mg, Ca, albumin, TSH

DIAGNOSTIC ISSUES

CONSTIPATION SCORE—constipation remains a clinical diagnosis and the role of abdominal X-ray remains controversial because existing scoring methods have poor inter-rater reliability. If used, they should be augmenting clinical diagnosis. First, divide into 4 quadrants (ascending, transverse, descending, and rectosigmoid colon). Second, rate the amount of stool in each quadrant from 0 to 3. A total score >6/12 suggests constipation may be present

Related Topic

Constipation (p. 143)

MANAGEMENT

PREVENTION IS KEY—a prescription for laxatives (e.g. *senna* 1–4 tabs PO q12h to start with) should **always** be given to the patient when starting an opioid

LIFESTYLE CHANGES—wheat **bran**, high-bran cereals, **exercise, hydration** (8–10 glasses/day)

SYMPTOM CONTROL

- **LAXATIVES**—*senna* 1–4 tabs daily-QID, *milk of magnesia* 15–30 mL BID, *sorbitol* 15–30 mL daily-BID, *lactulose* 15–60 mL daily, *magnesium citrate* 150–300 mL daily, *bisacodyl/dulcolax suppositories* 1 PR PRN, *tap water enema* 500 mL PRN, *mineral oil enema* 100–250 mL PRN, *polyethylene glycol* 17 g PO BID or *polyethylene glycol solution (GoLyteLy®)* 4 L PO/NG×1 for severe constipation. For patients with spinal cord compression, it is important to use rectal measures (enemas, suppositories), as significant diarrhea/leakage could occur with oral medications alone

MANAGEMENT (CONT'D)

- **μ-OPIOID RECEPTOR ANTAGONISTS**—indicated for patients with opioid-induced constipation despite at least 3 days of laxatives. *Methylnaltrexone* 12 mg SC × 1 day, repeat every other day as needed. These antagonists are peripheral acting, and thus do not affect pain control that happens centrally.

MANAGEMENT (CONT'D)

- Risk of bowel perforation in patients with intra-abdominal pathologies
 - **FECAL DISIMPACTION**—as a last resort. May be manual (digital) or endoscopic
- TREAT UNDERLYING CAUSE**—stop constipation-causing medications if possible

Anorexia-Cachexia**DIFFERENTIAL DIAGNOSIS**

MALIGNANCY—solid tumors (primary, metastatic), **hematologic**

CHRONIC INFECTION—atypical (TB), **viral** (HIV, HCV), **fungal, parasitic**

CONNECTIVE TISSUE DISEASE—seropositive (RA, SLE, dermatomyositis, polymyositis), **seronegative, vasculitis**

OTHER CHRONIC DISEASES

- **PULMONARY**—COPD, bronchiectasis
- **CARDIAC**—HF
- **ENDOCRINE**—type 1 diabetes, Addison disease

PATHOPHYSIOLOGY

CACHEXIA VS. STARVATION—cachexia is defined as accelerated loss of skeletal muscle (and to a smaller extent, adipose tissue) in the context of a chronic inflammatory response and excessive catabolism. The resulting weight loss cannot be adequately treated with aggressive feeding. In contrast, simple starvation is characterized by a loss of mostly adipose tissue and a caloric deficiency that can be reversed with appropriate feeding

CACHEXIA-ANOREXIA SYNDROME—due to a combination of pathophysiologic alterations including chronic inflammation from cytokine release (e.g. TNF, IL-1, IL-6), dysregulated ATP-ubiquitin-proteasome pathway, lipid mobilizing factor (cancer), neuro-hormonal dysregulation such as elevated cortisol levels, ghrelin and insulin resistance, low serum testosterone, and sympathetic activation. These changes result in a constellation of signs/symptoms such as increased basal energy expenditure, cachexia, disproportionate and excessive loss of lean body mass (muscle loss >fat loss), anorexia, xerostomia, dysphagia (oropharyngeal due to mechanical reasons), nausea, fatigue, autonomic dysfunction, and decreased performance status

PATHOPHYSIOLOGY (CONT'D)

NUTRITION IMPACT SYMPTOMS—in addition to an inflammatory catabolic process in primary cachexia, a number of associated symptoms may contribute to decreased appetite and weight loss (also known as secondary cachexia)

- **NAUSEA**—chemotherapy, bowel obstruction
- **MUCOSITIS**—chemotherapy, radiation
- **DENTAL ISSUES**—dentures, abscess
- **TASTE CHANGES**—medications, xerostomia
- **PAIN**—abdominal, other body sites
- **DYSPHAGIA**—oropharyngeal, esophageal
- **EARLY SATIETY**—autonomic neuropathy, opioid induced gastroparesis, ascites, hepatosplenomegaly
- **CONSTIPATION**—opioids, dehydration
- **DEPRESSION**

DIFFERENTIAL DIAGNOSIS**★ ANOREXIA ★****ACHES AND PAIN****NAUSEA AND VOMITING****ORAL CANDIDIASIS****REACTIVE DEPRESSION****EVACUATION**—constipation**XEROSTOMIA**—taste change**IATROGENIC**—chemotherapy, radiation to esophagus**ILLNESS**—underlying disease**ACID RELATED**—GERD**INVESTIGATIONS****BASIC**

- **LABS**—CBC, lytes, urea, Cr, Ca, PO₄, Mg, ESR, CRP, fasting glucose, TSH, AST, ALT, ALP, bilirubin, INR, albumin, fasting lipid profile, AM total testosterone level
- **BODY WEIGHT**—regular and frequent assessments
- **CALORIE COUNT**—determine daily intake

INVESTIGATIONS (CONT'D)**SPECIAL**

- **BODY COMPOSITION AND METABOLISM STUDIES**—bone density scan, bioelectrical impedance, indirect calorimetry
- **MALIGNANCY WORKUP** (if no obvious cause for cachexia)—serum protein electrophoresis, PSA (if male), fecal immunochemical test or fecal occult blood, Pap smear and pelvic examination, mammography, CXR
- **INFECTION WORKUP** (if no obvious cause for cachexia)—serologies (HBV, HCV, HIV, *Treponema pallidum*)
- **INFLAMMATORY WORKUP** (if no obvious cause for cachexia)—ANA, RF, C3, C4, p-ANCA, c-ANCA, cryoglobulins

MANAGEMENT

NUTRITIONAL COUNSELING—patients with advanced disease should be encouraged to eat the food they enjoy in small and frequent portions, without having to worry too much about their nutritional content. Dietitian referral may be useful. Aggressive measures such as parenteral or enteral feeding have limited impact on survival but may significantly decrease the quality of life. Their use should be limited to patients for whom starvation is a major component of weight loss (e.g. dysphagia from esophageal or head and neck cancer, bowel obstruction from peritoneal carcinomatosis)

OREXIGENIC AGENTS (appetite stimulants)—**corticosteroids** (*dexamethasone* 4 mg PO daily, patients may experience an increase in appetite and sense of well-being. Weight gain may not occur and duration of appetite stimulation is often short. Risk of myopathy and other steroid associated side effects). **Progestational agents** (*megestrol acetate* 400–800 mg PO daily has been shown to improve weight and appetite. However, it is associated with increased thromboembolic risk, swelling, impotence, and GI upset

MANAGEMENT (CONT'D)

and may shorten survival). **Serotonin antagonists**

ANTICATABOLIC AGENTS (antimetabolic and anticytokine)—insufficient evidence

ANABOLIC AGENTS (primarily hormonal)—insufficient evidence

CANNABINOIDS—approved for anorexia in HIV/AIDS but insufficient evidence in other diseases

OTHER POTENTIAL AGENTS—olanzapine and mirtazapine may be considered as appetite stimulants but insufficient evidence

TREATMENT OF NUTRITION IMPACT SYMPTOMS—consider treatment of nausea with antiemetics, mucositis with lidocaine viscous 2% or lidocaine spray, taste changes with *zinc sulfate* 220 mg PO BID, early satiety with metoclopramide, pain with analgesics, constipation with laxatives, and depressive mood with antidepressants

EXERCISE**TREATMENT ISSUES**

MEGESTROL ACETATE VS. CORTICOSTEROIDS—megestrol acetate has been shown to increase appetite and weight (but not lean body mass) and may be considered for intermediate-term use if weight loss is the predominant symptom. However, its significant side effect profile and cost should be taken into consideration. Corticosteroids may be useful for short-term (i.e., weeks) use, particularly if other symptoms (e.g. pain, fatigue, nausea, dyspnea) are present. Long-term use of steroids should be avoided due to side effects

Related Topics

Nausea and Vomiting (p. 127)

Supplemental Nutrition (p. 454)

Communication Issues**GOALS OF CARE DISCUSSIONS**

DEFINITION—an iterative, semi-structured communication process between patients living with serious illness and their clinicians to explore/enhance the patients' level of illness/prognostic understanding, to elicit the patients' values and preferences, and to formulate a personalized care plan. Topics of these conversations may involve life-prolonging measures (e.g. dialysis,

GOALS OF CARE DISCUSSIONS (CONT'D)

chemotherapy), advance care plans (e.g. living will, medical power of attorney), and resuscitation status (e.g. allow natural death)

QUESTIONS TO ELICIT VALUES AND GOALS

- "What are the things that are important to you as you think about your future?"
- "What makes a life worth living to you?"

GOALS OF CARE DISCUSSIONS (CONT'D)

- “What are your biggest fears as you get sicker?”
- “Have you thought about what treatments you would like or not like if your got sicker?”
- “What sort of quality of life would you consider acceptable? When would you consider it unacceptable?”

COMMUNICATION TECHNIQUES

1. **ASSESS PATIENT'S UNDERSTANDING** of their disease and their expectations before sharing information
2. **“ASK-TELL-ASK” APPROACH**—ask for patient's permission before starting, then share information tailored to their intellectual comprehension and emotional resilience and assess their need for further information before proceeding
3. **EMPATHIC RESPONSES**—acknowledge patient's emotion and facilitate its expression, using phrases such as “I can see this is a difficult time for you”
4. **ACTIVE LISTENING**—facilitate discussion by summarizing, use of appropriate pauses or phrases such as “Tell me more”
5. **NON-VERBAL COMMUNICATION**—pay attention to speech, posture, facial expression, appearance, and setting

BREAKING BAD NEWS: THE GENTLE ART OF TRUTH TELLING**★ SPIKES ★**

SETTING—establish an appropriate setting for the discussion. Sit down and talk slowly with good eye contact. Get healthcare team and family members involved (if appropriate). Be aware of cultural and religious differences

PERCEPTION: HOW MUCH DOES PATIENT KNOW?

- “What do you understand about your illness?”
- “What did the other doctors tell you?”
- “Are you worried about your illness?”
- “How do you think you are doing now?”

INFORMATION: HOW MUCH DOES PATIENT WANT TO KNOW? WARN AND PREPARE THE PATIENT

- “I have reviewed the tests and I'm afraid that I have some bad news for you.”
- “We have some difficult matters to discuss. Do you feel ready for this discussion?”
- “Would you like me to tell you everything? Or would you prefer a more general overview?”

BREAKING BAD NEWS: THE GENTLE ART OF TRUTH TELLING (CONT'D)

- “Some people like a whole lot of details, others do not. What would you prefer?”

KNOWLEDGE: DELIVER INFORMATION—discuss diagnosis, treatments, prognosis, and provide understanding of the natural history of disease. Pause frequently to check understanding. If delivering prognosis, discuss it in terms of “days,” “weeks,” “months,” or “years” instead of quoting median survival numbers. Check patient's understanding frequently: “Any questions? Would you like me to continue?”

EMOTIONS: EMPATHIC RESPONSE, NORMALIZE

- “This is a very difficult time for you and your family”
- “It is normal to feel sad and frustrated during this time”
- “I'd like to check so that I know your thoughts”

STRATEGY: EMPOWER PATIENT AND PROVIDE FOLLOW-UP, SUPPORT RESOURCES, AND APPROPRIATE COUNSELING

- “There is a lot we can do even though there is no cure for your disease. We will keep our eyes open for new treatments and discuss them together”
- “I know this is very difficult news and a lot of information. It may be very difficult for you to think right now. I am available anytime if you have any questions”

Baile et al. *Oncologist* 2000;5(4)

DISCUSSING RESUSCITATION STATUS

CONTEXT—establish an appropriate setting for the discussion. Sit down and talk slowly with good eye contact. Get healthcare team and family members involved (if appropriate)

WHAT DOES THE PATIENT UNDERSTAND?

- “What do you understand about your current health situation?”
- “Tell me about how you see your health”
- “What do you understand from what the doctors have told you?”

WHAT DOES THE PATIENT EXPECT?

- “What do you expect in the future?”
- “Have you ever thought about how you want things to be if you were much sicker?”
- “What are you hoping for?”

DISCUSS DNR ORDER, INCLUDING CONTEXT

- “If you should die despite all of our efforts, do you want us to use ‘heroic measures’ to bring you back?”
- “How do you want things to be when you die?”

DISCUSSING RESUSCITATION STATUS (CONT'D)

- "So, what you are saying is that you want to be as comfortable as possible when the time comes"
- "What I hear you saying is that you do not want us to 'call a code' if it would not do any good"
- "What you have said is that you want us to do everything we can to fight this cancer, but when the time comes, you want to die peacefully"
- "From what you have told me, I think it would be best if I put a DNR order on the chart"
- "Most patients who have expressed such opinions have a DNR order. I recommend that we put it on the chart"

RESPOND TO EMOTIONS

- "I can see this makes you sad"
- "Tell me more about how you are feeling"

ESTABLISH AND IMPLEMENT A PLAN

- "We will continue maximal medical therapy. However, if you die despite everything, we would not use CPR to bring you back"
- "It sounds like we should move to a plan that maximizes your comfort. Therefore, in addition to a DNR order, I would like to ask my palliative care colleagues to come give you some information"
- Document clearly in the chart "In the event of cardiorespiratory arrest, no CPR/defibrillation/

DISCUSSING RESUSCITATION STATUS (CONT'D)

intubation/mechanical ventilation/inotropes/ICU/CCU"

WHAT IF PATIENT INSISTS ON FULL CODE STATUS DESPITE YOUR BELIEF THAT THIS WOULD CLEARLY CAUSE MORE HARM THAN GOOD?

- **ENSURE GOOD COMMUNICATION**—between all parties, establish trust and try to understand patient's rationale. Do not rush—give the patient and family time to digest the information and respond emotionally
- **CONSIDER SOCIAL WORK CONSULT**—for family conference
- **ASK ABOUT RELIGION**—patients may want to involve pastoral care or their own spiritual support
- **CONSIDER BIOETHICIST CONSULT**
- **ASK FOR GUIDANCE FROM PATIENT**—"If someone is on life support, it becomes clear in a few days if they can recover or whether life support is prolonging an inevitable death. If you were unable to participate in the discussion at that time, please help us to determine what the guidelines should be for deciding whether to keep you on life support or not"

von Gunten *J Clin Oncol* 2001;19(5)

Prognostication in Far Advanced Cancer Patients**REASONS FOR DISCUSSING PROGNOSIS**

PATIENT AUTONOMY—patients have the right to know, cultural appropriateness

END-OF-LIFE PLANNING—important personal decisions influenced by time, time to express wishes (verbal, written), control of the situation/autonomy

CARE PLANNING—helps to avoid harm and discomfort by inappropriate therapies, initiation of medications (e.g. antidepressants), hospice admission

NOTE—advanced cancer is defined as locally advanced, metastatic or recurrent incurable cancer; far advanced cancer is defined as advanced cancer with a predicted survival of <3 months

PROGNOSTIC FACTORS

CLINICIAN PREDICTION OF SURVIVAL—clinician estimation of survival (generally 2–5× overestimation)

PROGNOSTIC FACTORS (CONT'D)

SYMPTOMS—poor performance status (median survival palliative performance scale 60–70% = 108 days, 30–50% = 41 days, 10–20% = 6 days), anorexia, cachexia, dysphagia, dyspnea, delirium

LABORATORY TESTS—elevated CRP, leukocytosis, lymphopenia, hypoalbuminemia, elevated LDH

OTHERS—cancer type and stage (less important in patients with far advanced cancer), comorbidities (less important if prognosis is poor. More useful in patients with longer expected survival such as those with prostate cancer)

Related Topics

Impending Death (p. 433)

Discussing Prognosis (p. 443)

PROGNOSTIC TOOLS**PALLIATIVE PROGNOSTIC SCORE (PaP)**

- **CLINICIAN PREDICTION OF SURVIVAL**—>12 weeks = 0, 11–12 weeks = 2, 7–10 weeks = 2.5, 5–6 weeks = 4.5, 3–4 weeks = 6, 1–2 weeks = 8.5
- **KARNOFSKY PERFORMANCE STATUS**—≥50% = 0, 10–40% = 2.5
- **ANOREXIA**—absent = 0, present = 1.5
- **DYSPNEA**—absent = 0, present = 1
- **TOTAL WBC**—4.8–8.5 = 0, 8.5–11 = 0.5, >11 = 1.5
- **LYMPHOCYTE PERCENTAGE**—20–40% = 0, 12–19.9% = 1, 0–11.9% = 2.5

PROGNOSTIC TOOLS (CONT'D)

- **UTILITY**—30 day survival for total score 0–5.5 = 97%, 5.6–11 = 59%, 11.1–17.5 = 25%
- **PALLIATIVE PROGNOSTIC INDEX (PPI)**
- **PALLIATIVE PERFORMANCE SCALE**—≥ 60% = 0, 30–50% = 2.5, 10–20 = 4
- **ORAL INTAKE**—normal = 0, moderately reduced = 1, severely reduced = 2.5
- **EDEMA**—absent = 0, present = 1
- **DYSPNEA AT REST**—absent = 0, present = 3.5
- **DELIRIUM**—absent = 0, present = 4
- **UTILITY**—with total score of 4 as cutoff, PPV for 6 week survival is 83%, NPV is 71%

PALLIATIVE PERFORMANCE SCALE (PPS)

PPS (%)	Mobility	Activity and evidence of disease	Self-care	Intake	Level of consciousness
100	Full	Normal activity and work No evidence of disease	Full	Normal	Full
90	Full	Normal activity and work Some evidence of disease	Full	Normal	Full
80	Full	Normal activity with effort Some evidence of disease	Full	Normal or reduced	Full
70	Reduced	Unable to do normal job Significant disease	Full	Normal or reduced	Full
60	Reduced	Unable to do hobby/ house work Significant disease	Occasional assist	Normal or reduced	Full or confusion
50	Mainly sit or lie	Unable to do any work Extensive disease	Considerable assist	Normal or reduced	Full or confusion
40	Mainly in bed	Unable to do most activity Extensive disease	Mainly assist	Normal or reduced	Full or drowsy ± confusion
30	Totally bed bound	Unable to do any activity Extensive disease	Total care	Normal or reduced	Full or drowsy ± confusion
20	Totally bed bound	Unable to do any activity Extensive disease	Total care	Minimal to sips	Full or drowsy ± confusion
10	Totally bed bound	Unable to do any activity Extensive disease	Total care	Mouth care only	Drowsy or coma ± confusion
0	Dead	—	—	—	—

Management of Other Distressing Symptoms

SYMPTOM CONTROL MEASURES

PRINCIPLES OF SYMPTOM MANAGEMENT

—the most critical aspect is to conduct a proper history and physical, along with targeted investigations, to identify and properly treat the underlying cause. The addition of palliative measures below may also improve quality of life

BLEEDING

- **NON-PHARMACOLOGIC MEASURES**—palliative radiation, arterial embolization and palliative surgeries may slow bleeding. Have dark towels by bedside in case of catastrophic bleed. Apply direct pressure and suction
- **PHARMACOLOGIC MEASURES**—antifibrinolytic agents (*tranexamic acid* 1000–1500 mg PO BID, or 10 mg/kg IV q6–8 h, or 1–6.5 mg/kg/h IV after 10 mg/kg of loading dose, *aminocaproic acid* 4–5 g IV over first hour, then 1 g/h in 50 mL over 8 h). If catastrophic life-threatening bleed, consider giving *midazolam* 5 mg IV in syringe for rapid sedation

COUGH

- **PHARMACOLOGIC MEASURES**—*benzonatate* 100 mg PO q8h PRN, *codeine* 7.5–60 mg PO BID, *dihydrocodeine* 5–10 mg PO TID, *hydrocodone* 5 mg PO BID, *morphine* 7.5–15 mg PO BID, *dextromethorphan* 10–30 mg PO q6h, *sodium cromoglycate* 10 mg NEB QID, *levodropropizine* 75 mg PO TID, *guaifenesin* 200–400 mg PO q4h or 600 mg PO BID, *gabapentin* 100–300 mg PO TID
- **NON-PHARMACOLOGIC MEASURES**—consider endobronchial therapy for cancer airway lesions, high intrathoracic vagotomy in refractory severe cases

DIARRHEA

- **NON-PHARMACOLOGIC MEASURES**—avoidance of laxatives, ensure adequate hydration
- **PHARMACOLOGIC MEASURES**—*loperamide* 4 mg PO qAM, then 2 mg PO after each loose stool (exclude *Clostridioides difficile* prior to treatment with anti-motility agents), *diphenoxylate/atropine* 5 mg PO QID, *tincture of opium* 0.6 mL (6 mg, 10 mg/mL) PO q6h PRN. *Octreotide* 100–500 mcg SC TID may be considered for secretory diarrhea

SYMPTOM CONTROL MEASURES (CONT'D)

HICCUPS

- **NON-PHARMACOLOGIC MEASURES**—breath holding, Valsalva maneuver, pressing on the eyeballs
- **PHARMACOLOGIC MEASURES**—*metoclopramide* 10 mg PO/IV q4h, *chlorpromazine* 25–50 mg PO QID, *haloperidol* 1–4 mg PO q4h, *baclofen* 5–20 mg PO TID

PRURITIS

- **NON-PHARMACOLOGIC MEASURES**—avoidance of irritants (e.g. soap), moisturizers, cooling lotions (e.g. calamine, Men-Phor®), and barriers (e.g. occlusive dressings)
- **PHARMACOLOGIC MEASURES**—antihistamines (e.g. *diphenhydramine* 25–50 mg PO q6–8 h, *loratadine* 10 mg PO daily), *naltrexone* 25–50 mg PO daily, *mirtazapine* 15–45 mg PO daily, *gabapentin* 100–300 mg PO TID, *aprepitant* 80 mg PO daily. For cholestasis induced pruritus, consider *cholestyramine* 4 g PO BID as first line, *rifampin* 300–600 mg PO daily as second line, and *naltrexone* as third line

SLEEP DISTURBANCE—cognitive behavioral therapy; sleep hygiene; melatonin, trazodone, mirtazapine; avoid benzodiazepines

THICK SECRETIONS—*guaifenesin* 200–400 mg PO q4h or 600 mg PO BID, *glycopyrrolate* 2–4 mg PO q4h

TASTE DISTURBANCE—*zinc sulfate* 200 mg PO BID ×14 days or 200 mg PO daily ×30 days

XEROSTOMIA—artificial saliva (*caphasol* 30 mL swish and swallow q4h)

EDEMA

- **LYMPHEDEMA**—consider non-pharmacological measures such as elevation, compression stockings, manual lymphatic drainage, complete decongestive therapy, and exercises. Diuretic therapy is often of limited effect
- **ANASARCA**—for selected patients with severe anasarca, consider *albumin* 25 g IV TID, *furosemide* 60 mg IV BID, fluid restriction

OVERREACTIVE BLADDER—*oxybutynin* 5 mg PO BID-QID



Obesity

Heymsfield et al. *NEJM* 2017;376(3)
de Cabo et al. *NEJM* 2019;381(26)

COMPLICATIONS AND ASSOCIATED DISORDERS

ENDOCRINE

- **INSULIN RESISTANCE**—hyperinsulinemia, diabetes
- **REPRODUCTION**—irregular menses, anovulatory cycles, infertility

CARDIOVASCULAR—hypertension, dyslipidemia (↑ chol, ↑ LDL, ↑ VLDL, ↑ TGL, ↓ HDL), coronary artery disease, heart failure, atrial fibrillation, stroke

RESPIRATORY

- **SLEEP APNEA**
- **OBESITY-ASSOCIATED HYPOVENTILATION SYNDROME** (Pickwickian syndrome; PaCO₂ ≥45 mmHg in absence of another cause)—↓ functional residual capacity, ↓ lung compliance, ↑ chest wall impedance, V/Q abnormalities (↓ ventilation but ↑ perfusion of lower lobes), ↓ strength and endurance of respiratory muscles, ↓ ventilatory drive, closure of small airways
- **PULMONARY HYPERTENSION**

GI—cholelithiasis, steatohepatitis, cirrhosis, gastroesophageal reflux, Barrett esophagus, chronic diarrhea, colonic adenomas, acute pancreatitis

GU—incontinence, kidney stones, glomerulopathy

MSK—osteoarthritis, gout

NEUROLOGIC—pseudotumor cerebri

DERMATOLOGIC—striae, acanthosis nigricans, hirsutism, pressure sores

CANCER

- **BREAST**
- **GENITOURINARY**—prostate
- **GYNECOLOGICAL**—endometrial, ovarian
- **GASTROINTESTINAL**—esophagus, colorectal, liver, gallbladder, pancreas, stomach
- **KIDNEY**
- **NON-HODGKIN LYMPHOMA**
- **MULTIPLE MYELOMA**

COMPLICATIONS AND ASSOCIATED DISORDERS (CONT'D)

PSYCHOSOCIAL—↓ education, ↓ employment, depression

PATHOPHYSIOLOGY

BODY MASS INDEX (BMI, weight/height²)—underweight <18.5 kg/m², normal 18.5–24.9 kg/m², overweight 25–29.9 kg/m², obesity class 1 30–34.9 kg/m², obesity class 2 35–39.9 kg/m², class 3/severe or morbid obesity ≥40 kg/m²

WAIST CIRCUMFERENCE

Ethnic group	Men	Women
Europid	≥94 cm [≥37 in.]	≥80 cm [≥31.5 in.]
South Asian, Chinese, Japanese	≥90 cm [≥35.4 in.]	≥80 cm [≥31.5 in.]

Waist circumference is better predictor of cardio-metabolic complications than BMI. Use Europid cutoff points for South and Central American, sub-Saharan African, Eastern Mediterranean, and Middle Eastern populations until more specific data are available

INVESTIGATIONS

BASIC

- **LABS**—CBC, lytes, Cr, AST, ALT, fasting glucose and/or HbA1C, lipid profile, TSH

SPECIAL

- **CARDIAC WORKUP**—after history and physical, consider ECG. Stress test if indicated
- **SLEEP APNEA WORKUP**—sleep study if clinical suspicion for obstructive sleep apnea

INVESTIGATIONS (CONT'D)

- **OBESITY HYPOVENTILATION WORKUP**— $\text{HCO}_3^- >27$ mEq/L is a reasonable screening test. ABG to confirm hypercarbia. PFT and sleep study
- **GI WORKUP**—if GERD symptoms, consider EGD to assess for Barrett esophagus

MANAGEMENT

LIFESTYLE CHANGES—**reduced calorie diet** (estimated energy requirement with 500 kcal/day deficit would lead to weight loss of 0.5 kg/week for first 3 months. A reduction of 5–10% of initial body weight is the initial goal, as this correlates with improvement in comorbidities ($\geq 10\%$ usually required for clinically important improvements). Low fat vs. low carbohydrate diets equivalent to facilitate weight loss. Intermittent fasting is a form of time restricted eating (16 hours fasting and 8 hours eating) that has shown promise as a weight management solution, improves lipid metabolism, blood pressure management and glycemic control. Consult **dietician** for dietary/behavior modification. **Exercise** (at least 150 min of moderate intensity physical activity/week). Additive benefits of combining exercise with caloric restriction on weight loss and preservation of fat free mass. Aerobic training optimal to reduce fat mass, while a resistance program is needed to increase lean body mass in middle-aged overweight/obese adults. Consult **psychologist** if psychological issues (depression, abuse, binge eating, emotional eating) are major barriers to weight loss success. Cognitive behavioural therapy (CBT) can help patients modify their insight and understanding of thoughts and beliefs concerning weight regulation, obesity and its consequences. Includes self-monitoring practices to modify behavior. CBT can be provided both by psychologists and other trained health care providers such as physicians and dieticians

Perdomo et al. *Nutrients* 2019;11(3)

DRUG THERAPY—consider for patients with BMI >30 kg/m² or BMI >27 kg/m² if comorbid conditions. **Pancreatic lipase inhibitor** reduces fat absorption (*orlistat* 120 mg PO TID ac meals). **Satiety enhancement/multiple mechanisms** (*phentermine/extended-release topiramate* 15–92 mg PO qAM [risk of teratogenicity]; *bupropion/naltrexone* 8/90–32/360 mg PO qAM). **GLP-1 agonist** (*liraglutide* 0.6 mg SC daily, increase by 0.6 mg/day weekly to target 3 mg SC daily). Efficacy of pharmacotherapy should be evaluated after 3 months. If weight loss

MANAGEMENT (CONT'D)

achieved is satisfactory ($>5\%$ in non-diabetic, $>3\%$ in diabetic patients), treatment should be continued

SURGERY—surgery is the most effective treatment for long-term weight loss in morbidly obese patients, leading to improvements in comorbidities and decreases in overall mortality. Consider for patients with BMI ≥ 40 kg/m² or BMI ≥ 35 kg/m² if comorbid conditions. Patients in consideration for bariatric surgery require multidisciplinary assessment and long-term follow-up. **Gastric restriction procedures** (*gastric banding* [adjustable band squeezes and restricts upper gastric area] is safest but requires close follow-up and long-term outcomes inferior to other procedures; *sleeve gastrectomy* [resection of greater curvature gaining popularity]). **Malabsorptive/diversionary procedures** decrease absorption via bypass of parts of small intestine and also result in a variable amount of restriction of gastric size (*Roux-en-Y gastric bypass*, *biliopancreatic diversion*). Outcomes of importance are the metabolic effects of the surgical procedures

RISK REDUCTION—**lipid control** (see HYPERTENSION p. 75). **Blood pressure control** (see HYPERTENSION p. 70). **Glycemic control** (see DIABETES p. 365)

TREATMENT ISSUES**OVERALL APPROACH**

1. Identify overweight or obese adults using BMI and waist circumference
2. If BMI >25 kg/m², conduct clinical (weight loss/gain history, comorbidities, diet and physical activity assessment, depression, mood and eating disorder assessment, HR, BP, waist circumference) and laboratory investigations (fasting glucose, lipid profiles, TSH), and treat comorbidities and other health risks if present
3. Assess readiness to change behaviors, barriers to weight loss
4. Devise goals and lifestyle modification program for weight loss and reduction of risk factors (5–10% of body weight or 0.5–1 kg/week [1.1–2.2 lb/week] for 6 months)
 - **NUTRITION**—reduce energy intake by 500–1000 kcal/day
 - **PHYSICAL ACTIVITY**—initially at least 150 minutes/week of moderate intensity aerobic exercise combined with 1–3 sessions/week of resistance exercise
 - **COGNITIVE BEHAVIORAL THERAPY**

TREATMENT ISSUES (CONT'D)

5. Reassess progress

- **SATISFACTORY**—regular monitoring. Reinforce lifestyle changes above. Address other risk factors. Periodic monitoring of weight, BMI, and waist circumference every 1–2 years
- **NON-SATISFACTORY**—in addition to reinforcement of lifestyle changes, consider the following:
 - **PHARMACOTHERAPY**—if BMI ≥ 27 kg/m² plus risk factors or BMI ≥ 30 kg/m². Consider if patient has not lost 0.5 kg/week [1.1 lb/week] by 3–6 months of lifestyle changes
 - **BIARIATRIC SURGERY**—if BMI ≥ 35 kg/m² plus risk factors or BMI ≥ 40 kg/m². Consider if other weight loss attempts have failed. Requires lifelong monitoring

2015 European Guidelines for Obesity Management in Adults
2020 CMAJ Guideline Obesity in Adults

TREATMENT ISSUES (CONT'D)

FAILURE TO LOSE AND MAINTAIN WEIGHT LOSS—referral to an obesity specialist, and weight management team should be considered if the patient fails to meet their weight loss targets in response to the prescribed interventions. Weight cycling, defined by repeated loss and regain of weight, should be limited as it has been linked to increased risk of hypertension, dyslipidemia and gallbladder disease

Related Topics

Cardiovascular Disorders (p. 29)
 Diabetes Mellitus (p. 365)
 Hyperlipidemia (p. 75)
 Hypertension (p. 70)
 Fatty Liver (p. 144)
 Sleep Apnea (p. 22)

Malabsorption Syndromes**DIFFERENTIAL DIAGNOSIS**

SALIVARY (lipase, amylase; rare cause)—radiation, sicca

STOMACH (intrinsic factor, R factor; rare cause)—pernicious anemia, gastrectomy, vagotomy

HEPATOBILIARY (bile acids; 10% of extra-colonic cases)—hepatic failure, cholestasis, biliary obstruction, terminal ileal resection

PANCREAS (lipase, amylase, HCO₃⁻; 90% of extra-colonic causes)—cancer, chronic pancreatitis, cystic fibrosis

SMALL INTESTINE (brush border/enterocytes)—celiac disease, lymphoma, infectious colitis, inflammatory colitis, ischemic colitis, radiation colitis

OTHERS— β -lipoprotein (abetalipoproteinemia), lymphatics (lymphoma)

PATHOPHYSIOLOGY

COMPLICATIONS OF MALNOURISHMENT—infections (sepsis, abscess, pneumonia), poor wound healing, respiratory failure, death

CLINICAL FEATURES

HISTORY—diarrhea (watery, steatorrhea), flatus, abdominal distension, abdominal pain (suggests chronic pancreatitis, Crohn disease, or

CLINICAL FEATURES (CONT'D)

pseudoobstruction as otherwise uncommon in malabsorption), N&V, symptoms in relation to meals (may occur within 90 min of carbohydrate ingestion), anorexia, weight loss, diet, past medical history (type 1 diabetes, celiac disease, IBD, recurrent peptic ulcer disease, previous surgery, psychiatric disorders, alcohol), medications (laxatives, diuretics, illicit drugs)

Related Topics

Cachexia (p. 442)
 Celiac Disease (p. 142)
 Vitamin B12 Deficiency (p. 453)

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT MALNOURISHED?

HISTORY—**weight change** (overall loss in past 6 months, change in past 2 weeks), **dietary intake change** relative to normal (duration, types include suboptimal solid diet, hypocaloric liquids, full liquid diet, starvation), **gastrointestinal symptoms >2 weeks** (nausea, vomiting, diarrhea, anorexia), **functional capacity** (duration,

CLINICAL FEATURES (CONT'D)

working suboptimally, ambulatory, bedridden)

PHYSICAL—loss of subcutaneous fat (triceps, chest), **muscle wasting** (quadriceps, deltoids), **swelling** (ankle edema, sacral edema, ascites)

RISK OF MAJOR POSTOPERATIVE COMPLICATIONS BASED ON SUBJECTIVE GLOBAL ASSESSMENT (SGA)

LR+

Well nourished

Defined as <5% weight loss or >5% total weight loss but recent gain and improvement in appetite 0.66

Moderately malnourished

Defined as 5–10% weight loss without recent stabilization or gain, poor dietary intake, and mild (1+) loss of subcutaneous tissue 0.96

Severely malnourished

Defined as ongoing weight loss of >10% with severe subcutaneous tissue loss and muscle wasting often with edema 4.44

APPROACH—SGA is an “accurate predictor of patients who are at higher risk of developing complications such as infection or poor wound healing.”

Detsky et al. JAMA 1994;271(1)

UPDATE—several markers have been compared to the SGA for predicting malnutrition. Serum albumin <3.0 g/dL increases likelihood of moderate/severe malnutrition (LR+ 3.3), but is not specific. A positive simplified Malnutrition Screening Tool (Have you lost weight without trying? How much weight have you lost [kg]? Have you been eating poorly because of decreased appetite?) increases likelihood of malnutrition (LR+ 13)

Simel et al. The Rational

Clinical Examination McGraw-Hill; 2009

INVESTIGATIONS**BASIC**

- LABS**—CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, fasting lipid profile, Ca, Mg, PO₄, albumin, pre-albumin, carotene, Fe, ferritin, antitransglutaminase antibody, vitamin B12, RBC folate
- IMAGING**—US abd

SPECIAL

- COLONOSCOPY**

INVESTIGATIONS (CONT'D)

- GASTROSCOPY**
- MRCP/ENDOSCOPIC US**—if suspect chronic pancreatitis
- STOOL FAT**—> 6 g/day suggests steatorrhea
- D-XYLOSE TEST**—if suspect malabsorption
- BREATH TEST**—for carbohydrate malabsorption, small bowel bacterial overgrowth and lactose intolerance, including H₂, ¹⁴CO₂, or ¹³CO₂
- ANTIINTRINSIC FACTOR ANTIBODY**—for vitamin B12 deficiency (has replaced historical Schilling test)

MANAGEMENT

SYMPTOM CONTROL—dietitian consult. Consider supplemental nutrition

TREAT UNDERLYING CAUSE**SPECIFIC ENTITIES**

MARASMUS SYNDROME—deficiency of calories resulting in stunted growth in children, loss of body fat, and generalized wasting of lean body mass without significant edema

KWASHIORKOR SYNDROME—deficiency of protein with preserved adipose tissue but significant edema, muscle atrophy, and amenorrhea

FAT-SOLUBLE VITAMIN DEFICIENCY ★KADE★

- VITAMIN K DEFICIENCY**—increased bleeding tendencies
- VITAMIN A DEFICIENCY**—follicular hyperkeratosis, night blindness
- VITAMIN D DEFICIENCY**—paresthesia, tetany, weakness, fractures due to osteomalacia
- VITAMIN E DEFICIENCY**—skeletal myopathy, spinocerebellar ataxia, pigmented retinopathy, and hemolysis

WATER-SOLUBLE VITAMIN DEFICIENCY

- VITAMIN B1 (THIAMINE) DEFICIENCY**—Wernicke syndrome, Korsakoff syndrome, Leigh syndrome (subacute necrotizing encephalomyopathy)
- VITAMIN B3 (NIACIN, NICOTINIC ACID) DEFICIENCY ★DDDD★**—Dermatitis (photosensitive, pigmented, pellagra), Diarrhea, Dementia, Death
- VITAMIN B6 (PYRIDOXINE) DEFICIENCY**—cheilosis, painless glossitis, acrodermatitis, angular stomatitis
- VITAMIN C DEFICIENCY**—scurvy with impaired collagen synthesis leading to ecchymoses, gum bleeding, petechiae, hyperkeratosis, impaired wound healing, arthralgia, weakness, neuropathy, and depression

Anorexia–Cachexia

See ANOREXIA–CACHEXIA (p. 442)

Vitamin B12 Deficiency

DIFFERENTIAL DIAGNOSIS

DIET—strict vegans, older adults, alcoholics

GASTRIC—pernicious anemia, gastrectomy, gastritis, achlorhydria

PANCREATIC—insufficiency

SMALL BOWEL—malabsorption syndromes, ileal resection, Crohn disease, blind loops, bacterial overgrowth

DRUGS—neomycin, metformin, proton pump inhibitors, N₂O

PATHOPHYSIOLOGY

DEFINITION OF VITAMIN B12 DEFICIENCY—vitamin B12 <148 pmol/L [<200 pg/mL]. Borderline is 148–222 pmol/L [200–300 pg/mL]. Normal values vary in different regions—check local laboratory ranges. Note that vitamin B12 is also called cobalamin (cbl)

VITAMIN B12 LEVELS—daily requirement 6–9 µg. Body store 2–5 mg. It takes years to deplete stores

VITAMIN B12 ABSORPTION PATHWAY

- **DIET**—vitamin B12–protein complex
- **IN STOMACH**—vitamin B12 in food is bound to protein. This is catalyzed by acid/pepsin (in stomach). Once released, vitamin B12 quickly binds to R factors produced in the saliva and gastric juice. This complex is not absorbable
- **IN DUODENUM**—pancreatic proteases break down B12–R factor bond. Vitamin B12 then binds to intrinsic factor (from stomach)
- **IN ILEUM**—absorption of vitamin B12–intrinsic factor complex

Related Topics

Macrocytic Anemia (p. 163)

Malabsorption (p. 451)

Vitamin Deficiencies (p. 452)

CLINICAL FEATURES

HISTORY—anemia, dyspnea, chest pain, fatigue, weight loss, dementia, paresthesia, weakness, falls, diet history, past medical history (gastritis,

CLINICAL FEATURES (CONT'D)

IBD, pancreatic disorders, bowel resection, alcoholism), medications

PHYSICAL—weight loss, lemon-colored skin tone (anemia and jaundice), dementia, decreased visual acuity, optic atrophy, Lhermitte sign, anemia, atrophic glossitis, spasticity, weakness, hyperreflexia, clonus, decreased vibration, and proprioception but preserved pain and temperature sensation, abnormal heel–shin test, Romberg (unsteady with eyes closed), pronator drift, gait (altered proprioception, spastic), peripheral neuropathy, vaginal atrophy

SUBACUTE COMBINED DEGENERATION—lateral (corticospinal tract) and dorsal (vibration and proprioception) columns affected. Spinothalamic tract (pain and temperature) spared. Legs affected more than arms

INVESTIGATIONS

BASIC

- **LABS**—CBC (megaloblastic anemia), peripheral smear (hypersegmented neutrophils), pancytopenia, bilirubin (↑), LDH (↑), vitamin B12, RBC folate

SPECIAL

- **SERUM ANTI - INTRINSIC FACTOR ANTIBODY**—sens 50–70%; spc near 100%
- **SERUM HOMOCYSTEINE LEVEL**—↑ if vitamin B12 deficiency. Perform if vitamin B12 level borderline
- **SERUM METHYLMALONATE LEVEL**—↑ if vitamin B12 deficiency. Perform if vitamin B12 level borderline
- **SCHILLING TEST**—rarely performed nowadays but may help to sort out etiology
 - **FIRST STAGE**—administer radiolabeled cyano-Cbl 1–2 µg PO, then Cbl 1000 µg IM 1 h later to saturate tissue-binding sites and flush out any orally absorbed radiolabeled Cbl into the urine. A 24-h urine is collected. Normally 10–35% of radiolabeled oral dose is eliminated in the urine. If Cbl malabsorption, <8% is eliminated. Diagnostic possi-

INVESTIGATIONS (CONT'D)

bilities include pernicious anemia, chronic pancreatitis, and ileal disease

- **SECOND STAGE**—if first stage is abnormal, repeat above but add oral intrinsic factor (after 4 weeks of vitamin B12 replacement). This helps to determine if vitamin B12 deficiency is related to pernicious anemia (improved absorption) vs. intestinal malabsorption (very low absorption)
- **OTHER VARIATIONS**—a trial of antibiotics (often 5 days of tetracycline) is given and the test is repeated again to investigate bacterial overgrowth syndrome. Another variation is to cook Cbl together with scrambled eggs. Patients with achlorhydria will be unable to split Cbl from food proteins and urinary excretion of Cbl will be <10%

MANAGEMENT

TREAT UNDERLYING CAUSE—see above for list. **Vitamin B12** 1000 µg SC/IM daily × 7 days, then 1000 µg SC/IM weekly for 1 month, and same dose monthly if pernicious anemia. Can continue with parenteral therapy or switch to oral (1–2 mg/day) once vitamin B12 levels are normalized. Alternatively, treatment with high dose oral cobalamin (1000–2000 mcg/day) can be used but parenteral replacement should be first line therapy in patients with neurologic deficit. Because absorption is variable, repeat levels to ensure they remain normal. Hematologic parameters improve within days to weeks; neurological often fail to remit fully on treatment, but improvement may be seen within months. Watch for hypokalemia, salt retention, and thrombocytosis early in the course of therapy

Diet and Supplemental Nutrition

Rahman et al. *JPEN* 2016;40(4)

Xue et al. *JPEN* 2011;35(1)

INTRODUCTION

This section provides an overview of nutritional assessment, hospital diet types, enteral feeds, and supplemental parenteral nutrition

OVERVIEW—malnutrition is prevalent in hospital settings (15–70% depending on population types, institution, and methods of assessment). Malnutrition independently associated with detrimental outcomes, increased healthcare costs. Nutrition screening should be completed routinely in all patients admitted to acute care settings. Nutrition assessment provides greater detail compared to nutrition screening. Nutrition screening does not require specialized expertise, and should be easy and quick to use with high sensitivity and specificity. However, the [Nutrition Care in Canadian Hospitals Study](#) reported an absence of a systematic approach related to nutrition care in the hospital setting

NUTRITION SCREENING—many nutrition screening tools have been developed both for general use and in specific disease populations. Nutrition screening is a primary mechanism for patients to be referred to a registered dietician for further nutrition assessment, diagnosis and intervention. Selected screening tools: NRS-2002, MNA-SF, MUST, NST/BAPEN, MST. Patients who screen positive, should be referred to a registered dietician for more comprehensive nutrition assessment and intervention

INTRODUCTION (CONT'D)

NUTRITIONAL ASSESSMENT—there are many different nutrition assessment tools available. Some techniques are sophisticated, expensive, or not widely available (e.g. cross-sectional measures of sarcopenia, whole body conductance and impedance, dual-energy X-ray absorptiometry, neutron activation). Other tools are more widely available and may be applied at the bedside (e.g. anthropometry, weight loss [>10% of usual body weight is strongly indicative of malnutrition and related to higher morbidity and mortality], mid-arm circumference, hand-grip strength, and global assessment tools (**Subjective Global Assessment** [SGA], and Global Leadership Initiative on Malnutrition [GLIM]). Biochemical markers such as serum albumin level, transferrin, retinol binding protein have been used but may be unreliable as they are affected by non-nutritional factors such as acute inflammatory states, protein losses (fistula, nephrotic syndrome etc), and may be normal even in states of chronic starvation due to compensatory decrease in protein degradation and shift from extracellular compartments to the intracellular. Similarly, sarcopenia may arise from both nutritional and other factors (age, lack of mobility, active inflammation), and therefore only partially responsive to nutrition therapy. A gold-standard nutrition assessment tool is still

INTRODUCTION (CONT'D)

lacking. In the clinical setting, the SGA and the instrument detailed in the Academy of Nutrition and Dietetics/ASPEN (AND/ASPEN) are very similar clinical tools for nutrition assessment, and cover aspects of nutrition history that include body weight changes, dietary intake and functional capacity, and muscle and fat measures on physical examination. These tools have predicted malnutrition compared to other instruments, and predict morbidity, mortality, hospital length of stay and cost. Given their simplicity, these tools are recommended as practical first line bedside nutrition assessment tools

FACTORS INFLUENCING ENERGY REQUIREMENTS—age, previous nutritional status, comorbidities (sepsis, obesity), activity

DAILY ENERGY REQUIREMENTS

- **14 kcal/kg [6.4 kcal/lb] BODY WEIGHT**—BMI >40 kg/m²
- **21 kcal/kg [9.5 kcal/lb] BODY WEIGHT**—BMI 30–39 kg/m²
- **25 kcal/kg [11.4 kcal/lb] BODY WEIGHT**—single organ failure, heavily sedated
- **30–40 kcal/kg [13.6–18.2 kcal/lb] BODY WEIGHT**—multi-organ failure, sepsis, trauma, postop major surgery, severe malnutrition

Energy requirement calculations assume a dry body weight (adjust for presence of ascites/peripheral edema)

ESTIMATION OF BASAL METABOLIC RATE (BMR)

20 kcal/kg [9.1 kcal/lb] BODY WEIGHT—can be used as a rough estimate

MIFFLIN-ST. JEOR EQUATION (Mifflin et al. *Am J Clin Nutr* 1990;51[2])—validated for ambulatory adults and overweight or obese individuals:

- Male: $RMR = [9.99 \times wt (kg)] + [6.25 \times ht (cm)] - [4.92 \times age (years)] + 5$
- Female: $RMR = [9.99 \times wt (kg)] + [6.25 \times ht (cm)] - [4.92 \times age (years)] - 161$

HARRIS-BENEDICT EQUATION—tends to underestimate BMR in overweight and obese patients:

- Male: $RMR = 66.47 + [13.75 \times wt(kg)] + [5 \times ht(cm)] - [6.76 \times age(years)]$
- Female: $RMR = 655.1 + [9.56 \times wt(kg)] + [1.85 \times ht(cm)] - [4.68 \times age (years)]$

ACTIVITY/STRESS FACTORS—the BMR or resting metabolic rate can be multiplied by a factor that captures stress or activity to calculate the total number of calories required

ESTIMATION OF DAILY REQUIREMENTS**DAILY PROTEIN REQUIREMENTS**

- **0.5–0.8 g/kg [0.23–0.36 g/lb] BODY WEIGHT** (protein restriction) for initial 48 h then **1.2–1.5 g/kg [0.55–0.68 g/lb] BODY WEIGHT**—decompensated cirrhosis, and hepatic encephalopathy (note: most cirrhotic patients suffer from malnourishment and protein restriction may not be warranted)
- **0.8–1 g/kg [0.36–0.45 g/lb] BODY WEIGHT** (protein restriction)—renal failure (no dialysis)
- **1–1.2 g/kg [0.45–0.55 g/lb] BODY WEIGHT**—not septic, minor trauma/surgery, non-malnourished, single system failure
- **1.2–1.5 g/kg [0.55–0.68 g/lb] BODY WEIGHT**—multi-organ failure, hemodialysis, sepsis, major trauma/surgery, closed head injury, malnutrition, peritoneal dialysis
- **1.5–2.0 g/kg [0.68–0.91 g/lb] (IDEAL) BODY WEIGHT**—multiple surgeries, trauma, severe burns, long bone fractures, peritonitis

FLUID REQUIREMENTS

- Fluid requirements are highly variable, depending on the patient's state of hydration, stress, and losses (e.g. ostomy losses). Fluid restrictions may be indicated in cases of heart failure, renal or liver failure, SIADH. Calculating fluid requirements can be done in two ways:

• **AGE BASED APPROACH:**

- 18–55 years = 35 mL/kg/day
- 55–65 years = 30 mL/kg/day
- 65 years = 25–30 mL/kg/day (minimum 1500 mL/day)

• **WEIGHT BASED APPROACH:**

- For the first 10 kg of body weight, give 100 mL/kg/day
- For the second 10 kg of body weight, add 50 mL/kg/day
- For each additional kg of body weight, add 20 mL/kg/day if <50 years of age **or** 15 mL/kg/day if >50 years of age

HOSPITAL DIET TYPES

STANDARD—regular, full fluid, clear fluid

THERAPEUTIC—heart healthy, diabetic, renal (predialysis, hemodialysis, peritoneal dialysis), sodium restricted (2 g Na), fiber restricted, high protein/cal, gluten/lactose free

SPECIAL—diets for cultural/religious modifications, disease-specific requirements (e.g. gluten free), various nutrient-specific therapeutic modifications (e.g. high K⁺, purine restricted), neutropenic, post-gastrectomy

HOSPITAL DIET TYPES (CONT'D)**DIET CONSISTENCY MODIFICATIONS**

- **MODIFIED SOLIDS**—pureed, diced, diced dysphagia, easy to chew, minced
- **THICKENED FLUIDS**—level 1 (nectar), level 2 (honey), level 3 (pudding)
- **NOTE**—if dysphagia suspected, consider swallowing assessment to determine most appropriate consistency

ENTERAL NUTRITION OVERVIEW

ADVANTAGES—maintains gut integrity, immunologically favorable, fewer complications compared to total parenteral nutrition

CONTRAINDICATIONS—hemodynamically unstable, severe ileus, bowel obstruction, bowel perforation, UGI bleed, distal anastomosis, NG output >1 L/24 h, high output proximal fistula, uncontrollable nausea, vomiting and/or diarrhea. While short bowel syndrome, radiation enteritis, and autoimmune enteropathy are not absolute contraindications, these conditions may exacerbate diarrhea, increase losses due to malabsorption, and worsen malnutrition. Transition to parenteral nutrition in these circumstances is frequently required to support hydration and maintain nutrition

ROUTES FOR ENTERAL FEEDS

NASOGASTRIC/KEOFEED/OROGASTRIC TUBE—expected use <6 weeks. Risk of aspiration (orogastric used for patients with basal skull fractures or choanal atresia)

NASOJUNAL TUBE—expected use <6 weeks. Less chance of aspiration/pneumonia; used for patients with high risk aspiration, delayed gastric emptying, or who require feeding past ligament of Treitz (e.g. pancreatitis)

GASTROSTOMY TUBE—expected use >6 weeks. Risk of aspiration, perforation, malposition

JEJUNOSTOMY TUBE—expected use >6 weeks. Decreased aspiration risk (used for long term post-pyloric feeds). Risk for tube migration, perforation

ADMINISTRATION OF ENTERAL FEEDS

CONTINUOUS—usually given over 24 h. Compared to bolus feed, decreased aspiration risk, and better glycemic control. Start full strength formula at 25 mL/h, increase by 25 mL q4h to goal rate. In select circumstances tube feeding rate may need to commence at a lower rate with slower advancement in feeding rate. Feeding rate advancement

ADMINISTRATION OF ENTERAL FEEDS (CONT'D)

should be completed in collaboration with the treating dietician. In hospitalized patients, check gastric residuals q4h and continue to increase if <250 mL. If >250 mL, hold feeds, initiate pro-motility therapies, and re-check after 4 h

NOCTURNAL—for patients eating 50% of requirements during daytime; wean off tube feed. Nocturnal feeds can also be used in the outpatient setting, to treat malnutrition together with full oral daytime diet

BOLUS/INTERMITTENT—for more mobile patients. More physiologic. Start with 1 can (250 mL) over 30–60 min 4x/day

ENTERAL NUTRITION FORMULAS

Broadly, EN formulas are divided into polymeric, semi-elemental and elemental formulas. Polymeric formulas contain whole proteins, carbohydrates and fats, and are the preferred formula for patients who do not have maldigestion or malabsorption. Semi-elemental formulas contain partially pre-digested proteins (peptide-based), while elemental formulas contain fully pre-digested proteins (amino-acids). Semi-elemental and elemental formulas are more expensive and should be reserved to treat patients who are intolerant of polymeric feeds, or in those who are diagnosed with maldigestion/malabsorption

ISOSOURCE HN—1.2 kcal/mL, goal usually 60–85 mL/h; 0.053 g protein/mL. Fiber containing. Standard formula

ISOSOURCE 1.5—1.5 kcal/mL, 0.068 g protein/mL, fiber containing

RESOURCE 2.0—2.025 kcal/mL, 0.084 g protein/mL. For fluid-restricted patients

PERATIVE—1.3 kcal/mL, 0.067 g protein/mL arginine containing, lower in fat

NOVASOURCE RENAL—2 kcal/mL, 0.074 g protein/mL For renal patients on dialysis or pre-renal with high electrolytes

ISOSOURCE VHN—1 kcal/mL, 0.063 g protein/mL. For catabolic patients, high protein

RESOURCE DIABETIC—1.06 kcal/mL, 0.064 g protein/mL. Higher fat, low carbs, fiber containing. For difficult to control blood sugars

PEPTAMEN 1.5—1.5 kcal/mL, 0.068 g protein/mL. Semi-elemental (low residue). Used for patients with malabsorption problems, severe diarrhea

PEPTAMEN AF 1.2 with PREBIO—1.2 kcal/mL, 0.0756 g protein/mL. Semi-elemental (low residue), higher protein, contains EPA/DHA and

ENTERAL NUTRITION FORMULAS (CONT'D)

fructo-oligosaccharides (FOS)/inulin (soluble fiber). For highly stressed individuals who may experience inflammation or feeding intolerance (malabsorption)

PULMOCARE—1.5 kcal/mL, 0.063 g protein/mL. Low carbohydrate to lower CO₂ production. For patients with COPD or CO₂ retention

ADDITIONS TO ENTERAL FEEDS

PECTIN—20 mL BID. Soluble fiber to decrease diarrhea

BENEPROTEIN—one scoop=6 g protein and 25 kcal

GLUTAMINE—main fuel for gut enterocytes. For burns and trauma. Consult dietician for recommendations

COMPLICATIONS OF ENTERAL FEEDS

DIARRHEA—due to osmotic load/rapid feeding rate, contamination, medications, gastroenteritis, *Clostridioides difficile* (formerly *Clostridium*)

VOMITING—associated with aspiration

ASPIRATION—prevent by using small bore feeding tube (<10 Fr), monitor tube migration, post-pyloric position of tube, continuous schedule, elevation of head of bed by >30° during feeding, positioning of patient on right side, ambulation, use of promotility agents 30 min before feeding (*metoclopramide* 10 mg PO QID) to decrease post-feed gastric residual volumes, ensure bowel routine

TUBE OBSTRUCTION

CONSTIPATION—due to reduced bowel motility, dehydration/inadequate free water, inadequate fiber, bowel obstruction

PARENTERAL NUTRITION OVERVIEW**TOTAL PARENTERAL NUTRITION (TPN)**

- **INDICATIONS**—unusable GI tract for at least 5–7 days, or malnourished with unusable GI tract at hospital admission. Bowel resection/obstruction/fistula without distal feeding access, intractable diarrhea/malabsorption/vomiting, acute GI bleed, failure of enteral nutrition to meet nutritional needs, short gut, prolonged ileus, mesenteric ischemia, radiation enteritis, autoimmune enteropathy
- **CONTRAINDICATIONS**—GI tract usable and capable of absorbing adequate nutrients to meet requirements within 5–7 days of NPO status in

PARENTERAL NUTRITION OVERVIEW (CONT'D)

a well-nourished patient, non-survivable injury/illness to be assessed on an individual basis, aggressive support not desired, risks of TPN outweigh benefits, inability to obtain appropriate venous access, severe hemodynamic instability

- **COMPLICATIONS**—GI tract mucosal atrophy, no maintenance of gut barrier, metabolic disturbances (hyperglycemia, cholestasis/hepatic steatosis, electrolyte imbalances, refeeding syndrome), cirrhosis, electrolyte derangements, volume overload, line sepsis

PERIPHERAL PARENTERAL NUTRITION (PPN)—short-term use only as nutritionally inadequate; must be <1000 mOsm, usually requires larger volumes of fluid for kcal/protein delivery. Prioritize PPN use for malnourished patients without central venous access

COMPONENTS OF TOTAL PARENTERAL NUTRITION**TRAVASOL**

PROTEIN—4 kcal/g, 10% amino acid

CARBOHYDRATE—3.4 kcal/g; 70% dextrose solution

LIPID—2 kcal/mL; 20% lipid emulsion. Note: for patients receiving propofol, (dispensed in a 10% lipid emulsion; 0.1 g fat/mL), this source of energy (1.1 kcal/mL) must be taken into account in the overall nutrition prescription. Older lipid emulsions include intralipid (primarily soybean lipid, with largely n-6 lipid composition). However, newer lipid emulsions include clinoleic (largely monounsaturated lipid) and SMOF lipid (mix of soybean oil, medium chain triglycerides, olive oil and fish oil). Newer lipid emulsions are thought to protect the liver from long term cholestasis and reduce the risk of cirrhosis

ELECTROLYTES—Na (1–2 mmol/kg/day), K (60–120 mmol/day or 1–2 mmol/kg/day), Ca (10–15 mmol/day), Mg (8–20 mmol/day), PO₄ (20–40 mmol/day)

MICRONUTRIENTS—multivitamin solution (10 mL/day), vitamin K (5–10 mg/week) as required, trace element solution (1 mL/day), acetate as required. Although medications such as insulin and H₂ antagonists can be added to the PN solution, this is not recommended routinely, as PN composition adjustment takes time and cannot be addressed immediately

COMPONENTS OF TOTAL PARENTERAL NUTRITION (CONT'D)

DAILY LIPID REQUIREMENTS (FOR PARENTERAL NUTRITION)—0.8–1 g/kg [0.36–0.45 g/lb] (ideal) body weight. No more than 30% of energy as fat and limit lipid to < 1.0 g/kg day for hepatoprotection. At least 2–4% of total caloric intake should be essential fatty acids to prevent deficiency states

DAILY CARBOHYDRATE REQUIREMENTS (FOR PARENTERAL NUTRITION)—2–4 mg/kg/min (start low and go slow if concern regarding refeeding syndrome)

REFEEDING SYNDROME

RISK FACTORS—severe malnutrition/chronic malnutrition due to underfeeding/chronic disease, anorexia nervosa, cancer, alcoholism, severe unintentional weight loss/morbid obesity with massive weight loss, prolonged fasting (7–10+ days)

REFEEDING SYNDROME (CONT'D)

MECHANISM—carbohydrate administration leading to a sudden shift from fat to carbohydrate metabolism → ↑ insulin secretion → stimulates cellular uptake of phosphate → ↓ Mg, ↓ PO₄, ↓ K. Key complications include cardiac (impaired contractility, heart failure, arrhythmias), neurological (seizures) and respiratory/muscular weakness

TIME FRAME—usually occurs within 3 days of initiation of feed (parenteral, enteral feed, oral intake, IV glucose)

MANAGEMENT—start carbohydrate/feeds low and increase slowly. Monitor electrolytes (lytes, Mg, PO₄, daily × 3 days and repeat PRN), monitor glycemic control, monitor fluid balance/signs of edema/fluid overload and weight, vitamin supplementation (e.g. *thiamine* 100 mg IV/PO daily for 5–7 days, *folic acid* 1 mg/day)



Physiologic Changes in Pregnancy

CLINICAL IMPLICATIONS—to maintain adequate uterine perfusion, fetal oxygenation, and nutrient delivery. May potentially mask and limit responses to serious maternal illness

IMPORTANT CHANGES IN PREGNANCY		
	Change	Clinical implication
Core temperature	Unchanged	Fever should be investigated and treated; maternal fever is teratogenic in T ₁ , and associated with adverse perinatal outcomes in T ₃
Upper airway	↑ edema and friability (hyperemia and glandular function)	Nasal congestion, epistaxis and snoring common. Failed/difficult intubation more common than non-pregnant state
Thorax	↑ circumference, elevated diaphragm (~4 cm) but normal excursion	Anatomical landmarks for thoracentesis shifted. ECG changes: QRS axis deviates to left in late pregnancy ± T-wave inversion ± ST depression in inferior and lateral leads
Tidal volume	↑ early in T ₁ at expense of FRC/RV	Expected PaO ₂ 100–110 mmHg, PaCO ₂ 28–32 mmHg (mild respiratory alkalosis), HCO ₃
Respiratory rate	Minimal increase by ~3–4 breaths/min at term	18–21 mmol/L (compensatory reduction), arterial pH 7.40–7.45 (normal/slight alkalosis). An elevated RR or low O ₂ sat should be investigated
Minute ventilation (RR × TV)	↑ by 50% at term	
Oxygen consumption	↑ by 15–20%	
Oxygen saturation	Median 97% (93–99%)	
Heart rate	↑ by 15–20 beats/min by T ₃	Pregnancy may unmask underlying heart disease, especially obstructive lesions.
Stroke volume	↑	Exacerbation of pre-existing tachyarrhythmias or <i>de novo</i> presentations are common. Compression of IVC by gravid uterus in supine position may ↓ cardiac output by up to 25%, thus left lateral decubitus position recommended
Cardiac output (HR × SV)	↑ by 30–50% (peaks ~28 weeks)	Greatest risk periods for cardiac decompensation are: between 28 and 32 weeks gestation (peak maternal blood volume), during labor (hemodynamic changes), and in early post-partum period (fluid shifts)
Ejection fraction	Unchanged	

IMPORTANT CHANGES IN PREGNANCY (CONT'D)

	Change	Clinical implication
Systemic vascular resistance	↓	
Blood pressure	↓ by 10–15 mmHg (nadir at ~18–24 weeks) with gradual increase back to baseline by 40 weeks	↓↓ DBP > ↓ SBP → widened pulse pressure
Renin-angiotensin-aldosterone system	Upregulated	↑↑ renin, ↑ aldosterone, ↓ aldosterone/renin ratio in response to systemic vasodilation, ↓ SVR and progesterone effects
Renal blood flow	↑ by 80%	↑ kidney length by 1–1.5 cm
Glomerular filtration rate	↑ by 40–50%	Hyperfiltration with ↓ in serum Cr to ~35–70 mmol/L [0.4–0.8 mg/dL]; higher levels suggest renal disease. Dose adjustments for renally-cleared drugs may be required
Collecting system	↑ dilatation of renal pelvis and calyces	↑ risk of urinary tract infections and kidney stones.
Plasma volume	↑ by 30–50% (1.1–1.6 L) by T ₃	JVP height remains normal. Dilution of albumin
RBC mass	↑ by 40%	Iron requirements ↑ by 50%. Disproportionate ↑ in plasma volume results in physiologic anemia (hemoglobin ↓ by ~20 g/L [2 g/dL] by T ₃)
Coagulation system	↑ levels of coagulation factors, decreased fibrinolysis	10 × ↑ risk for venous thromboembolism during pregnancy and up to 6 weeks postpartum (<0.1% of all pregnancies)
Gastric pH	↑	Impaired drug absorption, dose adjustments may be required
Lower esophageal sphincter pressure	↓ (progesterone effect)	GERD, nausea and vomiting common. ↑ risk of aspiration with intubation
GI motility	↓ (progesterone effect)	Constipation and abdominal bloating common. Impaired drug absorption, dose adjustments may be required
Hepatic metabolism	Changes in drug metabolism (e.g. cytochrome P450 system enzymes may be ↑ or ↓)	Dose adjustments may be required for hepatically-metabolized medications (e.g. antiepileptics)
Biliary system	↓ motility, ↑ bile cholesterol secretion and saturation	↑ risk for gallstones during pregnancy. ↑ ALP from placental production
Thyroid	↑ thyroid gland size by 18% ↑ estrogen → ↑ thyroxine-binding globulin → total T4 and ↑ total T3 (but free T4 and free T3 mostly remain normal)	Thyroid function tests should be interpreted using local trimester-specific TSH and total T4 reference ranges for pregnant women. For those already on levothyroxine replacement, ~75% of women will require an increased dose during pregnancy. Homology between hCG and TSH can result in hCG mediated hyperthyroidism during pregnancy
Glucose metabolism	↑ insulin resistance (peak ~30 weeks gestation) from human placental lactogen and progesterone	Screen for gestational diabetes at 24–28 weeks gestation

Adapted from Green et al. *Obstet Gynecol* 2020;135(3)

MATERNAL MORTALITY AND RESUSCITATION

MATERNAL MORTALITY—defined as death during pregnancy or up to 1 year postpartum. Most common causes are largely preventable and include cardiovascular disease, venous thromboembolism, amniotic fluid embolus, obstetric hemorrhage, infection (sepsis), suicide, and preeclampsia/eclampsia

MATERNAL RESUSCITATION—follow ACLS algorithm for non-pregnant adult population including medications, dosages (for medications, defibrillation, cardioversion, pacing), compressions, and ventilation rate. Special considerations include: (1) obtaining venous access above the

MATERNAL MORTALITY AND RESUSCITATION (CONT'D)

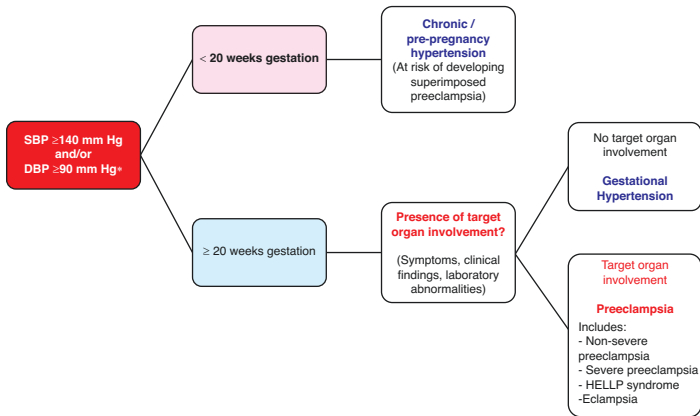
diaphragm (potential obstruction from gravid uterus below diaphragm); (2) chest compressions performed higher up on sternum; (3) left uterine displacement (first-line) or left lateral tilt (second-line) to relieve aorto-caval compression by gravid uterus; (4) difficult airway and ventilation require expertise; (5) perimortem caesarean section if no return of spontaneous circulation within 4 min; (6) remove fetal monitors for defibrillation if possible (theoretical risk to fetus). *Do not delay treatment: healthy baby requires healthy mother!*

Hypertensive Disorders of Pregnancy

2018 Hypertension Canada Guideline
Management of Hypertension in Pregnancy
2014 Society of Obstetricians and Gynaecologists of Canada Guideline
Hypertensive Disorders of Pregnancy

PATHOPHYSIOLOGY

CLASSIFICATION—see Fig. 1 for simplified classification of hypertensive disorders of pregnancy (HDP)



HELLP, hemolysis elevated liver enzymes and low platelets; SBP, systolic blood pressure.

*Rule out: white coat hypertension and transient hypertension

(Reprinted with permission from Butalia et al. *Can J Cardiol* 2018;34(5):526-31 courtesy of Elsevier)

PATHOPHYSIOLOGY (CONT'D)

- **HYPERTENSION**—SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg (average of at least 2 measurements taken at least 15 minutes apart). HDP occurs in ~7% (5–10%) of all pregnancies
- **SEVERE HYPERTENSION**—SBP ≥ 160 mmHg and/or DBP ≥ 90 mmHg. Associated with increased risk of maternal stroke (ischemic and hemorrhagic) and adverse fetal outcomes
- **CHRONIC (PRE-EXISTING) HYPERTENSION**—SBP ≥ 140 and adverse fetal outcomes and/or DBP ≥ 90 mmHg *prior to* 20th week of gestation. Complicates ~1–3% of pregnancies; ~20% risk of developing superimposed preeclampsia
- **GESTATIONAL HYPERTENSION**—new-onset hypertension ≥ 20 weeks gestation; ~35% risk of evolving to preeclampsia
- **PREECLAMPSIA**—occurring *de novo*, defined as gestational hypertension, with maternal or fetal end-organ complications, as outlined below. *Diagnosis of preeclampsia does not require presence of proteinuria*
- **SUPERIMPOSED PREECLAMPSIA**—pre-existing (chronic) hypertension with the development of one or more characteristic of preeclampsia (i.e. new or worsening proteinuria [≥ 300 mg/day with 24-h urine collection or ≥ 30 mg/mmol on spot urine protein/Cr ratio], or resistant hypertension [i.e., uncontrolled BP with ≥ 3 antihypertensive drugs], or development of end-organ complications (maternal or fetal) [as outlined below]) at ≥ 20 weeks gestation

MECHANISMS OF PREECLAMPSIA—multifactorial involving complex immunologic, genetic and maternal factors that lead to impaired placentation \rightarrow placental production of numerous circulating substances that directly impair maternal systemic vascular endothelial cell function \rightarrow a broad range of maternal and fetal end-organ involvement

- **MATERNAL END-ORGAN COMPLICATIONS OF PREECLAMPSIA**—headaches/visual symptoms, chest pain/dyspnea, oxygen saturation $< 97\%$, new-onset nausea/vomiting, elevated liver enzymes (AST/ALT) or creatinine, thrombocytopenia, hyperuricemia, oligohydramnios, IUGR, abnormal uterine artery or umbilical cord Doppler flow
- **SEVERE COMPLICATIONS OF PREECLAMPSIA**—these warrant consideration of delivery by obstetrical team: generalized tonic-clonic seizures (eclampsia), PRES (posterior reversible leukoencephalopathy syndrome), cortical blindness/retinal detachment, altered level of

PATHOPHYSIOLOGY (CONT'D)

- consciousness, stroke, pulmonary edema, acute kidney injury (creatinine > 150 $\mu\text{mol/L}$ [1.7 mg/dL]), hepatic dysfunction/hematoma/rupture, hemolysis, placental abruption, fetal demise. **HELLP** (Hemolysis, Elevated Liver Enzymes, Low Platelets) syndrome = constellation of findings considered a severe form of preeclampsia
- **RISK FACTORS**—extremes of age (< 18 , > 40), nulliparity, multifetal gestations, prior preeclampsia, obesity, chronic (pre-existing) hypertension, type 1 or 2 diabetes mellitus, chronic kidney disease, antiphospholipid antibodies, inter-pregnancy interval ≥ 10 years, infertility and use of fertility treatments

CAUSES OF DEATH—stroke (both ischemic and hemorrhagic) from uncontrolled hypertension, eclampsia, and cardiac involvement (myocardial infarction and heart failure)

CLINICAL FEATURES

HISTORY—inquire about headaches, visual disturbances, epigastric or RUQ pain, new-onset nausea/vomiting, new shortness of breath, rapid increase in swelling (face, hands, legs) and weight gain, and decreased fetal movements

PHYSICAL—check vitals, look for retinal changes (edema, ischemia, hemorrhages, etc.), heart failure, edema (facial, hands, legs), RUQ tenderness, hyperreflexia and clonus

INVESTIGATIONS**BASIC**

- **LABS**—CBC, Cr, spot urine for protein to creatinine ratio*, AST, ALT, albumin, uric acid (hyperuricemia associated with preeclampsia)

*If unavailable, consider spot albumin to creatinine ratio, dipstick, or 24 hour urine for protein

SPECIAL

- **BLOOD TESTS**—peripheral smear, lytes, urea, bilirubin, albumin, ALP, PTT/INR, fibrinogen, LDH if indicated

FETAL—biophysical profile and fetal US (with Dopplers)

MANAGEMENT

ACUTE—ABC, O₂ to keep sat $> 95\%$, IV with judicious fluid (\uparrow risk of volume overload)

ACUTE LOWERING OF SEVERE HYPERTENSION (SBP ≥ 160 mmHg or DBP ≥ 110 mmHg)—IV *labetalol* (start with 10–20 mg IV,

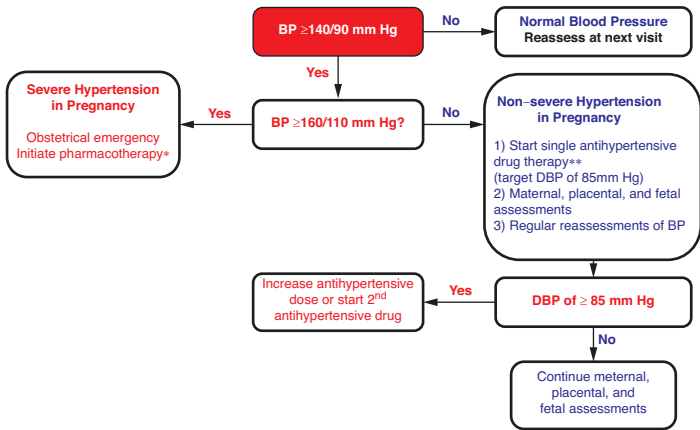
MANAGEMENT (CONT'D)

repeat 20–80 mg IV q10–30 min, or infusion 1–2 mg/min, max 300 mg), oral *nifedipine short-acting tablets or capsules* (pending availability) 5–10 mg PO q30min, or *hydralazine* (start with 5 mg IV, repeat 5–10 mg IV q20–30 min, max 20 mg). Severe cases may require continuous infusion in a monitored setting. Consider urgent delivery if not controlled. Regular maternal, placental and fetal assessments by interdisciplinary team are required

CHRONIC MANAGEMENT OF NON-SEVERE HYPERTENSION (SBP 140–159 mmHg or DBP 90–109 mmHg)—see **Fig. 2 Target DBP of 85 mmHg** (as per the CHIPS trial) to reduce episodes of severe maternal hypertension (a validated surrogate of adverse maternal and obstetrical outcomes) without significantly increasing risk of

MANAGEMENT (CONT'D)

adverse fetal outcomes. Start with single antihypertensive drug therapy of first-line drugs (e.g. *labetalol* 100–400 mg PO BID–TID, max 1200 mg/day, *nifedipine XL* 20–60 mg PO daily, max 120 mg/day, or *methyl dopa* 250–500 mg PO BID–TID, max 3 g/day, or other beta-blockers). Other antihypertensive drugs can be considered as second-line including: clonidine, hydralazine, and thiazide diuretics. If target DBP of 85 mmHg is not achieved with monotherapy, antihypertensive drugs from other classes should be added. Avoid ACE inhibitors and ARBs in pregnancy. Atenolol may be associated with fetal growth restriction and prazosin may be associated with toxicities. Regular maternal, placental and fetal assessments by interdisciplinary team are required



* see Magee et al. *Pregnancy Hypertens* 2014;4(2).

(Reprinted with permission from Butalia et al. *Can J Cardiol* 2018;34(5):526-31 courtesy of Elsevier)

MANAGEMENT (CONT'D)

SEIZURE PREVENTION AND TREATMENT—*MgSO₄* 4 g IV bolus, then 1–2 g/h × 24–48 h. Re-bolus on ongoing seizures. *MgSO₄* use generally requires 1:1 nursing to monitor for toxicity (respiratory depression, hypotension, muscle weakness, hyporeflexia). Give calcium gluconate if magnesium toxicity present. *MgSO₄* is contraindicated in myasthenia gravis (may precipitate myasthenic crisis). Benzodiazepines, phenytoin and phenobarbital can be considered as adjunctive therapy if ongoing seizures despite *MgSO₄*

MANAGEMENT (CONT'D)

DELIVERY—is the definitive treatment for pre-eclampsia, eclampsia, and HELLP, but the patient may continue to worsen for several days after delivery. Administer steroids to promote fetal lung maturation prior to 34 weeks if early delivery

POSTPARTUM—gestational hypertension, pre-eclampsia/eclampsia/HELLP syndrome can present *de novo* or worsen in the postpartum period. BP generally increases in the early postpartum period and may peak on days 3–6 postpartum due to volume redistribution. Monitor and

MANAGEMENT (CONT'D)

continue antihypertensive therapy. New onset of postpartum preeclampsia may require treatment with $MgSO_4$ and consideration of examination for retained placenta. Hypertension and biochemical abnormalities of preeclampsia generally resolve within 6–12 weeks, though these may remain present for up to a year depending on the severity. Laboratory abnormalities (e.g. proteinuria) that do not resolve by 3–6 months may require further work-up

RECURRENCE—preeclampsia recurrence rate is variable at ~10–40%. Consider antiphospholipid syndrome screen if preeclampsia or placental insufficiency <34 weeks, particularly with fetal growth restriction or placental abruption

PREVENTION OF PREECLAMPSIA—low dose ASA 81–162 mg PO nightly before 16 weeks' gestation has been shown to reduce the risk of early onset preeclampsia (with 162 mg dosage preferred). Exercise during pregnancy also reduced the risk of gestational hypertension and preeclampsia. Supplemental calcium 1000 mg/day (in women with dietary calcium intake <600 mg/day) is also recommended. Neither folic acid nor

MANAGEMENT (CONT'D)

vitamin D have been demonstrated to be effective in ↓ risk of preeclampsia

LONG-TERM—women with a history of HDP are at high risk of developing cardiovascular risk factors (chronic hypertension, type 2 diabetes, dyslipidemia, and obesity) within the first few years afterwards. Also 2–5 times higher risk of premature atherosclerotic vascular diseases (stroke, TIA, MI, angina, and peripheral arterial disease) and kidney disease. Routine vascular risk factor screening, prevention through lifestyle behaviours, and treatment with lifestyle and pharmacotherapy are essential. Importantly, women with history of preeclampsia experience high rates of postpartum mental health disorders (post-traumatic stress disorder, depression, and anxiety); monitor and provide mental health support

Related Topics

Hypertension (p. 70)

Proteinuria (p. 91)

Seizures (p. 335)

Pulmonary Diseases in Pregnancy**ASTHMA**

TREATMENTS—similar to non-pregnant patients. β -agonists, anticholinergics, and glucocorticoids (inhaled, systemic) have limited fetal risks. Leukotriene antagonists if refractory. Keep O_2 sat >95% to prevent fetal hypoxia. Consider stress dose steroids during delivery if patient required moderate systemic steroids for >3 weeks in the preceding year. Trigger avoidance and treatment (e.g. usual causes of asthma exacerbation, GERD, and infections)

VENOUS THROMBOEMBOLISM

PATHOPHYSIOLOGY—increased risk of DVT/PE due to ↑ factors I, VII, VIII, IX, X, von-Willebrand factor, and fibrin, ↓ protein S and fibrinolytic activity, and increased resistance to activated protein C, especially during T_3 . Also, stasis due to ↓ venous tone and flow and compression of vessels by gravid uterus. Similar risk of DVT/PE in each trimester but highest post-partum; 90% of DVT in pregnancies are left-sided and majority are pelvic
DIAGNOSIS—if suspect venous thromboembolism, consider initiation of LMWH while waiting for

VENOUS THROMBOEMBOLISM (CONT'D)

investigations. For DVT workup, perform compression US; if pelvic vein DVT suspected, consider MRV pelvis, Doppler study, or (postpartum) CT of pelvic veins. Otherwise, repeat compression US in 5–7 days if still symptomatic. For PE workup, perform V/Q scan if CXR normal. If CXR abnormal and/or V/Q scan non-diagnostic, proceed with CT chest (pulmonary angiogram protocol). Algorithms involving clinical features and D-dimer may help minimize radiology testing. CT (pulmonary angiogram protocol) is associated with lower fetal radiation exposure than V/Q scan in T_1 – T_2 , but higher risk of maternal breast cancer (14% increased lifetime risk) and may be non-diagnostic peri-partum due to increased maternal cardiac output limiting contrast filling

RADIATION RISKS—fetal exposure of <5 cGy [5 rad] accumulatively in each pregnancy is considered acceptable, but oncologic effects controversial (e.g. childhood leukemia). Consider proximity of fetus to radiation site (i.e., radiation from CT chest > V/Q scan in T_3) and limit where possible (i.e., abdominal shields) and timing of

VENOUS THROMBOEMBOLISM (CONT'D)

exposure (early T₁ and miscarriage, later T₁ and organogenesis, T₂₋₃ and CNS development as well as risk of childhood cancer). Gadolinium exposure in pregnancy associated with ↑ stillbirth, neonatal death and inflammatory conditions (skin and rheumatologic)

FETAL RADIATION EXPOSURE FOR COMMON IMAGING MODALITIES

Imaging	Estimated fetal radiation exposure (rad)
Ultrasound	None
CXR	<0.001
CT head	<0.001
V/Q scan	0.01–0.02 ventilation (V) 0.01–0.03 perfusion (Q)
CT chest (PE protocol)	0.0003–0.002 (T ₁) 0.0008–0.0077 (T ₂) 0.005–0.013 (T ₃)
Pulmonary angiogram	<0.05 via brachial route 0.2–0.3 via femoral route
Cardiac angiogram	<1
AXR	0.2–0.3
IVP	0.8 (complete series) 0.2 (limited series)
MRI/MRV/MRA	None

Related Topics

- Asthma (p. 1)
- Pulmonary Embolism (p. 12)

TREATMENT—LMWH dosed using current weight (not pre-pregnancy or ideal body weight). Consider monitoring of anti-Xa level (4–6 h after last dose, target 0.6–1.2 IU/mL) given increased metabolism and elimination. Duration of therapeutic anticoagulation 3–6 months, then transition to prophylactic dose of LMWH until end of 6 weeks postpartum. Peri-partum anticoagulation regimen is individualized based upon risks of bleeding (obstetrical and neuraxial) balanced against risk of clotting (new clot <1 month, location, etc.) and centre-specific practices. If neuraxial analgesia planned, hold therapeutic LMWH × 24 h and prophylactic LMWH × 12 h beforehand. If unable to hold anticoagulation (e.g. acute clot <4 weeks), consider bridging with

VENOUS THROMBOEMBOLISM (CONT'D)

IV unfractionated heparin (and hold when in active labor or 2 h prior to caesarean section), and/or consider IVC filter. Systemic thrombolysis generally contraindicated (risk of fetal demise). Warfarin generally not recommended during pregnancy (teratogenic in T₁; associated with fetal CNS hemorrhage/malformations, miscarriage, stillbirth, neonatal demise). May consider warfarin as an alternative to LMWH in the postpartum period while breastfeeding

FUTURE PREGNANCIES—provide antepartum and postpartum thromboprophylaxis to women with significantly increased risk (>1% absolute risk) of venous thromboembolism. Therapeutic-dose anticoagulation if already on long-term anticoagulation for established indication. Intermediate or therapeutic-dose if prior history of venous thromboembolism and high-risk thrombophilia (e.g. APLA, antithrombin deficiency), but not previously on anticoagulation. Prophylactic dose both during pregnancy and 6 weeks postpartum if prior history of venous thromboembolism (unprovoked, related to oral contraceptive pill, related to pregnancy, or in setting of low-risk thrombophilia), or for asymptomatic thrombophilia (e.g. homozygote with factor V Leiden mutation, homozygote prothrombin gene mutation, antithrombin deficiency). For all other low-risk thrombophilias, may consider 6 weeks of postpartum thromboprophylaxis in the setting of other VTE risk factors or with a positive family history of VTE

OTHER CONSIDERATIONS—compression stockings for symptom management. Caution against use of combined oral contraceptive pills
Chan et al. *J Obstet Gynaecol Can* 2014;36(6) 2012 ACCP Guideline VTE, Thrombophilia, Antithrombotic Therapy, and Pregnancy

AMNIOTIC FLUID EMBOLISM

PATHOPHYSIOLOGY—can occur during labor and delivery or with uterine manipulation. Risk factors include older age and multiparity. Amniotic fluid enters maternal circulation → inflammation, vasospasm, and venous occlusion → cardiogenic shock and respiratory failure

DIAGNOSIS—clinical diagnosis with classic triad of sudden-onset dyspnea and hypoxia, hypotension, and coagulopathy. Differential diagnosis includes septic shock, pulmonary embolism, aspiration pneumonia, uterine rupture, *abruptio placentae*, and venous air embolism

TREATMENTS—supportive, supplemental O₂, hemodynamic support (vasopressors ± IV fluids),

AMNIOTIC FLUID EMBOLISM (CONT'D)

ICU admission. Rapid delivery of the fetus (beware of risk of rapid blood loss with coagulopathy; may potentially require PRBC, FFP, platelet, and/or cryoprecipitate transfusion)

COMPLICATIONS—at least 20% maternal mortality, 25–50% of which die within the first hours

AMNIOTIC FLUID EMBOLISM (CONT'D)

of onset of the disease. Patients who survive are at high risk for ARDS, acute renal injury, and neurological complications due to cerebral hypoxia (up to 85%)

Cardiac Diseases in Pregnancy**PATHOPHYSIOLOGY**

HIGH-RISK CARDIOPULMONARY CONDITIONS—generally advise against pregnancy if any of the following conditions: tetralogy of Fallot with severe cyanosis, Eisenmenger syndrome, severe pulmonary hypertension, functional limitation NYHA 3 or 4, recent cardiac transplantation with high-dose immunosuppression, Marfan syndrome with aortic root >40 mm [1.6 in.], previous peripartum cardiomyopathy with persistent LVEF <30%, interstitial pulmonary fibrosis, lymphangioleiomyomatosis, and active lung cancer

GENERAL MANAGEMENT PRINCIPLES—**preconception counselling** to 1) advise on risks of cardiac, obstetrical and fetal complications during pregnancy, and 2) optimize cardiac medications/status prior to pregnancy. Pregnancy-specific risk tools available. **Delivery with supportive measures**, including aggressive pain control and early neuraxial analgesia during labor to reduce catecholamine HR response; assist second stage of labor with vacuum or forceps (to reduce prolonged Valsalva). Avoid fluid overload. Vaginal delivery recommended, but C-section may be necessary for fetal indications

Related Topics

Endocarditis (p. 65)

Heart Failure (p. 41)

Valvular Disorders (p. 64)

VALVULAR DISORDERS

REGURGITANT VALVULAR HEART DISEASE—may improve during pregnancy due to ↓ systemic vascular resistance

STENOTIC VALVULAR HEART DISEASE—may worsen during pregnancy. Symptomatic or

VALVULAR DISORDERS (CONT'D)

severe stenosis should be evaluated for correction prior to pregnancy. Valvuloplasty during pregnancy may be considered for worsening symptoms. β-blockers to decrease HR in mitral stenosis

PROSTHETIC HEART VALVE—for mechanical valves, continue oral anticoagulation until conception. During T₁ (within first 6 weeks), switch to therapeutic dose LMWH given BID (target anti-Xa level 0.7–1.2 IU/mL, 4–6 h after last dose [peak]), but avoid warfarin (teratogenic, ↑ risk if >5 mg/day). During T₂–T₃ and up until 36 weeks gestation, treatment options include therapeutic LMWH given BID or warfarin (target INR 2.5–3.5). Choice of anticoagulation depends on risk of thrombosis (i.e., type of valve) and patient preference. Consider either LMWH *plus* ASA 81 mg PO daily, or warfarin for highly thrombogenic valves (i.e., mitral position, older generation mechanical valve, history of thromboembolism). Warfarin more effective for prevention of valvular thrombosis but associated with higher risk of fetal CNS hemorrhage/malformations, miscarriage, stillbirth, neonatal demise. At 36th week, anticoagulation should be switched to IV unfractionated heparin or LMWH given BID in preparation for delivery, and allow at least 10–14 days for (fetal) warfarin washout. Switch to IV unfractionated heparin exclusively 36 hours before planned delivery, stopping 4–6 h before delivery, and restarting 4–6 h after delivery if no bleeding. Preconception counseling highly recommended

ENDOCARDITIS PROPHYLAXIS—not recommended for vaginal delivery and caesarean sections. May consider for select high-risk cardiac conditions (i.e. prosthetic valve, unrepaired cyanotic congenital heart defect, repaired cyanotic congenital heart defect with residual defects, cardiac transplant recipients with valvulopathy, previous endocarditis)

MYOCARDIAL DISORDERS

PERIPARTUM CARDIOMYOPATHY—dilated cardiomyopathy with LVEF <45% during last month of pregnancy or within 5 months postpartum in the absence of previous heart disease. Diagnosis of exclusion. Hypertensive disorder of pregnancy is a risk factor. Medical management similar to treatment of HF in non-pregnant individuals with diuretics, β -blockers (except atenolol, risk of fetal growth retardation), nitrates, hydralazine, and digoxin. Severe cases may require CCU care, inotropes, mechanical circulatory support, ventricular assist device, or transplant. During pregnancy, ACE inhibitors and ARBs are contraindicated, and aldosterone antagonists should be avoided if possible. During breastfeeding, ACE inhibitors (enalapril, captopril) and aldosterone antagonists (spironolactone) may be used. Anticoagulate if LVEF <35% or atrial fibrillation. Bromocriptine can be considered. Breastfeeding remains controversial. Overall prognosis variable (mortality in up to 30%, around 25–50% have full recovery of myocardial function within 6 months, and 4–7% have progressive disease eventually requiring cardiac transplant). Recurrence in up to

MYOCARDIAL DISORDERS (CONT'D)

30% with high risk of mortality in subsequent pregnancy if persistent \downarrow LVEF. Preconception counseling highly recommended for subsequent pregnancies

ISCHEMIC HEART DISEASE—stress echocardiogram (preferred), exercise stress test, MIBI, and angiograms (beware radiation) can be considered for investigations

RHYTHM DISORDERS

PALPITATIONS—sinus tachycardia, ectopic beats, and syncope are common. Increased SVT in patients previously diagnosed with SVT. May treat with adenosine, β -blockers (except atenolol), calcium channel blockers, or digoxin. DC cardioversion if unstable (remove fetal monitors if possible [theoretical risk to fetus] but do not delay treatment). Investigate for underlying arrhythmia, structural abnormality (cardiomyopathy, valvular disease), and precipitant (PE, sepsis, thyrotoxicosis) as appropriate

Siu et al. *Cleve Clin J Med* 2004;71(12)
2018 European Society Cardiology
Guidelines Management CVD Pregnancy

Hepatic Diseases in Pregnancy**DIFFERENTIAL DIAGNOSIS**

PREGNANCY-RELATED LIVER DISEASE—hyperemesis gravidarum, preeclampsia/eclampsia/HELLP syndrome, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy

- **HYPEREMESIS GRAVIDARUM** (T_{1-2} , incidence 0.3–1%)—**nausea, vomiting**, weight loss, \uparrow ALT >AST, N bili
- **PREECLAMPSIA/ECLAMPSIA** (T_{2-3} , incidence 5–10%)—see section under preeclampsia
- **HELLP SYNDROME** (T_3 , incidence 0.1%)—preeclampsia symptoms. \uparrow ALT, \uparrow AST, \uparrow bilirubin, \downarrow platelets, \uparrow LDH. May progress to DIC (30%)
- **INTRAHEPATIC CHOLESTASIS OF PREGNANCY** (T_{2-3} , incidence 0.1–0.2%)—functional disorder of bile formation with severe **pruritus**. \uparrow ALT, \uparrow AST, \uparrow bilirubin (less common), \uparrow **bile acids**. Associated with prematurity, intrauterine fetal demise, and neonatal respiratory distress syndrome
- **ACUTE FATTY LIVER OF PREGNANCY** (T_3 , incidence ~1 per 20,000 pregnancies)—may be associated with preeclampsia. Due to fetal long-

DIFFERENTIAL DIAGNOSIS (CONT'D)

chain 3-hydroxyacyl CoA dehydrogenase (L-CHAD) deficiency. Characterized by **severe liver dysfunction** (encephalopathy, hypoglycemia, coagulopathy) and commonly jaundice. Can develop central diabetes insipidus. \uparrow ALT, \uparrow AST, \uparrow bilirubin, \uparrow WBC, \uparrow PT, \uparrow **uric acid**. US is often normal (microvesicular fat on biopsy) and CT shows a low-density liver

PREGNANCY-AGGRAVATED LIVER DISEASE—hepatitis E, hepatitis A, HSV hepatitis, Budd-Chiari, cholelithiasis

- **HEPATITIS E**—may cause fulminant liver failure in pregnancy; mother to child transmission in 1/3 cases
- **HEPATITIS B**—pregnancy does **not** affect natural history of HBV infections (rare cases of fulminant hepatitis among immunocompromised). Routine screening at first prenatal visit (HBsAg). Prophylaxis and immunization for infant if mother HBV positive

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **HEPATITIS C**—pregnancy does **not** affect natural history of HCV infections. Mother to child transmission ~5% (up to 20% if HIV co-infection)
- **CHOLELITHIASIS**—associated with acute cholecystitis, choledocholithiasis, and ascending cholangitis
- **OTHER CONDITIONS**—drug-induced hepatitis, malignancy

CLINICAL FEATURES

HISTORY—jaundice, pruritus, abdominal pain, ascites, swelling, encephalopathy, nausea and vomiting, headache, visual disturbances, fever, obstetrical history (current pregnancy course, previous births, previous preeclampsia), past medical history (hypertension, hepatitis, alcohol, IDU), and medications

PHYSICAL—check vitals (hypertension), edema (facial, limbs), heart (elevated JVP, S3, S4), hepatic tenderness, ascites, jaundice, and hyperreflexia

INVESTIGATIONS**BASIC**

- **LABS**—CBC, peripheral smear, lytes, urea, Cr, spot urine for protein to creatinine ratio, AST, ALT, ALP (mild elevation could be from placenta), GGT, bilirubin, INR, bile acids (intrahepatic cholestasis), uric acid (acute fatty liver and preeclampsia), LDH, fibrinogen (DIC), TSH
- **MICROBIOLOGY**—HBV and HCV serology
- **IMAGING**—US abd

MANAGEMENT

HYPEREMESIS GRAVIDARUM—rule out molar pregnancy and hyperthyroidism. Consider alternative cause of N&V if persistent (adrenal insufficiency, eating disorder). Diclectin (doxylamine and pyridoxine) is first-line, then consider metoclopramide, ondansetron, dimenhydrinate, chlorpromazine, prochlorperazine, and promethazine. Supportive fluids, nutritional replacement, and treatment of GERD. TPN and/or feeding tubes are rarely needed

MANAGEMENT (CONT'D)

INTRAHEPATIC CHOLESTASIS OF PREGNANCY—*ursodeoxycholic acid* 500 mg PO BID or cholestyramine both may reduce pruritus but no impact on fetal outcomes. Increase fetal monitoring. Obstetrical team to consider early delivery if high bile acids >100 $\mu\text{mol/L}$ [40.8 mcg/mL] because of \uparrow risk of fetal demise. Cholestasis resolves following delivery without hepatic sequelae. Recurs in up to 70% of pregnancies

ACUTE FATTY LIVER OF PREGNANCY—vitamin K if coagulopathic, immediate delivery, and ICU support. May progress to acute hepatic failure and DIC in >75%. Increased maternal and fetal mortality. Can recur in future pregnancies

HELLP—anti-hypertensive, MgSO_4 , immediate delivery

HEPATITIS B—provide standard neonatal immunoprophylaxis and consider antiviral treatment (tenofovir) if high maternal HBV DNA levels during pregnancy. Internal fetal monitoring and prolonged rupture of membranes should be avoided

HEPATITIS C—no proven treatment during pregnancy. Internal fetal monitoring and prolonged rupture of membranes should be avoided

SPECIFIC ENTITIES**OTHER GI DISORDERS**

- **GERD**—very common during pregnancy. May cause chronic cough and reactive airway disease symptoms. Treatments include lifestyle changes, antacids, ranitidine, PPIs, and metoclopramide
- **CHOLECYSTITIS**—pregnant women are at increased risk due to hormonal changes. Medical management with IV fluids, NG, and opioids. Broad-spectrum antibiotics may be added for severe disease. Cholecystectomy lowest risk during T_2

Related Topics

Acute Liver Failure (p. 145)
Dyspepsia (p. 130)

Infectious Diseases in Pregnancy

IMMUNIZATIONS IN PREGNANCY

VACCINATIONS—many infections follow a more severe course in pregnancy (i.e. due to changes in cell-mediated immunity), thus immunization history should be obtained in all pregnant or preconception women. Avoid live-attenuated virus vaccines in pregnancy. All pregnant women should be offered diphtheria and tetanus toxoids and acellular pertussis between 21–32 weeks of every pregnancy, regardless of previous immunization history; influenza vaccine should also be given to women pregnant during influenza season (with passive antibody transfer to newborns who cannot be vaccinated)

Castillo et al. *J Obstet Gynaecol Can* 2018;40(4)

INFECTIONS ASSOCIATED WITH BIRTH DEFECTS

★**TORCHES CLLAPZ**★—**T**oxoplasma, **R**ubella, **C**MV, **H**SV, **E**nteroviruses, **S**yphilis, **C**hickenpox, **L**yme, **L**CMV, **A**IDS, **P**arvoviruses and **Z**ika virus infections during pregnancy are associated with birth defects (e.g. CMV 1/5 have hearing loss). Data are emerging on many other potential pathogens that may also be associated with birth defects, such as *Brucella melitensis*, *Coxiella burnetii* (Q fever), *Babesia microti* (babesiosis), human T-cell lymphotropic virus types I and II, hepatitis G, TT viruses, human herpesvirus 6, and dengue

SEPSIS

CLINICAL FEATURES—common cause of maternal morbidity in developed and developing world. Assess vital signs (BP, HR, RR [tachypnea never normal], temperature), and for end-organ perfusion (level of consciousness, skin mottling), as well as for potential sources of infection

TREATMENTS—medical management similar to treatment of sepsis in non-pregnant individuals with IV fluids and early empiric antibiotic therapy (see below for acceptable antibiotic choices)

INFLUENZA

CLINICAL FEATURES—increased risk of influenza-related morbidity and mortality (5 × higher risk of hospital admission overall, one out of six influenza-related deaths occur in young pregnant women). Influenza associated with adverse pregnancy outcomes (preterm birth, small for gestation age newborns). All pregnant women should receive inactivated influenza vaccine regardless of trimester

SARS AND SARS-CoV-2 (COVID-19)

CLINICAL FEATURES—pregnancy does not increase the risk of acquiring the infection but may worsen the clinical course. Pregnant women infected with COVID-19 have markedly higher risk of ICU admission and mortality compared to non-pregnant women (particularly if obese, age ≥35, hypertension or pre-existing DM). Risks of congenital malformations are unlikely (but cannot be excluded); congenital infection low; neonatal infection may be acquired postpartum

TREATMENTS—supportive (oxygen) with VTE prophylaxis and dexamethasone if clinically indicated. Limited data to date (December 2020) on other treatments due to exclusion of pregnant women from clinical trials. Individualized assessment or risks/benefits required. Vaccination is recommended in pregnancy by SOGC

URINARY TRACT INFECTIONS

PATHOPHYSIOLOGY—hydronephrosis and hydroureter R>L, urinary stasis, higher protein and amino-acid excretion → UTI

ASYMPTOMATIC BACTERIURIA—defined as 10⁵ CFU/mL on a “clean” sample. Occurs in 2–7% of pregnancies, associated with preterm birth, low birth weight, and perinatal mortality. Screen for bacteriuria between 12 and 16 weeks gestation, as 30–40% will develop symptomatic UTI if untreated. Treatment depends on culture and local antibiotic resistance pattern; consider *amoxicillin-clavulanate* 500 mg PO BID × 7 days, *nitrofurantoin* 100 mg PO BID × 7 days (risk of hemolytic anemia). Avoid trimethoprim if alternatives available. Follow-up culture 1 week following treatment completion and then monthly until pregnancy complete

ACUTE CYSTITIS—occurring in 1% of pregnancies, with treatment and follow-up as asymptomatic bacteriuria

PYELONEPHRITIS—occurring in <1% of pregnancies, complicated by septic shock and ARDS in 20%. In-patient treatment with IV antibiotics (cefazolin, ceftriaxone, or ampicillin plus gentamicin) until symptomatic improvement and afebrile for 24–48 h then PO based on drug sensitivities. Low-dose suppressive antibiotics (*nitrofurantoin* 50–100 mg PO nightly [risk of hemolytic anemia] or *cephalexin* 250–500 mg PO nightly) for remainder of pregnancy as recurrent pyelonephritis occurs in 6–8% of women without prophylaxis

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

TREATMENTS—pregnant women with HIV infection should be treated with combination antiretroviral therapy (regardless of CD4 count or viral load) during pregnancy and postpartum to maintain an HIV viral load below the limit of detection throughout pregnancy. Involve an interdisciplinary team experienced in HIV in pregnancy and delivery. Treatment goals are to ↓ perinatal HIV transmission to the infant, prevent sexual HIV transmission to partners without HIV, and for a female's lifelong health

2014 Society Obstetricians Gynaecologists Canada Guidelines Care Pregnant Women with HIV and Interventions to Reduce Perinatal Transmission

TUBERCULOSIS

CLINICAL FEATURES—natural history not affected by pregnancy, but delayed recognition is common. Tuberculin skin testing and IFN- γ release assays require expert interpretation in pregnancy

TREATMENTS—treat TB, if identified, as risk of infection to fetus is greater than risk of medications. Isoniazid, rifampin, and ethambutol safe for

TUBERCULOSIS (CONT'D)

use during pregnancy and breastfeeding. *Pyridoxine* 25 mg PO daily is recommended for all pregnant or breastfeeding women taking isoniazid to prevent peripheral neuropathy

ANTIBIOTICS

ACCEPTABLE—penicillins, cephalosporins, azithromycin, vancomycin, metronidazole, clindamycin, erythromycin (except erythromycin estolate), nitrofurantoin (caution as risk of hemolytic anemia), and acyclovir. Consider trimethoprim-sulfamethoxazole (avoid in first trimester but use with folate if no other alternatives) and aminoglycosides (except streptomycin) in some circumstances

AVOID—tetracyclines (infant teeth staining), streptomycin (theoretical concern for fetal ototoxicity), fluoroquinolones (abnormal cartilage development in animals, but not demonstrated in humans)

Related Topics

HIV (p. 276)

Tuberculosis (p. 267)

Urinary Tract Infections (p. 259)

Diabetes in Pregnancy

2018 Diabetes Canada Guidelines

PATHOPHYSIOLOGY

RISK FACTORS FOR GESTATIONAL DIABETES—previous history of gestational diabetes, impaired fasting glucose or impaired glucose intolerance, prior delivery of macrosomic infant or current fetal macrosomia (>4000 g or >90th percentile), polyhydramnios, high-risk ethnic group (indigenous, Hispanic, Arab, South Asian, Asian, Black), maternal age ≥ 35 , obesity (BMI ≥ 30 kg/m²), family history of type 2 diabetes, corticosteroid use, PCOS, acanthosis nigricans

PRECONCEPTION CARE FOR PRE-EXISTING DIABETES (T1DM & T2DM)—optimize glycaemic control prior to pregnancy (HbA1c $\leq 7\%$; ideally $\leq 6.5\%$) to lower risks of spontaneous abortion, congenital anomalies, preeclampsia, progression of retinopathy and stillbirth. Support weight reduction (if overweight) and ensure appropriate vaccinations. Screen and treat retinopathy and nephropathy. Patients on oral agents other than metformin and/or glyburide should be switched to insulin for glycaemic control. Discontinue ACE inhibitors, ARBs, and statins prior

PATHOPHYSIOLOGY (CONT'D)

to conception (or immediately upon detection of pregnancy). Supplemental *folic acid* 1 mg PO daily starting at least 3 months preconception until at least 12 weeks gestation, then 0.4–1 mg PO daily. Counsel on risk of hypertensive disorder of pregnancy and ASA to reduce this risk (see Preeclampsia section) and weight gain targets (see Obesity section)

DIAGNOSIS

DIAGNOSIS OF GESTATIONAL DIABETES—screen all pregnant women between 24–28 weeks (or in first trimester) for diagnosing pre-existing diabetes if at high risk of gestational diabetes (see risk factors above):

- **Step 1: 1-h 50 g oral glucose challenge test (non-fasting)**
 - If 1 h blood glucose ≥ 11.1 mmol/L [≥ 200 mg/dL] → GDM
 - If 1 h blood, glucose 7.8–11.0 mmol/L [140–200 mg/dL] → perform 75 g OGTT

DIAGNOSIS (CONT'D)

- If 1 h blood glucose <7.8 mmol/L [<140 mg/dL] \rightarrow no GDM, but may consider re-testing if ongoing suspicion (e.g. macrosomia, polyhydramnios)
- **Step 2 (if needed): 2-h 75 g oral glucose tolerance test (fasting)**
 - If fasting blood glucose ≥ 5.3 mmol/L [≥ 95 mg/dL] \rightarrow GDM
 - If 1 h blood glucose ≥ 10.6 mmol/L [≥ 190 mg/dL] \rightarrow GDM
 - If 2 h blood glucose ≥ 9.0 mmol/L [≥ 160 mg/dL] \rightarrow GDM

MANAGEMENT

ANTEPARTUM—diabetic diet and exercise. Aim for excellent glycemic control with HbA1C ≤ 6.5 (ideally $\leq 6.1\%$ if possible). Monitor blood glucose before and after each meal. Target fasting blood glucose <5.3 mmol/L [95 mg/dL], 1 hour <7.8 mmol/L [140 mg/dL], and 2 h postprandial blood glucose <6.7 mmol/L [120 mg/dL] (modify targets if hypoglycemia occurs). Test urine for ketones during illness, or if patient suspected of over-restricting diet (starvation) in order to achieve tight glycemic control. Monitor blood pressure at each visit. In patients with pre-existing diabetes (type 1 or 2), screen for retinopathy (ophthalmologist) and nephropathy (serum creatinine and urine albumin/Cr ratio) in first trimester and again as needed. Fetal surveillance as per OB

- **PREVENTION**—nutritional counselling for patients with risk factors for GDM to prevent excessive weight gain; ideally <15 weeks' gestation
- **GESTATIONAL**—dietitian referral. If glycemic targets not achieved within 1–2 weeks, start insulin (lispro or aspart SC ac meals, and/or NPH SC nightly–BID). Adjust dose weekly, as needed. Consider glyburide or metformin for women non-adherent to or who refuse insulin (off-label use in pregnancy, discuss risks with patient)
- **TYPE 1 DIABETES**—basal-bolus insulin therapy or insulin pump. Continuous glucose monitoring improves glycemic control and \downarrow neonatal complications
- **TYPE 2 DIABETES**—switch from oral agents to insulin, preferably preconception (lispro or aspart SC ac meals, and/or NPH SC nightly–

MANAGEMENT (CONT'D)

BID). Adjust dose weekly, as needed. Metformin added to insulin improves glycemic control and several neonatal outcomes. Consider glyburide or metformin for women non-adherent to or who refuse insulin (off-label use in pregnancy, discuss risks with patient)

INTRAPARTUM—target blood glucose 4.0–7.0 mmol/L [72–126 mg/dL] during labor (to minimize risk of neonatal hypoglycemia). NPO, IV fluids, and monitor blood glucose q1h. Consider insulin IV infusion (rarely required for GDM), according to current blood glucose level, time of last meal, and time of last insulin injection. Women may use their own insulin pumps during labor if comfortable self-managing (but not for C-section)

POSTPARTUM—insulin requirements rapidly drop after delivery to doses similar to pre-pregnancy levels, especially if breastfeeding (beware of hypoglycemia). Continue blood glucose monitoring. Breastfeeding should be encouraged to reduce risk of neonatal hypoglycemia, offspring obesity, and metabolic syndrome in mother

- **GESTATIONAL DIABETES**—insulin rarely required postpartum. Risk of type 2 diabetes ($\sim 20\%$ in 10 years); screen from 6 weeks to 6 months postpartum with 2 h 75 g OGTT; reminders for screening \uparrow uptake
- **TYPE 1 DIABETES**—reduce insulin (using preconception dosages as guideline). Screen for postpartum thyroiditis 6–8 weeks postpartum with TSH
- **TYPE 2 DIABETES**—reduce or discontinue insulin (using preconception dosages as guideline). Metformin and glyburide are the only known safe oral agents while breastfeeding

COMPLICATIONS—fetal complications include congenital anomalies (usually with preexisting diabetes), macrosomia (shoulder dystocia, birth trauma) or intrauterine growth restriction (uncommon), neonatal hypoglycemia, respiratory distress syndrome, hypocalcemia, hyperbilirubinemia, and intrauterine death. Offspring at risk for diabetes and obesity in long-term. Maternal complications include gestational hypertension, pre-eclampsia, polyhydramnios, preterm birth, C-section, and progression of diabetic retinopathy and nephropathy

Obesity in Pregnancy

COMPLICATIONS

FETAL COMPLICATIONS—congenital anomalies, larger for gestational age, preterm birth, and neonatal metabolic complications

MATERNAL COMPLICATIONS—infertility, miscarriage, gestational hypertension, preeclampsia, gestational diabetes, C-section, and VTE

MANAGEMENT

PRECONCEPTION—counsel on combined behavioural interventions (nutrition and physical activity) weight management prior to pregnancy to reduce the above risks. Stop pharmacotherapy for weight management because safety unknown in pregnancy

ANTEPARTUM—counsel on combined behavioural interventions to achieve weight gain targets of 5–9 kg (11–20 lbs)

POSTPARTUM—aim for weight loss of (at minimum) the amount gained during pregnancy in

MANAGEMENT (CONT'D)

order to improve long-term health and future pregnancy outcomes. Breastfeeding support to help with initiation and continuation

WEIGHT GAIN TARGETS—according to pre-pregnancy BMI to ↓ adverse pregnancy outcomes (adapted from Institute of Medicine, 2009)

Category	Total gestational weight gain targets
Underweight (BMI <18.5 kg/m ²)	12.5–18 kg (28–40 lbs)
Normal weight (18.5–24.9 kg/m ²)	11.5–16 kg (25–35 lbs)
Overweight (25.0–29.9 kg/m ²)	7–11.5 kg (15–25 lbs)
Obese (≥30.0 kg/m ²)	5–9 kg (11–20 lbs)

Obesity Canada 2020

Thyroid Diseases in Pregnancy

HYPOTHYROIDISM IN PREGNANCY

PATHOPHYSIOLOGY—hypothyroidism, when present, usually diagnosed prior to conception (most commonly Hashimoto). Around 75% of women will require an increase in levothyroxine during pregnancy. ↑ estrogen → ↑ thyroxine-binding globulin → ↓ total T4 and total T3. Estimated required increase in T4 to maintain euthyroidism is 25–50%. Fetus is dependent on maternal thyroid hormone until 18–20 weeks. Hypothyroidism may also be diagnosed in pregnancy (uncommon). ↑ thyroid hormone synthesis and ↑ renal clearance of iodine → ↑ iodine requirements during pregnancy, but if iodine intake insufficient (endemic) → ↓ T4 and ↑ TSH

MONITORING—screen high risk individuals (history of goiter, thyroid dysfunction, thyroid ablation, thyroidectomy, neck irradiation, autoimmune conditions, family history). Screening of low-risk women not recommended. Preconception, target TSH 0.2–2.5 mU/L (lower normal range). Use of pregnancy-specific local reference ranges recommended. If locally-validated reference ranges unavailable, use the following: in T₁, target TSH 0.1–2.5 mU/L (and free T4 in upper normal range); T₂, target TSH 0.2–3 mU/L (and total T4 in normal of *pregnancy-adjusted* range);

HYPOTHYROIDISM IN PREGNANCY (CONT'D)

and T₃, target TSH 0.3–3 mU/L (and total T4 in normal of *pregnancy-adjusted* range). Use FT4 in first trimester and total T4 in second/third trimesters. Monitor TSH and free T4 (or total T4) levels q4weeks during first half of pregnancy and at least once between 26 and 32 weeks' gestation

TREATMENTS—levothyroxine can be safely given during pregnancy. As soon pregnancy is confirmed, ↑ dose by 30% empirically. Levothyroxine should be taken separately from vitamins, calcium, and/or iron supplements, and ideally on an empty stomach for best absorption. Avoid liothyronine (T3) because it does not cross placenta

COMPLICATIONS—untreated hypothyroidism associated with neonatal neuropsychological and cognitive impairment, preeclampsia and gestational hypertension, preterm labor, placental abruption, and perinatal morbidity and mortality

SPECIFIC ENTITIES

SUBCLINICAL HYPOTHYROIDISM—elevated trimester-specific TSH with normal FT4. No benefit (maternal, obstetrical, fetal, or long-term child development outcomes) with treatment

HYPERTHYROIDISM IN PREGNANCY

PATHOPHYSIOLOGY—most commonly Graves disease. TSH receptor stimulating antibody → ↑ thyroid hormone production. Hyperthyroidism may also arise from excess hCG (self-limited surge in T_1 [transient gestational thyrotoxicosis], multiple gestation, hyperemesis gravidarum, or molar pregnancy [hydatidiform mole]) → hCG α -subunit nearly identical to TSH α -subunit → ↑ thyroid hormone production → ↓ TSH

COMPLICATIONS—preeclampsia, premature labor, placental abruption, intrauterine growth restriction, fetal goiter (from excess antithyroid drug treatment), neonatal thyrotoxicosis (typically when TSH receptor antibodies $>3-5 \times$ upper limit of normal), ↑ mortality (maternal and perinatal), and thyroid storm (rare)

SUBCLINICAL HYPERTHYROIDISM—not associated with adverse outcomes. Supportive care, reassurance, and postpartum follow-up

EXCESS hCG EFFECT—transient gestational thyrotoxicosis may be present in 5–10% of pregnancies during T_1 (↓ TSH, normal/slightly ↑ FT4). Self-limited and typically resolves by T_2 . Treatment is supportive with reassurance

GRAVES DISEASE—most common cause of primary hyperthyroidism in pregnancy (95%). TSH receptor antibodies can cross placenta to cause fetal thyrotoxicosis. Classically improves in pregnancy. Exacerbations may happen in T_1 and postpartum

- **DIAGNOSIS**—presence of symptoms predating pregnancy, eye signs, weight loss despite adequate intake, and pretibial myxedema suggestive of Graves disease. However, presence of mild–moderately enlarged thyroid gland, hypervascularity, and/or nodularity usually unhelpful in differentiating between Graves disease vs. normal physiological changes. Presence of ↑ TSH receptor antibodies suggests Graves disease. Nuclear imaging contraindicated in pregnancy. Postpartum course can also help clarify etiology
- **MONITORING**—use of pregnancy-specific local reference ranges recommended. If locally-validated reference ranges unavailable, use the

HYPERTHYROIDISM IN PREGNANCY (CONT'D)

following: in T_1 , target TSH 0.1–2.5 mU/L (and free T4 in upper normal range); T_2 , target TSH 0.2–3 mU/L (and total T4 in normal pregnancy-adjusted range); and T_3 , target TSH 0.3–3 mU/L (and total T4 in normal pregnancy-adjusted range). Use FT4 in first trimester and total T4 in second/third trimesters. Monitor TSH and free T4 (or total T4) levels q4weeks

- **TREATMENTS**—**antithyroid drugs**, preferably propylthiouracil during T_1 and methimazole during T_2 – T_3 (propylthiouracil associated with idiosyncratic liver injury, methimazole associated with aplasia cutis). Mild under-treatment preferred to hypothyroidism. May require lower dosages of antithyroid medication as pregnancy progresses. Taper or discontinue medication, if possible, towards delivery date to decrease risk of neonatal goiter. **β -blockers** (prefer propranolol; avoid atenolol) for symptom control, but may lead to fetal bradycardia, fetal hypoglycemia, and intrauterine growth restriction at higher doses. Avoid radioiodine during pregnancy. If surgery required (rare), ideally during T_2 . Consult high-risk obstetrician to monitor maternal and fetal health

POSTPARTUM THYROIDITIS—painless (silent) and affects 10% of postpartum women within first postpartum year (usually first 3–6 months) and may be associated with postpartum depression. Classically begins with a hyperthyroid phase followed by hypothyroid phase. Only 25% have hypothyroid phase. Most cases resolve within 1 year. Risk of recurrence is up to 25% in subsequent pregnancies. Approximately 20–40% go on to develop permanent hypothyroidism

- **TREATMENTS**—most patients have mild thyrotoxicosis ($\times 1-2$ months) and do not require treatment. For symptomatic thyrotoxicosis give β -blocker. Most eventually return to euthyroid state, but some become hypothyroid. If levothyroxine is needed, start 50–100 μ g PO daily, and slowly withdraw after around 6 months as hypothyroidism may have resolved. Monitor TSH q6–8 weeks

Other Disorders in Pregnancy

SEIZURES IN PREGNANCY

PATHOPHYSIOLOGY—for women with known epilepsy, 25% will have ↑ frequency (secondary to non-adherence or inappropriately low antiepileptic drug levels), 25% will have ↓ frequency, and 50% will not change in pregnancy. Risk of uncontrolled seizures in pregnancy outweighs risks of antiepileptic drugs (because ↑ maternal death from ↓ recognition and ↓ treatment). Risk of seizures in offspring is elevated at 5%. Eclampsia, intracerebral bleed, and cerebral vein thrombosis may lead to seizures in pregnancy

TREATMENTS—valproic acid has a relatively high risk of neural tube defects and should be switched to alternate antiepileptic pre-pregnancy if possible. Phenytoin, carbamazepine, and phenobarbital are potentially teratogenic (especially if polytherapy required) but can be used if indicated and after appropriate counseling. Lamotrigine and levetiracetam monotherapy have reasonable data in pregnancy. Women often require higher doses of antiepileptic meds in pregnancy due to ↑ volume distribution, ↑ metabolism, ↑ renal clearance. Measurement of drug levels and symptoms may guide dosing. *Folic acid* 0.4 mg PO daily should be prescribed to all women on antiepileptics in the childbearing age. Those planning a pregnancy should take *folic acid* 5 mg PO daily in the preconception period and in first trimester, then 1 mg PO daily throughout remainder of pregnancy. Higher risk of seizures peripartum and early postpartum due to ↓ seizure threshold. Treat seizures in pregnancy with benzodiazepine. Postpartum counselling on safety precautions with newborn and titrate (↓) medications to pre-pregnancy dose (or slightly above). Antiepileptic drugs may increase metabolism of hormonal contraceptive agents

LUPUS IN PREGNANCY

LUPUS EXACERBATIONS—may have increased flares during pregnancy and postpartum if not in remission for >6 months prior to conception. Plaquenil, azathioprine, and corticosteroids may be used during pregnancy. Avoid NSAIDs in T₃

COMPLICATIONS—increased risk of prematurity and in utero fetal death. Patients with nephritis may have severe exacerbations with acute kidney injury, preeclampsia, and maternal death. Test for maternal anti-SSA and anti-SSB antibodies (associated with increased risk of congenital heart block and neonatal lupus) and

LUPUS IN PREGNANCY (CONT'D)

monitor fetus with fetal heart rate and echocardiogram between 18 and 26 weeks gestation with treatment guided by high-risk obstetrics team. Patients with antiphospholipid antibodies are at increased risk of preeclampsia, miscarriage, and possibly thrombosis

BREAST CANCER IN PREGNANCY

DIAGNOSIS—often delayed given physiological changes. Staging workup similar to non-pregnant women. Use MRI or US instead of CT if imaging of abdomen required

TREATMENTS—mastectomy preferred over lumpectomy to avoid radiation. If adjuvant radiation indicated, it should be deferred until after delivery. Anthracycline containing adjuvant chemotherapy can usually be safely given during T₂ and T₃, but not in T₁ or within 2 weeks of delivery. Methotrexate is absolutely contraindicated and taxane/dose dense regimens should be avoided. Hormonal therapy is contraindicated during pregnancy. Breast-feeding contraindicated in women on hormonal therapy or chemotherapy. Stage by stage, gestational breast cancer has similar prognosis to non-pregnant counterpart

PAIN CONTROL IN PREGNANCY AND BREASTFEEDING

ACCEPTABLE—acetaminophen, opioids (watch for neonatal abstinence syndrome with higher, prolonged doses). In breastfeeding, NSAIDs can be used with little effect on BP; caution with codeine due to newborn metabolism

WITH CAUTION—NSAIDs in T₁ and T₂

CONTRAINDICATED—NSAIDs in T₃ (premature closure of ductus arteriosus, fetal renal insufficiency, and periventricular hemorrhage)

THROMBOCYTOPENIA IN PREGNANCY

PERIPARTUM CONSIDERATIONS—neuraxial anesthesia (epidural) generally safe if platelet >75 × 10⁹/L; caesarean delivery safe if platelet >50 × 10⁹/L; vaginal delivery safe if platelets >30 × 10⁹/L

GESTATIONAL THROMBOCYTOPENIA (T₃)—asymptomatic and resolves rapidly after pregnancy. May be difficult to distinguish from ITP initially (until postpartum). Platelet count usually higher (>70 × 10⁹/L) in gestational thrombocytopenia. Follow platelet count q4weeks initially then q1week after 36th week

THROMBOCYTOPENIA IN PREGNANCY (CONT'D)

ITP (T_1 - T_3)—may use prednisone and IVIG in pregnancy. (Avoid dexamethasone, which crosses the placenta) Platelet transfusion if acute. Monitor closely. Splenectomy is last resort (safest in T_2). 10% of newborns may also develop thrombocytopenia due to placental transfer of maternal antibodies, but intracranial hemorrhage rare (<1%). Maternal platelet count does not predict fetal platelet count. Newborn platelet counts should be tested and monitored, as needed, after birth

PREECLAMPSIA/HELLP (T_2 - T_3)—supportive, early delivery, steroids for lung maturity if delivered <34 weeks (see earlier sections)

TTP/HUS—presence of severe thrombocytopenia and microangiopathic hemolytic anemia ($\uparrow\uparrow$ LDH) and differentiates TTP/HUS from HELLP. Requires plasma exchange \pm dialysis; rarely platelet transfusions

OTHERS—DIC, nutritional deficiencies (vitamin B12, folic acid), HIV, hepatitis B and C, drugs, autoimmune diseases (APLA), hypersplenism, and primary bone marrow disorders

ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN PREGNANCY

PATHOPHYSIOLOGY—persistent presence of antibody against phospholipids or cell surface proteins bound to anionic phospholipids. These include lupus anticoagulants (associated with thrombotic events), anticardiolipin antibody (associated with thrombotic events and obstetric complications; false-positive VDRL), and anti- β 2GP1 antibody \rightarrow most lead to hypercoagulable state, some may inhibit coagulation. Higher risk associated with higher antibody titer

CLINICAL FEATURES—venous and arterial thrombosis and rarely hemorrhage affecting the

ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN PREGNANCY (CONT'D)

lungs, heart, CNS, GI, kidneys, skin, and eyes. Also, thrombocytopenia (via ITP, TTP), Raynaud phenomenon, \uparrow risk of preeclampsia/eclampsia, recurrent fetal losses (see below), and intrauterine growth restriction

CAUSES—primary APS, secondary APS (various rheumatic diseases such as SLE, infections such as HIV and drugs)

DIAGNOSIS—clinical criteria of VTE or arterial thrombosis, or ≥ 3 unexplained losses <10 weeks, or ≥ 1 unexplained loss of morphologically normal fetus ≥ 10 weeks, or ≥ 1 premature births <34 weeks because of preeclampsia/eclampsia/placental insufficiency; *plus* laboratory criteria of elevated anticardiolipin antibodies, or lupus anticoagulant, or anti- β 2GP1 antibodies, confirmed >12 weeks apart. Diagnosis requires at least one clinical and one laboratory criteria

TREATMENTS—for women with APS associated with adverse obstetric outcomes, give prophylactic LMWH and low-dose ASA during pregnancy to 6 weeks postpartum. For women with APS associated with arterial thrombosis or VTE on anticoagulation prior to pregnancy, treatment dose LMWH plus low-dose ASA during pregnancy and resume warfarin postpartum (see p. 176 for more details on ANTIPHOSPHOLIPID ANTIBODY SYNDROME)

Related Topics

Antiphospholipid Antibody Syndrome (p. 176)
 Breast Cancer (p. 210)
 Lupus (p. 304)
 Thrombocytopenia (p. 168)
 Seizures (p. 335)



Approach to Diagnostic Tests and Clinical Trials

DIAGNOSTIC TESTS

2 × 2 TABLE

	Disease present	Disease absent	Total
Test positive	a (true positive)	b (false positive)	a + b
Test negative	c (false negative)	d (true negative)	c + d
Total	a + c	b + d	a + b + c + d

SENSITIVITY ★ SNOUT ★

$$= a / (a + c)$$

=out of 100 patients with disease, how many have a positive test result? Independent of prevalence, high sensitivity rules **out** disease (fewer false negatives)

SPECIFICITY ★ SPIN ★

$$= d / (b + d)$$

=out of 100 people without disease, how many have a negative test result? Independent of prevalence, high specificity rules **in** disease (fewer false positives)

POSITIVE PREDICTIVE VALUE (PPV)

$$= a / (a + b)$$

=out of 100 patients with a positive test result, how many actually have disease? Increases as prevalence increases

NEGATIVE PREDICTIVE VALUE (NPV)

$$= d / (c + d)$$

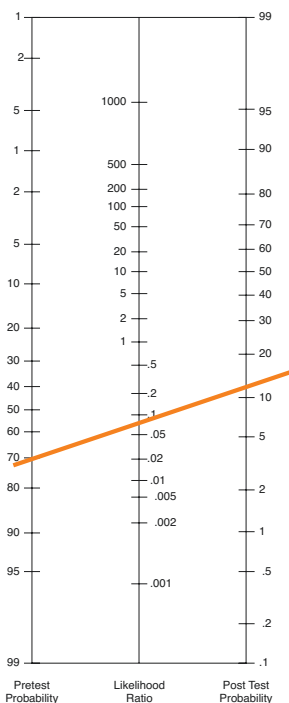
=out of 100 patients with a negative test result, how many do not have disease? Decreases as prevalence increases

LIKELIHOOD RATIOS (LR)—indicates how much a given diagnostic test result will change the pretest probability of the disorder under investigation, using Fagan nomogram:

- LR 1.0 no change: pre-test probability = post-test probability
- LR > 1.0 increases the post-test probability
- LR < 1.0 decreases the post-test probability

DIAGNOSTIC TESTS (CONT'D)

FAGAN NOMOGRAM—easily converts from pre-test probability to post-test probability using LR (alleviating tedious calculations above)



From Gaddis M. (2020) Epidemiology. In: Waseem M et al. (eds) *Prepare for the Pediatric Emergency Medicine Board Examination*. Springer, Cham. https://doi.org/10.1007/978-3-030-28372-8_33, with permission Springer Nature

DIAGNOSTIC TESTS (CONT'D)**POSITIVE LIKELIHOOD RATIO (LR+)**

$= (\text{positive test in disease}) / (\text{positive test in no disease})$

$= \text{sensitivity} / (1 - \text{specificity})$

NEGATIVE LIKELIHOOD RATIO (LR-)

$= (\text{negative test in disease}) / (\text{negative test in no disease})$

$= (1 - \text{sensitivity}) / \text{specificity}$

ACCURACY

$= (a + d) / (a + b + c + d)$

= how often is test correct in predicting true positive and true negative

TO CALCULATE THE POST-TEST PROBABILITY OF A DIAGNOSIS AFTER A TEST• **PRE-TEST PROBABILITY**

= probability of disease prior to performing test of interest

= disease prevalence (if no other diagnostic test previously performed) or post-test probability (after other initial investigations)

• **PRE-TEST ODDS**

= pre-test probability / (1 - pre-test probability)

• **POST-TEST ODDS**

= pre-test odds \times likelihood ratio

• **POST-TEST PROBABILITY**

= (post-test odds) / (1 + post-test odds)

THERAPEUTIC INTERVENTIONS**2 \times 2 TABLE**

	Outcome positive	Outcome negative	Total
Exposure positive	a	b	a + b
Exposure negative	c	d	c + d
Total	a + c	b + d	a + b + c + d

ODDS RATIO (OR)

- Use to express effect of exposure in a case control study
 $= (a/b) / (c/d) = ad/bc$. Odds ratio approximates RR if the disease is relatively rare
 = odds of the event in the treatment group / odds of the event in the control group

RELATIVE RISK (RR)

- Use to express effect of exposure in a cohort study
 $= \text{experimental event rate} / \text{control event rate}$
 $= [a/(a+b)] / [c/(c+d)]$

RELATIVE RISK REDUCTION (RRR)

$= [\text{experimental event rate} - \text{control event rate}] / \text{control event rate}$
 $= [a/(a+b) - c/(c+d)] / [c/(c+d)]$

ABSOLUTE RISK REDUCTION (ARR)

$= [\text{experimental event rate} - \text{control event rate}]$
 $= a/(a+b) - c/(c+d)$

NUMBER NEEDED TO TREAT (NNT)

$= 1/ARR$ = number of patients you would need to treat for one patient to benefit from the treatment of interest

Alcohol Withdrawal and Complications of Alcohol Use Disorder**PATHOPHYSIOLOGY**

ALCOHOL EQUIVALENTS—360 mL (12 oz) of beer = 150 mL (5 oz) of wine = 45 mL (1.5 oz) of distilled spirits = 12 g of alcohol (a standard drink)

THRESHOLD FOR INCREASED HEALTH RISKS—>14 drinks/week or >4 drinks/session for men and >7 drinks/week or >3 drinks/session for women or those \geq 65 years old. Cirrhosis generally requires >80 g/day (8 beers, 1 bottle of wine, or 250 mL of hard liquor) for 10–20 years

PATHOPHYSIOLOGY (CONT'D)**ALCOHOL USE DISORDER**

- A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least 2 of the DSM V problematic drinking criteria, occurring within a 12 month period
- Mild = 2-3 criteria
- Moderate = 4-5 criteria
- Severe = 6 or more criteria

PATHOPHYSIOLOGY (CONT'D)**COMPLICATIONS OF EXCESS ALCOHOL**

- **ACUTE INTOXICATION**
- **ACUTE WITHDRAWAL**—minor withdrawal, seizures, hallucinations, delirium tremens
- **CHRONIC EXCESS ALCOHOL**
 - **NEUROLOGIC**—Wernicke–Korsakoff syndrome, cognitive dysfunction, cerebellar degeneration, Marchiafava–Bignami disease, peripheral neuropathy, myopathy
 - **PSYCHIATRIC**—dependence, depression, homicide, suicide
 - **CARDIOVASCULAR**—hypertension, coronary heart disease, dilated cardiomyopathy, arrhythmias
 - **LIVER**—fatty liver, alcoholic hepatitis, cirrhosis
 - **PANCREAS**—acute or chronic pancreatitis
 - **NUTRITION**—hypokalemia, hypomagnesemia, hypophosphatemia, malnutrition, overweight
 - **HEMATOLOGY**—macrocytic anemia, thrombocytopenia, splenomegaly
 - **CANCER**—oral cavity, esophagus, pharynx, larynx, liver, breast
 - **ENDOCRINE**—hypoglycemia, ketosis, pseudo-Cushing disease, hyperuricemia, hypogonadism
 - **SOCIAL**—accidents, domestic violence, fetal alcohol syndrome

DSM V CRITERIA FOR ALCOHOL WITHDRAWAL

- A. Cessation/reduction of alcohol use that has been heavy and prolonged
- B. Two or more of the following within several hours to a few days of cessation or reduction in use: autonomic hyperactivity (e.g. sweating, tachycardia), tremor, insomnia, nausea or vomiting, transient visual, tactile, or auditory hallucinations or illusions, psychomotor agitation, anxiety, generalized tonic-clonic seizures
- C. Symptoms/signs above cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
- D. Rule out general medical conditions or other mental disorders

MINOR WITHDRAWAL

- **TIMING**—occurs within 6 h of cessation, resolves in 24–48 h
- **SYMPTOMS**—due to CNS and sympathetic hyperactivity, may include insomnia, tremulousness, mild anxiety, gastrointestinal upset, headache, diaphoresis, palpitations, anorexia

ALCOHOLIC HALLUCINATIONS

- **TIMING**—develop within 12–24 h of abstinence and resolve within 24–48 h

PATHOPHYSIOLOGY (CONT'D)

- **SYMPTOMS**—usually visual, although auditory and tactile phenomena may also occur. Unlike DT, there is usually no decreased level of consciousness/global confusion or autonomic dysfunction

WITHDRAWAL SEIZURES

- **TIMING**—usually occur within 48 h after the last drink; however, may occur after only 2 h of abstinence. Occur in 10–30% of patients in alcohol withdrawal
- **SYMPTOMS**—generalized tonic-clonic convulsions, usually multiple/recurrent. Predominantly seen in patients with a long history of chronic alcoholism use. Be wary of intracerebral hemorrhage with focal seizures

DELIRIUM TREMENS (DT)

- **TIMING**—typically begin between 72 and 96 h after the last drink and lasts 1–5 days
- **SYMPTOMS**—hallucinations, disorientation, tachycardia, hypertension, low-grade fever, agitation, and diaphoresis
- **RISK FACTORS**—increasing age, history of sustained drinking, history of previous delirium tremens, concurrent illness, greater number of days since the last drink, development of alcohol withdrawal with a positive blood alcohol level

INVESTIGATIONS**BASIC**

- **LABS**—CBC (macrocytosis, cytopenias), lytes, urea, Cr, glucose, TSH, AST, ALT (AST/ALT >2), ALP, bilirubin, GGT, Ca, Mg, PO₄, osmolality, ETOH level, ferritin
- **MICROBIOLOGY**—blood C&S, urinalysis, urine C&S (if delirious)
- **IMAGING**—CXR
- **ECG**
- **ABG**
- **URINE DRUG SCREEN**

SPECIAL

- **HEAD CT**—if significant or prolonged delirium, focal neurologic deficits, or focal seizures

ACUTE MANAGEMENT OF ALCOHOL WITHDRAWAL

ACUTE—**ABC**, O₂ to keep S_pO₂ ≥92%, **IV** (1 L crystalloid bolus, then 100 mL/h). Consider causes of patient's symptoms other than alcohol withdrawal

TREAT/PREVENT COMPLICATIONS

- **SEIZURES OR DELIRIUM TREMENS**—*diazepam* 5–10 mg IV q5min **or** *lorazepam* 2–4 mg IV q15–20min until patient calm, then put symptom triggered therapy

ACUTE MANAGEMENT OF ALCOHOL WITHDRAWAL (CONT'D)

- **AT RISK FOR WITHDRAWAL** (fixed schedule dosing)—*chlordiazepoxide* 50–100 mg PO q6h and PRN $\times 1$ day, then 25–50 mg q6h and PRN $\times 2$ days. Alternatively, consider CIWA-Ar scale below
- **REFRACTORY DELIRIUM TREMENS**—propofol, phenobarbital

NUTRITIONAL SUPPLEMENT—**thiamine deficiency** (*thiamine* 100–250 mg IV/IM $\times 5$ days must be given before glucose solution or may worsen Wernicke encephalopathy); consider high dose thiamine for Wernicke encephalopathy (500 mg IV TID $\times 2$ days, 500 mg IV/IM daily $\times 5$ days). **Multivitamin** 1 tab PO daily. Replace electrolytes (K, Mg, PO₄) if low

LONG-TERM MANAGEMENT OF ALCOHOLISM

COUNSELING—**support social network** (Alcoholics Anonymous, counseling). **Abstinence programs** (outpatient, inpatient). **Education** (alcoholism is a chronic-relapsing disease, explain withdrawal)

MEDICATIONS—**naltrexone** (mu-opioid receptor antagonist) 25 mg PO daily $\times 1$ week, then 50 mg PO daily for at least 3–4 months, coupled with psychosocial intervention. Depot injection can be used if significant risk of non-adherence. Contraindicated in hepatic failure, hepatitis, elevated liver enzymes ≥ 3 times normal, and recent/comorbid opioid use or opioid withdrawal. **Acamprosate** (GABA Agonist) 666 mg PO q8h can be used in patients with liver disease. Dose adjustment required for renal dysfunction, contraindicated if CrCl < 30 mL/min. **Disulfiram** (aldehyde dehydrogenase inhibitor) which causes a highly unpleasant sensation when patient consumes alcohol is another option

TREATMENT ISSUES FOR ALCOHOL WITHDRAWAL

REVISED CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT FOR ALCOHOL (CIWA-AR) SCALE (for use in patients who are able to answer questions)

- **NAUSEA AND VOMITING** (0–7)—“Do you feel sick to your stomach? Have you vomited?”
- **TREMOR** (0–7)
- **PAROXYSMAL SWEATS** (0–7)
- **ANXIETY** (0–7)—“Do you feel nervous?”
- **AGITATION** (0–7)
- **TACTILE DISTURBANCES** (0–7)—“Do you have any itching, pins-and-needles sensations, burning,

TREATMENT ISSUES FOR ALCOHOL WITHDRAWAL (CONT'D)

or numbness, or do you feel like bugs are crawling on or under your skin?”

- **AUDITORY DISTURBANCES** (0–7)—“Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?”
- **VISUAL DISTURBANCES** (0–7)—“Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?”
- **HEADACHE, FULLNESS IN HEAD** (0–7)—“Does your head feel different? Does it feel like there is a band around your head?”
- **ORIENTATION AND CLOUDING OF SENSORIUM** (0–4)—“What day is this? Where are you? Who am I?”
- **UTILITY**—mild withdrawal $\leq 8/67$ points, moderate withdrawal 9–15 points, severe withdrawal > 15 points (higher risk of delirium tremens and seizures). Use of benzodiazepines recommended when score ≥ 9 . Symptom-triggered regimens require intense monitoring, but have been shown to result in less medication use and shorter duration of treatment

SPECIFIC ENTITIES

THIAMINE DEFICIENCY SYNDROMES

- **WERNICKE ENCEPHALOPATHY**—encephalopathy (profound disorientation, indifference, inattentiveness, delirium, altered level of consciousness), oculomotor dysfunction (nystagmus, lateral rectus palsy, and conjugate gaze palsies), gait ataxia
- **KORSAKOFF SYNDROME** (irreversible)—selective anterograde and retrograde amnesia, confabulation, apathy, intact sensorium, relative preservation of long-term memory and other cognitive skills

METHANOL AND ETHYLENE GLYCOL OVERDOSE

- **CAUSES**—methanol and ethylene glycol can be found in anti-freeze, de-icing solutions, windshield fluids, cleaners, solvents, and fuels. The methanol metabolite formate and the ethylene glycol metabolites glycolate, glyoxylate, and oxalate result in toxic injuries. A lethal dose is around 1 g/kg
- **CLINICAL FEATURES**—anion (and osmolar) gap metabolic acidosis with associated Kussmaul breathing, hypotension, seizures, and altered level of consciousness. Methanol specifically is associated with mydriasis, afferent pupillary

SPECIFIC ENTITIES (CONT'D)

defect, optic disc hyperemia, retinal edema resulting in permanent blindness and ischemic injury to the basal ganglia. Ethylene glycol can result in cranial nerve palsies, tetany, and acute kidney injury with hematuria due to crystalline nephropathy

- **TREATMENTS**—**supportive** measures. **NG suction** may be helpful if recent ingestion (no role for activated charcoal). **NaHCO₃** 1–2 amps IV bolus, then 3 amps in 1 L D5W at 250 mL/h (if metabolic acidosis pH 7.1 mmol/L, increase rate to 3 mL/kg/h on dialysis; alternatively PO 1 mL/kg 95% ethanol, then 0.15 mL/kg/h). **Cofactor therapy** includes *folic acid* 50 mg IV q4h until methanol no longer measurable (accelerates formic acid → CO₂ + H₂O); *thiamine* 100 mg IV q6h and *pyridoxine* 50 mg IV q6h until ethylene

SPECIFIC ENTITIES (CONT'D)

glycol no longer measurable (accelerates glycoxylation → glycine + α-hydroxy-β-ketoadipate. This reaction requires magnesium supplementation). **Hemodialysis** for confirmed intoxication (methanol level >15.6 mmol/L [>500 μg/mL] or ethylene glycol level >8 mmol/L [>50 mg/dL]), refractory metabolic acidosis, or acute kidney injury. Folic acid, thiamine, and multivitamin as supportive measures

Rhabdomyolysis**DIFFERENTIAL DIAGNOSIS****SKELETAL MUSCLE DAMAGE**

- **MEDICATIONS** —alcohol, cocaine, statins, neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia
- **INFECTIONS**
- **HYPERACTIVITY** —seizures, exertion
- **IMMOBILITY**
- **COMPARTMENT SYNDROME**
- **TRAUMA OR SURGERY**
- **ELECTROLYTE ABNORMALITIES** —hypokalemia, hypophosphatemia
- **MYOPATHIES** —polymyositis, dermatomyositis

CARDIAC MUSCLE DAMAGE—myocardial infarction

PATHOPHYSIOLOGY

DEFINITION OF RHABDOMYOLYSIS—CK >5 × of upper normal limit

HYPOCALCEMIA AND HYPERCALCEMIA—calcium initially decreases due to ↑ deposition in muscle and ↓ bone responsiveness to PTH. May see rebound hypercalcemia in 20% of patients when rhabdomyolysis resolves

COMPLICATIONS—acute kidney injury, DIC from release of thromboplastin

INVESTIGATIONS**BASIC**

- **LABS**—lytes, urea, Cr, CK, AST, ALT, Ca, PO₄, Mg, uric acid, troponin, LDH, urine myoglobin (positive urine dipstick for blood without RBC on microscopy)

DIAGNOSTIC ISSUES

MONITORING IN RHABDOMYOLYSIS—CK, urine output, Cr, Ca, PO₄ should be checked regularly (q4–24 h) until CK normalized (monitor hyperK, hyperPO₄, hyperuricemia, metabolic acidosis)

MANAGEMENT

ACUTE—**ABC**, O₂ to keep sat >90%, **IV PREVENT COMPLICATIONS**—**IV crystalloid** 3–4 L in first 3–4 h bolus, then maintenance rate that achieves a urine output of 200–300 mL/hr to prevent acute kidney injury (avoid large volumes of NS as this may cause NAGMA). However, if acute kidney injury already established, be careful not to cause fluid overload. Fasciotomy for compartment syndrome

Alkaline diuresis (add 3 amps NaHCO₃ to 1 L D5W to keep urine pH >6.5, little evidence for this)

SPECIFIC ENTITIES**NEUROLEPTIC MALIGNANT SYNDROME (NMS)**

- **PATHOPHYSIOLOGY**—an idiosyncratic reaction due to dopamine receptor blockade, usually with typical, and sometimes atypical, antipsychotic agents. The syndrome typically occurs within a few days of treatment, with drug levels usually within therapeutic range. May also develop after withdrawal of exogenous dopa-

SPECIFIC ENTITIES (CONT'D)

minergic agonists, such as levodopa therapy in Parkinson disease patients

- **CLINICAL FEATURES**—**classic tetrad** of high fever, autonomic instability (tachycardia, hypertension), neuromuscular rigidity, and altered mental status. CK may be elevated if rigidity present
- **DIAGNOSIS**—clinical based on history and physical. Check CK
- **TREATMENTS**—discontinue all antidopaminergic medications. Supportive measures. Specific treatments include benzodiazepines (lorazepam), dantrolene (skeletal muscle relaxant), bromocriptine (dopamine agonist), and amantadine (dopaminergic and anticholinergic)

SEROTONIN SYNDROME

- **PATHOPHYSIOLOGY**—overstimulation of central and peripheral serotonin receptors, usually related to overdose of SSRIs or drug interactions that increase serotonergic neuro-

SPECIFIC ENTITIES (CONT'D)

transmission (e.g. SSRIs in combination with MAOIs or TCAs)

- **CLINICAL FEATURES**—**classic triad** of autonomic instability (fever, tachycardia, hypertension), neuromuscular rigidity and altered mental status. CK may be elevated if rigidity present. While many of the symptoms may be similar to neuroleptic malignant syndrome, **shivering, hyperreflexia, myoclonus, and ataxia** may be present in serotonin syndrome but not in neuroleptic malignant syndrome
- **DIAGNOSIS**—clinical based on history and physical
- **TREATMENTS**—discontinue all serotonergic medications. Supportive measures (oxygen, IV crystalloids for volume depletion, cardiac monitoring). In mild cases, symptoms usually resolve within 24 h. Consider benzodiazepines (if significant agitation), cyproheptadine (histamine-1 receptor antagonist) in select cases

Multisystem Disorders**SELECTED MULTISYSTEM DISORDERS****INFECTIONS**

- **BACTERIAL**—endocarditis, TB, Whipple disease
- **VIRAL**—HIV, HBV, HCV, EBV, CMV
- **FUNGAL**—histoplasmosis, aspergillosis
- **PARASITIC**—schistosomiasis

MALIGNANCY

- **SOLID**—metastatic, paraneoplastic
- **LYMPHOPROLIFERATIVE**—leukemia, lymphoma

INFLAMMATORY—vasculitis, rheumatoid arthritis, scleroderma, SLE, IBD

IATROGENIC—drugs

INFILTRATIVE—cryoglobulinemia, hemochromatosis, amyloidosis, sarcoidosis, porphyria

ENDOCRINE—diabetes, hyperthyroidism

HEMOCHROMATOSIS

INHERITANCE—autosomal recessive with low penetrance. Among the North American population of European descent, approximately 10% are heterozygous and 0.4% are homozygous for hemochromatosis

PATHOPHYSIOLOGY—mutation of HFE gene (90% homozygous for C282Y, other common mutation is the C282Y/H63D compound heterozygote); results in low hepcidin levels → ↑ intestinal absorption of heme and non-heme iron → iron deposition in organs

HEMOCHROMATOSIS (CONT'D)

CLINICAL FEATURES—generally manifest after age 40 (later in women). **Skin** (bronze), **joints** (arthralgia, destructive arthritis, classically 2nd and 3rd MCP, chondrocalcinosis), **heart** (arrhythmia, cardiomyopathy, heart failure), **pancreas** (“bronze” diabetes), **thyroid** (hypothyroidism), **liver** (↑ LFT, hepatomegaly, fibrosis, cirrhosis, hepatocellular carcinoma 200 × ↑ risk), **gonads** (hypogonadism, impotence), **pituitary** (hypopituitarism), **infections** (*Listeria*, *Yersinia*, *Vibrio*), fatigue

DIAGNOSIS—↑ transferrin % saturation (serum iron/TIBC × 100%, most useful for screening if >45%), Fe (↑), ferritin (↑), **HFE genotype testing**. Liver biopsy for hepatic iron content if elevated liver enzymes or ferritin >1000 in C282Y/C282Y homozygotes, liver biopsy versus T2-weighted MRI (can estimate hepatic iron concentration and differentiate HH from secondary iron overload) in non-C282Y homozygotes with suspected iron overload. Rule out secondary iron overload and iron loading anemias (e.g. sickle cell anemia, thalassemia major, and chronic hemolytic anemia)

TREATMENTS—**alcohol cessation, phlebotomy** (remove 1–2 U weekly until ferritin 50–100 ng/mL then initiate maintenance phlebotomy),

HEMOCHROMATOSIS (CONT'D)

avoid iron and vitamin C supplements, avoid raw seafood/shellfish (risk of *Vibrio*), screen first degree relatives. Chelation only if phlebotomy contraindicated (e.g. moderate/severe anemia) or not tolerated (e.g. hypotension)

2019 American College Gastroenterology Guideline Hereditary Hemochromatosis

SARCOIDOSIS

PATHOPHYSIOLOGY—cause unknown, may involve antigen exposure → activation of T-cell immunity → non-caseating granuloma formation

CLINICAL FEATURES—constitutional (fatigue, weight loss, fever), **pulmonary** (cough, dyspnea, chest pain. Staged according to CXR: stage I = bilateral hilar adenopathy, stage II = hilar adenopathy with parenchymal reticular opacities, upper > lower, stage III = parenchymal reticular opacities without hilar adenopathy, stage IV = advanced fibrosis with evidence of volume loss, honey-combing, hilar retraction, bullae, cysts, and emphysema. Stages not necessarily chronological), **cardiac** (arrhythmia especially conduction blocks, HF, sudden death), **GI tract** (hepatomegaly, rarely ulcers, obstruction), **renal** (interstitial nephritis, nephrocalcinosis, nephrolithiasis), **neurologic** (cranial nerve palsies especially CN VII, aseptic basilar meningitis, pituitary dysfunction, peripheral neuropathy, neuromuscular, transverse myelitis), **ocular** (uveitis, optic neuritis, scleritis, retinitis), **endocrine** (hypercalcemia, hypercalciuria, abnormal vitamin D metabolism, hypopituitarism), **lymphatics** (lymphadenopathy, hypersplenism), **joints/bone** (symmetrical acute polyarthritis of ankles, chronic arthritis of large or small joints of hands and feet, bone pain with periosteal resorption), and **skin** (erythema nodosum, lupus pernio, subcutaneous nodules), lacrimal and parotid gland enlargement. **Lofgren syndrome** is an acute presentation characterized by bilateral hilar lymphadenopathy, erythema nodosum and/or peri-articular arthritis; associated with a good prognosis with >80% remission in 2 years. **Heerfordt syndrome** is facial palsy, fever, anterior uveitis and parotid gland enlargement

INVESTIGATIONS—blood tests (CBC, lytes, urea, Cr, Ca, ALP, serum ACE level), **urine tests** (urinalysis), **imaging** (CXR, high resolution CT chest), **special** (TST or IGRA, ECG, cardiac MRI if suspected cardiac involvement, TTE if suspected pulmonary hypertension, PFTs, LP and gadolinium enhanced brain MRI if neurologic

SARCOIDOSIS (CONT'D)

symptoms, lymph node sampling [EBUS recommended over mediastinoscopy—see below for indications], biopsy of affected organ(s), ophthalmology referral)

DIAGNOSIS—requires compatible clinical findings plus non-necrotizing granulomatous inflammation on biopsy (not required if high clinical suspicion such as in the case of Lofgren syndrome, Heerfordt syndrome, or lupus pernio) plus exclusion of alternate causes

PROGNOSIS—50–60% have spontaneous remission within 3 years. Poor prognostic factors include age at onset >40, Black race, progressive pulmonary sarcoidosis, pulmonary hypertension and extra-thoracic disease

TREATMENTS

- **LUNG INVOLVEMENT**—observation if asymptomatic stage I-III disease with normal/mild PFT changes (follow up symptoms, PFTs, and imaging) or Lofgren syndrome as high chance of spontaneous remission. Inhaled steroids for mild cough (*budesonide* 800–1600 mcg BID × 4–8 weeks) and systemic steroid (*prednisone* 20–40 mg PO daily × 3 months) for progressive/severe disease, symptoms that interfere with quality of life. Cytotoxic agents (methotrexate, azathioprine, leflunomide, or mycophenolate mofetil) +/- anti-TNF therapy (infliximab) second line.
- **SKIN AND EYE INVOLVEMENT**—topical steroid
- **JOINT INVOLVEMENT**—NSAIDs first line, prednisone second line, hydroxychloroquine or colchicine third line
- **CARDIAC INVOLVEMENT**—*prednisone* 40–60 mg PO daily, cytotoxic agents second line, anti-TNF or cyclophosphamide if severe disease. Concurrent management of arrhythmias and reduced EF, and consideration for device therapy and transplantation
- **NEUROLOGIC INVOLVEMENT**—*prednisone* 40–60 mg PO daily in mild disease, *methylprednisolone* 60–80 mg IV daily in severe disease, cytotoxic agents second line, anti-TNF therapy or cyclophosphamide for severe disease

2020 American Thoracic Society Guideline Sarcoidosis

West Curr Opin Rheumatol 2018;30(3)

AMYLOIDOSIS

PATHOPHYSIOLOGY—soluble amyloid precursor protein (amyloidogenic proteins: AL/primary amyloidosis = monoclonal Ig light chain variable region in plasma cell dyscrasias; AA/

AMYLOIDOSIS (CONT'D)

secondary amyloidosis = serum amyloid A in chronic inflammatory conditions; ATTR (acquired or hereditary) = derived from mutant transthyretin protein, $A\beta = A\beta$ protein precursor in Alzheimer disease, $\beta 2$ -microglobulin in CKD/ hemodialysis) → insoluble fibrils deposit in different organs
CLINICAL FEATURES—constitutional (fatigue, weight loss), **skin** (waxy, thick, easy bruising, racoon eyes/periorbital purpura), **renal** (nephrotic proteinuria, distal RTA, nephrogenic diabetes insipidus), **cardiac** (diastolic > systolic HF, cardiomyopathy, arrhythmia, heart block, MI), **neurologic** (mixed sensory/motor peripheral neuropathy, autonomic neuropathy, bowel/bladder dysfunction, intracranial bleeding, carpal tunnel syndrome), **pulmonary** (pleural effusion, parenchymal nodules, tracheo-bronchial infiltration), **GI tract** (hepatosplenomegaly, GI bleed, malabsorption, pseudo-obstruction/dysmotility), **hematologic** (reduced activity of factor X, binding of Ca-dependent factors to amyloid), **endocrine** (adrenal insufficiency, hypothyroidism), **soft tissues** (muscle pseudo-hypertrophy, shoulder pad sign, nail dystrophy, alopecia, macroglossia is specific to AL, occurring in 20%)

DIAGNOSIS—biopsy of involved organ(s) (subcutaneous fat pad, minor salivary glands, or rectal tissue). Amyloid stains red with Congo red dye and shows “apple-green” birefringence under polarized light

INVESTIGATIONS—investigate cause: serum and urine protein electrophoresis and immunofixation, free light chain assay, bone marrow biopsy, and skeletal imaging (AL), immunohistochemical staining for specific amyloid protein (AA and TTR), genetic testing. **Investigate for end organ disease:** CBC, Cr, 24h urine protein, AST, ALT, ALP, bilirubin, INR, ECG, BNP, troponin, echocardiogram +/- cardiac MRI. Amyloidosis usually involves λ light chain, whereas light chain deposition disease involves κ light chain

PROGNOSIS—median survival 1–2 years for AL, only 6 months if cardiac involvement. Up to 15 years in ATTR. Prognosis dependent on underlying disease in AA

TREATMENTS—supportive (dialysis if renal failure). Treatment of underlying infectious/inflammatory disorder (AA) and plasma cell dyscrasia (AL), altered dialysis mode or renal transplant in dialysis-associated amyloidosis, tafamidis (transthyretin stabilizer) in ATTR cardiomyopathy, liver transplantation in hereditary amyloidosis

Wechalekar et al. *Lancet* 2016;387(10038)

Maurer et al. *NEJM* 2018;379(11)

Falk et al. *NEJM* 1997;337(13)

CRYOGLOBULINEMIA

PATHOPHYSIOLOGY—production of cryoglobulins (immunoglobulins that precipitate at temperatures <37 °C and re-dissolve on warming) that can cause end organ damage, hyperviscosity, and systemic vasculitis of small to medium vessels. Type I = monoclonal IgG/IgM/IgA/free light chains, produced by protein-secreting monoclonal gammopathies (Waldenström macroglobulinemia/multiple myeloma/MGUS/CLL). Type II = mixed cryoglobulins, monoclonal IgM with RF activity and polyclonal IgG. Type III = polyclonal IgM with RF activity and polyclonal IgG, may be essential or due to immune activation from persistent viral infections (HCV/HIV/HBV), autoimmune disease, or lymphoproliferative disorders

CLINICAL FEATURES OF TYPE I—symptoms from vascular occlusion/thrombosis +/- small vessel vasculitis. **Skin** (livedo reticularis, necrosis, Raynaud phenomenon, acrocyanosis, digital ischemia), arthralgia, **renal** (MPGN), **hyperviscosity syndrome** (blurred vision, confusion, headache, coma, epistaxis, oral bleeding)

CLINICAL FEATURES OF TYPE II/III—symptoms from immune complex vasculitis. **Constitutional** (fatigue, weight loss, arthralgia, myalgia), **neurologic** (peripheral neuropathy), **renal** (proteinuria, hematuria, MPGN), **pulmonary** (small airway disease), **rheumatologic** (Sjögren, Raynaud), **skin** (palpable purpura), splenomegaly, lymphadenopathy. Meltzer triad (purpura, weakness, and arthralgia)

DIAGNOSIS—laboratory (↑ cryoglobulin or cryocrit >1%, hypocomplementemia, ↑ ESR/CRP), **clinical** (vasculitis, thrombosis), **pathological** (biopsy of affected organ), **secondary causes** (serum protein electrophoresis, ANA, RF, HCV, HBV, HIV serology)

PROGNOSIS—10-year survival 50%. Death usually due to infection or cardiovascular disease. At risk for end-stage renal disease, secondary non-Hodgkin lymphoma

TREATMENTS—treat underlying cause, avoid cold exposure. For moderate/severe mixed cryoglobulinemia consider steroids and rituximab. Plasmapheresis for hyperviscosity syndrome, life-threatening vasculitis, RPGN requiring dialysis

Muchtar et al. *Blood* 2017;129(3)

Ramos-Casals et al. *Lancet* 2012;379(9813)

PORPHYRIA

INHERITANCE—mainly autosomal dominant with incomplete penetrance

PORPHYRIA (CONT'D)

PATHOPHYSIOLOGY—enzymatic defect in the heme synthesis pathway → continued production of toxic heme precursors by liver or bone marrow (porphobilinogen in acute intermittent porphyria) → accumulation in neurovisceral organs (acute hepatic porphyrias) and/or skin (photocutaneous porphyrias), with specific symptoms related to the nature of precursors. Eight types of porphyria representing defects at each of the steps of the pathway

CLINICAL FEATURES OF ACUTE HEPATIC PORPHYRIAS—acute intermittent porphyria most common, triad of seizures, abdominal pain, and hyponatremia, most commonly in young females, attacks can be precipitated by OCP use/P-450 inducing medications. Attacks preceded by fatigue, anxiety, restlessness → **autonomic neuropathy** (tachycardia, hypertension, arrhythmia, abdominal pain, vomiting, constipation/diarrhea), **sensory neuropathy** (extremity pain, back pain, numbness), **motor neuropathy** (weakness), **cranial neuropathy** (dysarthria, dysphagia, dysphonia, facial paresis), **metabolic changes** (dark/red urine, hepatic dysfunction, hyponatremia), and **CNS symptoms** (confusion, hallucinations, seizures). Occasionally may progress to diffuse muscle weakness with respiratory muscle paralysis. Long term, patients at risk of renal failure, hepatocellular carcinoma, and cholangiocarcinoma

CLINICAL FEATURES OF PHOTOCUTANEOUS PORPHYRIAS—porphyria cutanea tarda most common. Associated with hepatic iron overload, HCV, HIV, alcohol, and estrogen. Protoporphyrin second most common and presents in childhood with severe burning/stinging/itching in sun exposed areas. Chronic photosensitive skin symptoms include excessive fragility, blistering, scarring, particularly on the back of hands, hypertrichosis on sun exposed skin, hyperpigmentation of face, and red/brown urine

DIAGNOSIS—for diagnosis of acute porphyria, measure spot urinary porphobilinogen (most elevated during attacks and substantial elevation confirms diagnosis) and spot urinary total porphyrins (elevated during attacks). If elevated PGB or total porphyrins, check plasma and fecal porphyrins to differentiate between types. If all normal, check urinary ALA. Ideally collect samples during acute attack. Once confirmed, genetic screening of first-degree family members. For diagnosis of porphyria cutanea tarda: total porphyrins (plasma, serum, or urinary). If elevated, perform porphyrin

PORPHYRIA (CONT'D)

fractionation and other specialized testing to determine type

TREATMENTS—for acute porphyria with moderate/severe symptoms: exogenous heme infusions (*hematin* 4 mg/kg IV daily x 4 days), supportive care including IV fluids (D10 in 1/2NS), analgesia, antiemetics, **avoid precipitating medications** (<http://porphyriafoundation.com/drug-database>), alcohol, fasting, and infections, if possible. High-dose carbohydrate (400 g/day) diet can be considered in mild attacks. If recurrent acute attacks, prophylactic medications and liver transplantation can be curative. For cutaneous porphyria: therapy to deplete hepatic iron (phlebotomy or hydroxychloroquine), avoidance of exacerbating factors (sun, alcohol, tobacco, estrogen), treat underlying cause (e.g. HCV treatment)

Bissell et al. *NEJM* 2017;377(9)

Kauppinen *Lancet* 2005;365(9455)

WHIPPLE DISEASE

PATHOPHYSIOLOGY—*Tropheryma whipplei* (Gram-positive bacillus, non-acid-fast, periodic acid-Schiff positive, found in soil, fresh and seawater sediments) → infiltration of various organs without significant inflammatory response → accumulation of organisms eventually causing organ failure. Typically white male predominance, mean age 50

CLINICAL FEATURES—**GI** (diarrhea, abdominal pain, malabsorption with weight loss and iron deficiency, GI bleed, abdominal mass, ascites), **joints** (seronegative, migratory, small joint predominant polyarthralgia), **CNS** (headache, delirium, dementia, seizures, coma, hypothalamic pituitary axis dysfunction, cerebellar ataxia, meningitis, myelopathy), **eyes** (supranuclear vertical gaze palsy, oculomasticatory myorhythmia, oculo-facial-skeletal myorhythmia, uveitis), **skin** (hyperpigmentation, subcutaneous nodules, purpura), **cardiac** (myocarditis, pericarditis, CHF, murmur, culture negative endocarditis, hypotension), **pulmonary** (interstitial fibrosis, pleural effusion, hilar lymphadenopathy, chronic cough), **hematologic** (anemia, lymphadenopathy), **constitutional** (fever, weight loss)

DIAGNOSIS—often misdiagnosed as rheumatologic disease, immunosuppression can shorten time between prodromal symptoms and classic disease. Diagnosis usually made on small bowel biopsy (PAS-positive macrophages). Two tests required for diagnosis (i.e. PAS test followed by RT-PCR or immunohistochemistry). If biopsies

WHIPPLE DISEASE (CONT'D)

negative, consider testing other symptomatic tissues/fluid or CSF

TREATMENTS—fatal if untreated. Antibiotics (ceftriaxone 2 g IV daily \times 2 weeks, then trimethoprim-sulfamethoxazole DS 1 tab PO BID \times 1–2 years), nutritional supplement (protein,

WHIPPLE DISEASE (CONT'D)

iron, folate). Disease can relapse even after many years and follow up duodenal biopsies are recommended during/after treatment

Marth et al. Lancet Infect Dis 2016;16(3)
Fenollar et al. NEJM 2007;356(1)

Perioperative Assessment for Non-Cardiac Surgery and Postoperative Complications

2016 Canadian
Cardiovascular Society Guidelines
Perioperative Cardiac Risk Assessment
Patients Noncardiac Surgery

PERIOPERATIVE CARDIAC RISK ASSESSMENT**CCS PERIOPERATIVE SUMMARY**

- **DEFINING SURGICAL URGENCY**—CCS guidelines define surgical urgency without providing specific timing. Perioperative evaluation is dictated by the surgical urgency
- **EMERGENCY PROCEDURE**—acute limb or life-threatening (e.g. aortic aneurysm rupture). Emergency procedures should not be delayed for cardiac assessment
- **URGENT & SEMI-URGENT PROCEDURES**—limb or life-threatening (e.g. hip fracture, cancer with a potential to metastasize). Evaluate for unstable cardiac disease or obstructive cardiac disease (obtain echocardiogram): **unstable angina**, severe **aortic stenosis** (symptomatic, aortic valve area 40 mmHg, or maximum aortic velocity \geq 4.0 m/s), **severe mitral stenosis** (symptoms, mitral valve area 40 mmHg or right heart failure or symptoms). Discussion with patient, surgical team, and anesthesiologist about the risks and benefits of delaying or cancelling the procedure
- **ELECTIVE**—procedures that can be delayed without worsening of a medical condition (e.g. knee arthroplasty). Undergo formal cardiac risk assessment

PREOPERATIVE CARDIAC ASSESSMENT—for elective procedures with expected length of stay greater than 24 hours. CCS guidelines recommend against using METS, cardiac stress testing, and routine echocardiograms to differentiate high vs. low risk

1. Risk stratification with revised cardiac risk index (**RCRI**): predicts risk of MI, cardiac arrest,

PERIOPERATIVE CARDIAC RISK ASSESSMENT (CONT'D)

or death at 30-days: 0/6 = 3.9%, 1/6 = 6.0%, 2/6 = 10.1%, \geq 3/6 = 15.0%

- **HIGH-RISK SURGERY**—thoracic, intraperitoneal, or suprainguinal vascular surgery
 - **CAD**—any MI, current angina, current nitrate use, positive exercise stress test, Q waves on ECG
 - **HF**—history of HF, PND, pulmonary edema, S3, crackles, vascular redistribution on CXR
 - **CVD**—history of stroke or TIA
 - **DIABETES**—use of insulin
 - **RENAL FAILURE**—creatinine $>$ 177 μ mol/L
2. If age $>$ 65 years, RCRI $>$ 1, or age 45–64 years with cardiovascular disease (known CAD, CVD, peripheral arterial disease, CHF, severe pulmonary hypertension, or severe obstructive intracardiac abnormality), order a preoperative BNP
 3. If BNP $>$ 92 mg/L or NT-proBNP $>$ 300 mg/L or result unavailable, order troponins daily for 3 days after surgery or until discharge, whichever is sooner
 4. If BNP $<$ 92 mg/L or NT-proBNP $<$ 300 mg/L, no additional testing is required

POSTOPERATIVE TROPONIN SURVEILLANCE—more than half of postoperative MIs are asymptomatic and only detected with routine postoperative troponin measurement. Patients with postoperative troponin elevations are at increased risk of 30-day and 1-year mortality (50% cardiac mortality, 50% other cause mortality). Measure troponins daily for three days after surgery or until discharge (whichever comes first) in patients who are staying in hospital for \geq 24-hours after surgery and have postoperative cardiac com-

PERIOPERATIVE CARDIAC RISK ASSESSMENT (CONT'D)

plication risk $\geq 5.0\%$ (\uparrow BNP, age ≥ 65 years, 45–64 years and cardiovascular disease, or RCR1 ≥ 1)

- **MYOCARDIAL INJURY AFTER NONCARDIAC SURGERY (MINS)**—postoperative troponin elevation not explained by another systemic disease (e.g. pulmonary embolism, sepsis). Defined by troponin T ≥ 0.03 ng/mL, hs-troponin ≥ 65 ng/L or ≥ 20 ng/L and increasing by 5 ng/L or more. Treatment: evaluate/treat systemic disease, consider ASA and statin, consider dabigatran

SURGICAL TIMING

- **PREVIOUS MYOCARDIAL INFARCTION**—bare metal stent (delay elective, non-cardiac surgery for at least 1 month), drug eluting stent (delay elective, noncardiac surgery for at least 3 months). Continue ASA perioperatively whenever possible; withhold clopidogrel and ticagrelor for 5–7 days and prasugrel for 7–10 days before surgery and restart as soon as deemed safe by the surgeon
- **RECENT STROKE/TIA**—delay elective surgery for 9 months when possible
- **RECENT VTE**—delay elective surgery for at least 1 month and ideally 3 months when possible

2018 CCS/CAIC Focused Update Guidelines Antiplatelet Therapy

PERIOPERATIVE ANTICOAGULATION MANAGEMENT

RISK STRATIFICATION

- **LOW BLEEDING RISK**—do not hold anticoagulation for low bleeding risk procedures (e.g. cataract surgery, dermatologic biopsies, colonoscopies, cardiac device insertion, dental procedures, thoracentesis, paracentesis, arthrocentesis)
- **MODERATE BLEEDING RISK**—abdominal, general, intrathoracic, orthopedic, vascular, angiography
- **HIGH BLEEDING RISK**—any neuraxial anesthesia, neurosurgery, open heart surgery, major vascular surgery (aneurysm repair, bypass), major orthopedic surgery (hip/knee arthroplasty), lung resection, urologic, large cancer surgeries, intestinal anastomosis, plastic surgery

BRIDGING—use of heparin products to continue anticoagulation when off warfarin prior to surgery. LMWH started two days after stopping warfarin with a half-dose given the day before surgery. UFH started two days after stopping warfarin and continued until 4 hours before surgery

- **INDICATIONS FOR BRIDGING**—all mechanical prosthetic mitral valves, cage-ball/disc mechanical aortic valves, atrial fibrillation with a CHADS2 score of 5 or 6, arterial or venous thromboembolism within 3 months, arterial or venous thromboembolism during interruption of anticoagulation, severe thrombophilia with previous VTE, rheumatic valvular heart disease
- **BRIDGING NOT INDICATED**—atrial fibrillation with CHADS2 < 4 , VTE further than 12 months ago, bi-leaflet mechanical aortic valve, bioprosthetic heart valves

2018 CCS Focused Update Guideline Management Atrial Fibrillation

Drug	Renal function	Moderate bleed risk	High bleed risk
Dabigatran	eGFR > 50 mL/min	Hold for one day before surgery	Hold for 2 days before surgery
Dabigatran	eGFR 30–49 mL/min	Hold for 2 days before surgery	Hold for 4 days before surgery
Rivaroxaban	eGFR > 30 mL/min	Hold for one day before surgery	Hold for 2 days before surgery
Apixaban	eGFR > 30 mL/min	Hold for one day before surgery	Hold for 2 days before surgery
Warfarin	-	Hold for five days before surgery	

PERIOPERATIVE ANTICOAGULATION MANAGEMENT (CONT'D)

POSTOPERATIVE DVT PROPHYLAXIS—extended duration (beyond 3 weeks) is preferable to short-term prophylaxis (<2 weeks) in patients undergoing major surgery

- **MECHANICAL PROPHYLAXIS**—sequential compression devices are recommended over no prophylaxis
- **ORTHOPEDIC SURGERY**—for hip/knee arthroplasty, use ASA or DOACs, followed by LMWH. Use LMWH for hip fracture
- **GENERAL OR GYNECOLOGIC SURGERY**—LMWH
- **NEUROSURGERY**—mechanical prophylaxis is preferable unless high risk of VTE
- **UROLOGIC PROCEDURES**—for TURP, radical prostatectomy, mechanical prophylaxis unless high risk of VTE
- **CARDIAC OR MAJOR VASCULAR SURGERY**—LMWH or mechanical prophylaxis

2019 American Society Hematology Management Venous Thromboembolism

PERIOPERATIVE PULMONARY RISKS

RISK REDUCTION—smoking cessation with evidence-based pharmacotherapy for all patients, ideally 4 weeks preoperatively. Interventions with evidence to reduce postoperative pulmonary complications: postoperative CPAP, prophylactic mucolytics, respiratory physiotherapy, enhanced recovery after surgery protocols. Interventions with evidence of no effect on postoperative pulmonary complications: prophylactic inhaled beta-agonists, restrictive fluid regimens, epidural analgesia, postoperative high-flow nasal cannula, incentive spirometry

ADDITIONAL PERIOPERATIVE RISK ASSESSMENT

BLEEDING RISK ASSESSMENT—inquire about any recurrent bleeding tendencies and bleeding complications from past surgeries. Review Hb, platelets, INR, and PTT

ANESTHETIC RISK ASSESSMENT—inquire about past surgeries and family history of malignant hyperthermia

DELIRIUM RISK ASSESSMENT—inquire about alcohol and illicit drug use, diagnosis of dementia to assess the risk of post-operative delirium

PERIOPERATIVE DIABETES MANAGEMENT

RISK REDUCTION—do not delay surgery for patients with elevated HbA1c. Measure point-of-care test (POCT) q6h postoperative in all patients

PERIOPERATIVE DIABETES MANAGEMENT (CONT'D)

with abnormal HbA1c or known diabetes. Note that 10% of patients without diabetes may have postoperative hyperglycemia. Target POCT 4.0–10.0 mmol/L in all patients after surgery. Postoperative hyperglycemia should be treated with **basal bolus insulin regimens** and *not* sliding scale insulin alone, even if the patient is NPO. **Patients with type 1 diabetes must always receive basal insulin, even when NPO, to prevent DKA.** Patients receiving insulin should undergo POCT q6h

• PERIOPERATIVE ORAL MEDICATION MANAGEMENT

- **METFORMIN, DPP4-INHIBITORS (-GLIPTINS), GLP-1 ANALOGUES (-TIDES)**—continue in the perioperative period unless eGFR <25 ml/min
- **SGLT-2 INHIBITORS (-GLIFLOZINS)**—hold three days before surgery and restart when eating and drinking well
- **REPAGLINIDE, SULFONYLUREAS (GLICLAZIDE, GLYBURIDE)**—hold on the day of surgery and restart when eating and drinking well

• PERIOPERATIVE INSULIN MANAGEMENT

- **ULTRA-LONG-ACTING INSULIN (DEGLUDEC)**—give 80% of usual dose starting three days before surgery. Resume usual dose when eating well. Continue even if NPO
- **LONG-ACTING INSULIN (GLARGINE, LEVEMIR)**—give 80% of usual dose on the day before and day of surgery. Resume usual dose when eating well. Continue even if NPO
- **INTERMEDIATE-ACTING INSULIN (NPH)**—give 80% of usual dose at HS before surgery and 50% of usual dose on the morning of surgery. Resume usual dose when eating well. Continue even if NPO
- **MEALTIME DOSES OF SHORT- OR RAPID-ACTING INSULIN**—hold only when NPO. Resume usual dose when eating well
- **CORRECTION DOSES OF SHORT- OR RAPID-ACTING INSULIN**—continue at usual dose throughout perioperative period, even if NPO

2018 Diabetes Canada Guidelines

INVESTIGATIONS FOR PERIOPERATIVE PATIENTS

PRINCIPLE—asymptomatic patients undergoing low-risk noncardiac surgery do not require routine laboratory tests. Consider type and screen, CBC, electrolytes, and creatinine in select patients undergoing high risk procedures

2019 Choosing Wisely Canada

INVESTIGATIONS FOR PERIOPERATIVE PATIENTS (CONT'D)

CARDIAC INVESTIGATIONS

- **ECG**—not required in asymptomatic patients undergoing low risk noncardiac surgery
- **ECHOCARDIOGRAPHY**—should only be ordered to investigate for suspected intracardiac obstructive disease or pulmonary hypertension
- **NON-INVASIVE TESTING**—exercise stress test, stress MIBI, dobutamine stress echocardiogram are associated with surgical delays and no difference in cardiac outcomes. Should only be ordered if otherwise clinically indicated
- **ANGIOGRAPHY**—associated with surgical delays and no difference in outcomes. Should only be ordered if otherwise clinically indicated

PULMONARY INVESTIGATIONS

- **ABG**—for patients with suspected hypoxia or hypercapnia
- **CXR**—should not be obtained in asymptomatic patients
- **PULMONARY FUNCTION TESTS**—required only to diagnose or stage patients with lung disease of unknown severity
- **LUNG RESECTION WORKUP**—patients with preoperative FEV1 >2L (>80% predicted) and DLCO >80% predicted can likely tolerate pneumonectomy. Patients with FEV1 60% predicted can probably tolerate lung resection. Predicted postoperative FEV1 or DLCO 20 mL/kg/min will likely tolerate surgery

2013 ACCP Guideline Physiologic Evaluation Patient Lung Cancer Resectional Surgery

BACTERIAL ENDOCARDITIS PROPHYLAXIS

Only given to patients with the highest risk of developing endocarditis, which include the following

HIGH-RISK CARDIAC CONDITIONS

- **PROSTHETIC**—any prosthetic cardiac valve, prosthetic material used for cardiac valve repair
- **CYANOTIC CONGENITAL HEART DISEASE**—unrepaired, recently repaired (<6 months), completely repaired but with residual defects at the site or adjacent to the site of the prosthetic device
- **CARDIAC TRANSPLANT RECIPIENTS WITH REGURGITANT VALVULOPATHY**
- **PREVIOUS ENDOCARDITIS**

PROCEDURES

- **ORAL CAVITY**—manipulation of gingival or periapical region of teeth, perforation of oral mucosa
- **RESPIRATORY TRACT**—if incision/biopsy of respiratory mucosa (tonsillectomy, adenoidectomy), bronchoscopy with a rigid bronchoscope, or flexible bronchoscopy if biopsy performed

BACTERIAL ENDOCARDITIS PROPHYLAXIS (CONT'D)

- **GI/GU TRACT**—generally not recommended in the absence of active infection
- **MSK**—if infected skin, skin structure, or musculoskeletal tissue

PROPHYLAXIS REGIMENS—give one of the following 30–60 min prior to procedure: amoxicillin 2 g PO/IM/IV, cefazolin 1 g IV/IM, ceftriaxone 1 g IV/IM, cephalixin 2 g PO, clindamycin 600 mg PO/IM/IV, azithromycin 500 mg PO, clarithromycin 500 mg PO

2007 AHA Guidelines Prevention of Infective Endocarditis

PERIOPERATIVE MEDICATION MANAGEMENT

CARDIOVASCULAR AGENTS—β-blockers (continue throughout the perioperative period).

α-Agonists (continue up to and including day of surgery. If prolonged NPO, substitute with TD clonidine or IV methyldopa). **Calcium channel blockers** (continue throughout the perioperative period). **ACE inhibitor/ARB** (hold within 24-hours of surgery). **Diuretics** (hold within 24-hours of surgery). **Statins** (continue throughout perioperative period). **Fibrates/niacin/cholestyramine/ezetimibe** (hold within 24-hours of surgery)

NSAIDS—some vascular protective effect but also potential renal failure. Hold 3 days before surgery, substitute with acetaminophen as needed

STEROIDS—patients taking prednisone >20 mg/day for >3 weeks or with Cushingoid features should be assumed to have HPA axis suppression.

For **minor stress** (local anesthetic), no stress dose steroids needed. For **moderate stress** (orthopedic, perivascular), consider 2× physiologic replacement (*hydrocortisone* 50 mg IV on call to OR, then 25 mg q8h × 24 h, then normal dose). For **major stress** (intra-abdominal, cardiac), consider high-dose steroid (*hydrocortisone* 100 mg IV on call to OR, then 50 mg q8h × 24 h, then 25 mg q8h × 24 h, then resume maintenance) **LEVOTHYROXINE** (T4)—may be continued throughout the perioperative period

NEUROLOGIC AGENTS—anti-epileptics (continue up to and including day of surgery. If NPO, substitute with IV phenytoin or phenobarbital). **Antidepressants/Li** (continue up to day before surgery but stop day of surgery. Resume postop with oral intake)

PERIOPERATIVE MEDICATION MANAGEMENT (CONT'D)**2016 Canadian Cardiovascular Society Guidelines Perioperative Cardiac Risk Assessment Patients Noncardiac Surgery****POSTOPERATIVE COMPLICATIONS****MAJOR CARDIAC COMPLICATIONS**—myocardial infarction, arrhythmia**MAJOR PULMONARY COMPLICATIONS**—pneumonia, respiratory failure with prolonged mechanical ventilation, bronchospasm, atelectasis, exacerbation of underlying chronic lung disease**HEMATOLOGIC COMPLICATIONS**—bleeding, thrombosis**POSTOPERATIVE FEVER ★7WS★**

- **WOUND**—infection
- **WIND**—pulmonary (pneumonia, atelectasis, PE)
- **WEINS** ('veins')—DVT/PE
- **WATER**—UTI
- **WONDER** drugs
- **WHAT THE HECK**—sepsis
- **WHAT ELSE**—thyroid storm

POSTOPERATIVE DELIRIUM ★DIMS★ (see p. 422 for more details)

- **DRUGS**—alcohol withdrawal, benzodiazepines, pain (i.e. lack of appropriate drugs)
- **INFECTIONS**—pneumonia, UTI, sepsis
- **METABOLIC**—myocardial infarction, hypoxia (pulmonary embolism), electrolyte abnormalities
- **STRUCTURAL**—stroke, intracranial hemorrhage

POSTOPERATIVE HYPERTENSION (see p. 70 for more details)

- **PHYSIOLOGIC**—pain, bladder distension/atony, confusion/agitation, thyroid storm
- **PATHOLOGIC**—infections, stroke
- **DRUGS**—alcohol withdrawal, withdrawal of antihypertensive medications, neuroleptic malignant syndrome, malignant hyperthermia

POSTOPERATIVE COMPLICATIONS (CONT'D)**POSTOPERATIVE ACUTE RENAL FAILURE** (see p. 83 for more details)

- **PRE-RENAL**—blood loss, fluid loss, ACE inhibitors, NSAIDs, cyclosporin
- **RENAL**—ATN (ischemic, contrast, aminoglycosides), AIN (penicillins, cephalosporins), microvascular (cholesterol emboli)
- **POST-RENAL**—urinary retention

POSTOPERATIVE BLEEDING (see p. 171 for more details)

- **↑ INR**—factor deficiency or inhibitor (VII), liver disease, vitamin K deficiency, DIC, warfarin
- **↑ INR AND PTT**—factor deficiency (X, V, II, I), liver disease, vitamin K deficiency, DIC, warfarin
- **↑ PTT**—factor deficiency and inhibitor (VIII, IX, XI), heparin, von Willebrand disease
- **PLATELET DISORDER**—von Willebrand disease, renal failure, liver failure, myeloproliferative disorders

POSTOPERATIVE THROMBOCYTOPENIA (see p. 168 for more details)

- **PSEUDOTHROMBOCYTOPENIA**—platelet clumping (recollect in citrate)
- **DILUTIONAL**—transfusions, bleeding
- **DECREASED PRODUCTION**—less likely but possible
- **SEQUESTRATION**—less likely but possible
- **DESTRUCTION**—DIC, drugs (HITT with heparin, GPIIb/IIIa inhibitors, thiazides, sulfonamides, rifampin, indomethacin), alloimmune (post-transfusion)

Smoking Cessation**COMPLICATIONS AND SMOKING-ASSOCIATED DISORDERS****CANCER**—lung, head and neck (larynx, pharynx, oral cavity), esophagus, pancreas, bladder, kidney, stomach, cervix, AML**CARDIOVASCULAR DISEASES**—CAD, CVD, PVD, Buerger disease**RESPIRATORY DISEASES**—COPD, pneumonia**COMPLICATIONS AND SMOKING-ASSOCIATED DISORDERS (CONT'D)****METABOLIC**—diabetes mellitus, infertility, premature menopause, osteoporosis**COAGULOPATHY****MORTALITY**—all-cause mortality ~3-fold higher (death most commonly from neoplastic, vascular or respiratory causes)

PATHOPHYSIOLOGY OF SMOKING

NICOTINE ADDICTION—related to the combination of: (1) pleasurable effects of nicotine (e.g. relief of anxiety and arousal); (2) pleasurable effects of associated environmental triggers (e.g. coffee and meals); and (3) the unpleasurable effects of nicotine withdrawal (e.g. dysphoria, anxiety, irritability, insomnia, decreased concentration, increased appetite and over the long-term increased weight)

LUNG CANCER—cigarette smoke contains numerous carcinogens: *N*-nitrosamines and polycyclic aromatic hydrocarbons are metabolized to nitrosamine ketone and *N*'-nitrosonornicotine by the cytochrome P450 system, which form DNA adducts, leading to mutations and eventually cancer. Duration of cigarette exposure is a greater risk factor than the number of cigarettes smoked per day. Cigarette smoking is a greater risk factor than pipe or cigar smoking. Smokers have a 10–30 × increased risk of lung cancer. The risk of lung cancer returns close to baseline (80–90% reduction) after 10–15 years of smoking cessation. Second-hand smokers have up to 2 × increased risk of lung cancer

LIFE EXPECTANCY—on average, 13.2 and 14.5 years shorter for male and female smokers compared to non-smokers, respectively. Smoking cessation between 45 and 54 years of age reduces risk of death associated with continued smoking by two-thirds.

MANAGEMENT OF SMOKING CESSATION (COMBINATION THERAPY SUPERIOR TO MONOTHERAPY)

COUNSELING—identify smoking cues, use cognitive and behavioral methods to break the link.

Remove cues (remove ash trays, avoid settings where smoking occurs, suggest other smokers in the household quit at the same time). **Coping** (inform family/friends/co-workers about quitting and seek support, plan strategies for stress management). **Referral** to a nicotine cessation program

DRUG THERAPY—should be individualized (considerations include cost, prior use, contraindications, and preference). **Controller medications:** **Varenicline** (nicotinic acetylcholine receptor partial agonist—decreases nicotine reward pathway) 0.5 mg PO daily for days 1–3,

MANAGEMENT OF SMOKING CESSATION (COMBINATION THERAPY SUPERIOR TO MONOTHERAPY) (CONT'D)

then 0.5 mg PO BID days 4–7, then 1 mg PO BID. Standard therapy is 12 weeks but can be extended up to 12 months. Recommended over bupropion. More effective if prescribed in combination with a nicotine patch but increased risk of adverse events when combined. **Bupropion SR** (dopamine/norepinephrine reuptake inhibitor) 150 mg PO daily × 3 days, then BID × 7–12 weeks, can be extended for up to 1 year. Target quit date after at least 1 week of treatment. **Reliever medications** (more effective when combined with controller medications): **Nicotine replacement** (gum, lozenges, inhaler, nasal spray, *transdermal patch* – if smoking >10 cigarettes/day, dose is 21 mg daily × 6 weeks, then 14 mg daily × 2 weeks, then 7 mg daily × 2 weeks). **E-cigarettes/personal vaporizers** may assist with abstinence; however, some safety concerns are emerging (including e-cigarette or vaping product use associated lung injury)

TREATMENT ISSUES

APPROACH TO COUNSELING

- SCREENING**—screen for tobacco use at every visit, identify dependence and explore willingness to quit. All patients can be offered combination therapy (counseling and pharmacotherapy) and followed longitudinally. All patients should be referred to adjunct behavioral support programs (web based, phone based, or in person)
- EXPLORE PATIENT'S OWN REASONS TO QUIT**—current health, social (e.g. children), or economic issues. Explain comorbidities associated with smoking. "As your doctor, I need you to know that quitting smoking is the most important thing you can do to protect your health"
- IF PATIENT READY TO QUIT OR REDUCE SMOKING WITHIN 30 DAYS**—offer counseling (quit date, what works, what does not, express confidence, problem solving strategies) and drug therapy
- IF PATIENT WANTS TO QUIT BUT NOT NOW**—explore barriers to smoking cessation (nicotine dependence, fear of failure, lack of social support or self-confidence, concern about weight gain, depression, substance abuse). Explore reasons

TREATMENT ISSUES (CONT'D)

- to quit. Offer counseling and drug therapy. Set quit date. Follow-up
5. **IF PATIENT NOT READY TO QUIT**—avoid argument. Offer counseling and drug therapy. Use the 5R's of motivational intervention (relevance, risks of continued use, rewards of quitting, roadblocks to quitting, repeat every 6–12 months)

OBSTACLES TO CESSATION

- **WEIGHT GAIN AFTER CESSATION**—2.3–4.5 kg [5–10 lb]
- **PHYSIOLOGICAL**—withdrawal symptoms (see pathophysiology) usually begin few hours after the last cigarette, peak 2–3 days later, and wane over several weeks
- **PSYCHOLOGICAL**—smoking is a learned behavior/ritual. High risk of relapse (40% at 5 years); requires clinical follow-up

SIDE EFFECTS OF SMOKING CESSATION METHODS

- **NICOTINE REPLACEMENT THERAPY**—increased blood pressure and heart rate, palpitations. Other side effects specific to delivery method include: gum/lozenges—mouth irritation, jaw pain, dyspepsia, patch-skin irritation, nasal spray/inhaler-nose/throat/oral irritation, cough. No absolute contraindications but not recommended in unstable angina, recent MI, or pheochromocytoma (increases catecholamine release). Inhalers not recommended in bronchospastic disease

TREATMENT ISSUES (CONT'D)

- **BUPROPION SR**—insomnia, headache, dry mouth, nausea and vomiting, agitation, reduced seizure threshold (contraindicated if seizure disorder or increased seizure risk). Discontinuation rate ~10%. Contraindicated if current/recent use of MAO inhibitors. Not recommended during treatment with linezolid (increased risk of serotonin syndrome)
- **VARENICLINE**—dose-related nausea and vomiting, insomnia, abnormal dreams, headaches, constipation, diarrhea, flatulence, and dyspepsia. Not recommended in pregnancy. Prior black box warning about neuropsychiatric side effects and increased suicidality was removed after a large RCT showed no difference in these outcomes. Monitoring for these symptoms is still recommended

PROGNOSTIC ISSUES**CESSATION RATE**

- **WITHOUT HELP**—<10%
- **COMBINED DRUG THERAPY AND COUNSELING**—25–30% long term

2020 ATS Guideline Initiating Pharmacologic Treatment Tobacco-Dependent Adults
 Reid et al. *CMAJ* 2016;188(17-18)
 Rigotti *NEJM* 2002;346(7)
 Hays et al. *NEJM* 2008;359(19)

Medical Fitness to Drive**2019 Canadian Medical Association Fitness to Drive****GENERAL PRINCIPLES**

- A single diagnosis does not determine a patient's right to drive but does signal the possible need for a **functional assessment**. A functional assessment is a structured assessment to exercise judgement and take necessary actions required to drive. It may or may not include a road test
- **MOTOR VEHICLE LICENSING AUTHORITY**—final responsibility for issuing/revoking licenses
 - **PHYSICIANS**—responsible for reporting people they believe to be unfit drivers. In some jurisdictions, it is mandatory to report (varies by jurisdiction). Physicians have been held liable for negligence if a patient is involved in a motor vehicle accident.

GENERAL PRINCIPLES (CONT'D)

- **UNCERTAINTY**—if not sure about medical fitness for driving, advise patient not to drive. Document and inform the appropriate government agency
 - **BALANCE**—interest of public has priority over confidentiality and rights of individual driver
 - **LICENSE TYPE**—commercial license vs. private vehicle
- OLDER DRIVERS**—★**CANDRIVE**★ (Cognition, Acute or fluctuating illness, Neuromuscular disease or neurological effects, Drugs, Record prior accidents, In-care experiences suggesting high-risk, Vision, Ethanol use)

GENERAL PRINCIPLES (CONT'D)

DURATION OF NO DRIVING FOR SPECIFIC DISORDERS

Disorders	Private driver	Commercial driver
Seizures		
Single, unprovoked seizure before diagnosis	3 months, neuro assessment needed with EEG and MRI	12 months, neuro assessment needed with EEG and MRI
Epilepsy	6 months seizure-free on meds. Patient must be adherent to medications	5 years seizure-free on or off meds
After initiating or changing anti-epileptics	3 months from a change in medications	6 months from a change in medications
Alcohol withdrawal seizures	6 months (alcohol and seizure free, adherent and completed rehabilitation)	6 months (alcohol and seizure free, adherent and completed rehabilitation)
Syncope		
A single episode that is explained and unlikely to recur	No restriction	No restriction
A single episode that is unexplained	1 week	12 months
Diagnosed or treated syncope (e.g. pacemaker inserted)	1 week	1 month
Reversible etiology of syncope	Successful treatment	Successful treatment
Recurrent unexplained syncope	3 months	12 months
Cardiovascular		
Stable angina	No restrictions	No restrictions
Unstable angina	48 h after PCI, 7 days after discharge if no PCI	7 days after PCI, 30 days after discharge if no PCI
NSTEMI with PCI	48 h	7 days
NSTEMI no PCI	7 days after discharge	30 days after discharge
STEMI	1 month after discharge	3 months after discharge
CABG	1 month after discharge	3 months after discharge
Heart failure	No if NYHA IV, home inotropes, or LV assist	No if NYHA \geq III, EF <35%
VF	6 months	Never
Unstable VT	6 months	Never
Sustained VT, LVEF \geq 35%	4 weeks	3 months
Sustained VT, LVEF < 35%	3 months	Never

GENERAL PRINCIPLES (CONT'D)

Disorders	Private driver	Commercial driver
SVT, AF or atrial flutter	No restriction if no impairment in consciousness, satisfactory rate control; consider anticoagulation	No restriction if no impairment in consciousness, satisfactory rate control; consider anticoagulation
Mobitz II 2° AVB, acquired 3° AVB, alternate LBBB or RBBB	No driving	No driving
Permanent Pacemaker	1 week after implant (regular PM checks required)	
ICD	Depends on indication	No driving
AAA	No if >6 cm (men), >5.5 cm (women)	
Cerebrovascular		
TIA	Requires medical assessment	Requires medical assessment
Stroke	1 month	
Other disorders		
Vision	No if poor vision <20/50, hemianopsia, or diplopia	No if poor vision <20/30, hemianopsia, or diplopia
Diabetes on insulin	Must have no microvascular or macrovascular complications that impair capacity to drive and no episodes of severe hypoglycemia in last 6 months while awake	Must have regular physician monitoring and cannot have uncontrolled DM (including A1c over 12%). See Canadian Diabetes Guidelines for details. Must have no microvascular or macrovascular complications that impair capacity to drive and no episodes of severe hypoglycemia in last 6 months while awake
COPD, on supplemental oxygen	Road test required	No driving

NOTE—regulations for reporting/restriction in individual jurisdictions may vary

Obtaining Consent for Medical Procedures

CONSENTING PROCESS

CONTEXT—establish an appropriate setting for the discussion

WHAT DOES THE PATIENT UNDERSTAND?

- “What do you understand about your illness?”
- “Have you had any similar procedures before?”
- Obtain a general impression of patient’s competence

DISCUSS THE RATIONALE AND POTENTIAL BENEFITS REGARDING THE PROCEDURE, EXPLAIN DETAILS OF PROCEDURE

- **POSITIONING**
- **LOCAL ANESTHETIC**—ask about allergies
- **ACTUAL PROCEDURE**—degree of detail tailored to patient’s comprehension and interest. Assess bleeding risk

CONSENTING PROCESS (CONT'D)

- **ESTIMATED DURATION**
- **POTENTIAL COMPLICATIONS**—bleeding, infections, puncture/injury of surrounding tissue, and other specific risks related to procedure

EXPLAIN ALTERNATIVES—including risk of deferring procedure, step-by-step

ASSESS UNDERSTANDING—use simple language and ask the patient to summarize what they understand

DISCUSS CONSENT FORM—patient may wish to read the consent form carefully and have some time to think about procedure

PROVIDE REASSURANCE AND FOLLOW-UP

Biomedical Ethics

ETHICAL JUDGMENT

MORAL JUDGMENT—the decision-making process is based on both ethical principles and facts

- **ETHICAL PRINCIPLES**—beneficence, non-maleficence, autonomy, and justice
- **FACTS**—patient preference, competence, prognosis, and others (finances, resources)

TRUTH TELLING

EXAMPLE—patient's family members do not want bad news disclosed to patient

FACTORS TO CONSIDER—autonomy, loss of trust, patient will eventually find out, patient's need to make plans

APPROACH—ask patient if they want bad news disclosed. Ensure good communication with family

EXCEPTIONS—specific cultures, harm to patient (legally may exercise therapeutic privilege, but seldom used)

INFORMED CONSENT

EXAMPLE—patient asks to stop treatment

FACTORS TO CONSIDER—autonomy, law, CMA policy

INFORMED CONSENT—disclosure (discuss condition, treatment proposed, alternatives, risks, and benefits), capacity (competence), and voluntariness

CAPACITY

EXAMPLE—patient refuses treatment but may not be competent

REQUIREMENT—ability to understand information and appreciate consequences of *individual* decision. Competence assessment may be required, involve multidisciplinary team (p. 417)

SUBSTITUTE DECISION MAKING—legally through advance directive proxy (also known as representative agreement or personal directive), the court, or court-appointed guardian (spouse > children > parents > siblings > relatives > public trustee). The selection of guardian is based on patient's wishes, values, and beliefs more than his/her best interest judgment. Practically, however, decisions are usually made by family members and healthcare team together

BATTERY AND NEGLIGENCE

CRITERIA FOR BATTERY—doing anything (e.g. touching) without patient's consent

CRITERIA FOR NEGLIGENCE

1. Physician owes patient duty of care

BATTERY AND NEGLIGENCE (CONT'D)

2. Physician breaches standard of care
3. Breach causes harm to patient
4. Physician's mistake is responsible for patient's loss (causation)

CONFIDENTIALITY

EXAMPLE—HIV disclosure to spouse

FACTORS TO CONSIDER—autonomy, need trust for therapeutic relationship

APPROACH—breaching confidentiality is based on a balance of beneficence, non-maleficence, and autonomy. Legally can breach confidentiality if required by court/law, patient consent obtained, or if public interest at stake (e.g. HIV, child abuse, and people who are unfit to drive)

FUTILITY

EXAMPLE—CPR in patient with advanced cancer

FACTORS TO CONSIDER—limits of patient autonomy and considerations of justice and resource allocation

APPROACH—communication (understand patient's rationale), negotiation, mediation (bio-ethicist), and arbitration. No legal obligation to provide treatment outside of standard of care

MAY REFUSE PROVIDING TREATMENT—if harm to self/others, futility, or excessive cost to society

MEDICAL ASSISTANCE IN DYING (MAID)

EXAMPLE—ALS patient asks for medical assistance in dying

ARGUMENTS FOR—autonomy, the relief of suffering, and discrimination against physically disabled persons who cannot commit suicide

ARGUMENTS AGAINST—respect for human life, protection of vulnerable persons, and fear of abuse

LEGALLY—withdrawal of care and palliative sedation (for the purpose of maximizing comfort) are acceptable. Legality of medical assistance in dying varies by jurisdiction

GENERAL GUIDANCE FOR MAID—**assessment from multidisciplinary team** including physicians providing original and independent assessment. Differentiate **clinician-administered** (physician or nurse practitioner who directly administers substance that causes death) vs. **self-administered** MAID (provide drug that eligible person takes themselves to bring about their own death). General eligibility: mentally **competent**, ≥18 years old, have a **grievous and irremediable** medical

MEDICAL ASSISTANCE IN DYING (MAID) (CONT'D)

condition, **voluntary request** for MAiD that is not the result of outside pressure or influence, **informed consent** to receive MAiD. **Waiting/ reflection period** after request to allow consideration of request, may withdraw request at any time in the process and not obligated to proceed with MAiD even if found eligible

RESOURCE ALLOCATION

EXAMPLE—selection of organ transplant recipients

FACTORS TO CONSIDER—justice

1. No one disputes that resources are scarce and rationing decisions are required
2. It is unfair to ration based on implicit criteria that may vary from physician to physician
3. Rationing criteria must be explicit, evenly applied, publicly known, and open to review
4. It is unfair to begin rationing by denying resources to the most vulnerable patients
5. An alternative to rationing is to augment the availability of the scarce resource

LEVELS—macro (provincial/national), meso (hospital), micro (individual patient)

RATIONING—discrimination based on age, gender, or religion is legally and morally not feasible. Allocation based on greater benefit and/or more urgent need is acceptable. Financial considerations should be taken into account, but do not justify omission of appropriate care

RESEARCH ETHICS

EXAMPLE—placebo control

FACTORS TO CONSIDER—beneficence, non-maleficence, autonomy, and justice. Physician torn between best interest of research community and patient

APPROACH—patient's right to care comes first
ETHICAL RESEARCH METHODS—clinical equipoise (there is genuine uncertainty within the expert medical community, not necessarily on the part of the individual investigator, about the preferred treatment between the various arms of a randomized controlled trial), good experimental design (treatment arms, likely benefit > harm, inclusion and exclusion criteria, respect rights of research subjects, informed consent), and ethics review board approval

CONFLICT OF INTEREST

EXAMPLE—pharmaceutical company funded lunch

PROFESSIONAL JUDGMENT—physicians trusted by patients and society because of the fiduciary duty doctors accept to rank their primary interests (appropriate patient care, valid research, truthful, and unbiased teaching) above such secondary interests as personal gain, promotion, fame, or other benefits

APPROACH—cannot eliminate all conflicts of interest, as they are inextricable from our lives, but prevent secondary gain from dominating or appearing to dominate professional decisions or choices

Hospital Admission and Discharge Issues**PRINCIPLES OF MEDICAL MANAGEMENT**

★THE 5C'S★

CAUSES—identify and treat the underlying cause of disease

COMPLICATIONS—anticipate and treat complications as they arise

COMMUNICATION—educate patients regarding **lifestyle changes** and precautions (e.g. driving, sports, medical alert bracelet). Provide counseling on **risk reduction** (e.g. quit smoking, blood pressure, and lipid control) and **appropriate use of medications**

PRINCIPLES OF MEDICAL MANAGEMENT (CONT'D)

CONSULT—seek advice from other disciplines when indicated (physiotherapy, dietitian, specialists)

CONTINUITY—provide appropriate follow-up

REASONS FOR ADMISSION

MEDICAL—diagnostic workup, monitoring, IV therapy (hydration, antibiotics, chemotherapy), surgery

REASONS FOR ADMISSION (CONT'D)

NURSING—ADL assistance (eating, bathroom, mobility), monitoring (critically ill)

MENTAL—suicide or homicide risk due to psychiatric disorder

SOCIAL—usually in combination with factors above, cannot cope at home/lack of support, out-of-town, homeless

DISCHARGE CRITERIA

CRITERIA—depends on the functional, medical, mental, and social situations

DISCHARGE PLANNING—should take place from the time of admission. The goal of hospital stay is to get the patient well enough to leave hospital

DISPOSITION

HOME ± COMMUNITY PROGRAMS—home care (clinical care, home IV, support services, coordinating care), day program (day hospital, day support)

SUPPORTIVE HOUSING—lodge/assisted living, group homes (mental, disabled)

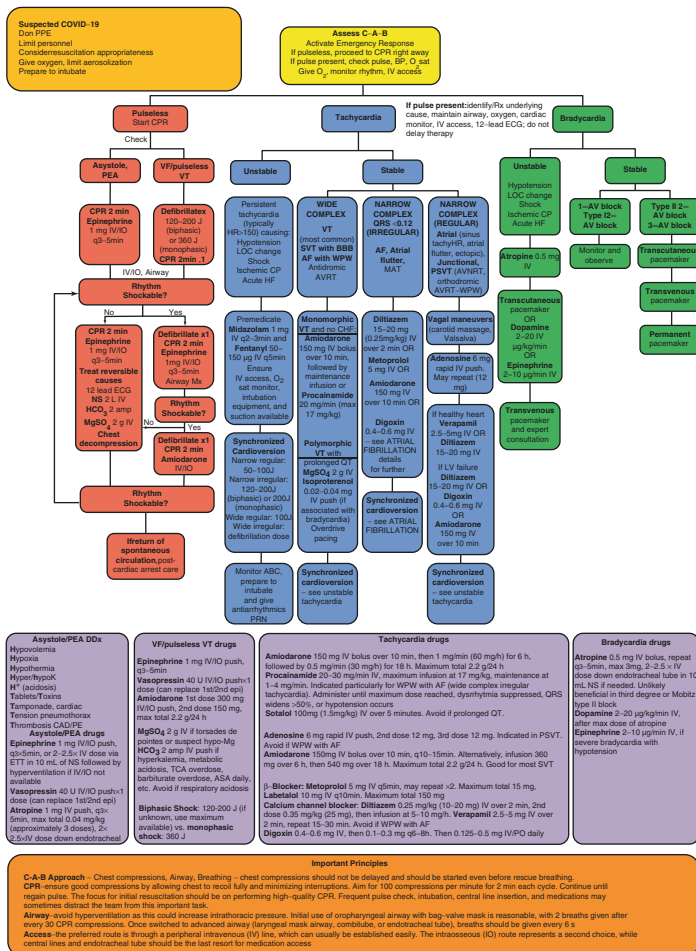
CARE FACILITY—long-term care, respite, sub-acute, rehabilitation, psychiatry

PALLIATIVE CARE—palliative care unit, home palliative care, hospice (home-based, inpatient)

Appendix A

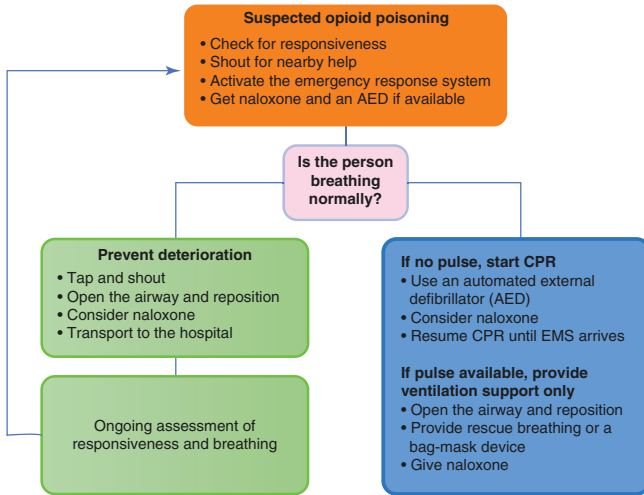
ADVANCED CARDIAC LIFE SUPPORT

2020 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2020 142:S366–S468



OPIOID-ASSOCIATED EMERGENCY FOR HEALTHCARE PROVIDER ALGORITHM

2020 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2020 142:S366–S468



Appendix B

LIST OF COMMON ABBREVIATIONS

% sat	Percentage saturation	AP	Anterior–posterior
5-FU	5-Fluorouracil	APA	Antiphospholipid antibody
5-HIAA	5-Hydroxyindoleacetic acid	APACHE	Acute physiology and chronic health evaluation
5HT	Serotonin	APC	Adenomatosis polyposis coli
AAA	Abdominal aortic aneurysm	APS	Antiphospholipid antibody syndrome
ABC	Airway, breathing, circulation	ARB	Angiotensin receptor blocker
Abd	Abdomen	ARDS	Acute respiratory distress syndrome
ABG	Arterial blood gas	ARR	Absolute risk reduction
ABI	Ankle brachial index	AS	Aortic stenosis
ABPA	Allergic bronchopulmonary aspergillosis	ASA	Acetylsalicylic acid, American Society of Anesthesiologists
ABx	Antibiotics	ASD	Atrial septal defect
ACE	Angiotensin-converting enzyme	ASO	Anti-Streptolysin- O
ACI	Acute cardiac ischemia	AST	Aspartate aminotransferase
ACR	American College of Rheumatology	ATC	Around the clock
ACS	Acute coronary syndrome	ATN	Acute tubular necrosis
ACTH	Adrenocorticotrophic hormone	AV	Atrioventricular or arteriovenous
ADL	Activity of daily living	AVM	Arteriovenous malformation
ADP	Adenosine diphosphate	AVNRT	Atrioventricular nodal reentry tachycardia
AF	Atrial fibrillation	AXR	Abdominal X-ray
AFB	Acid fast bacilli	BAC	Bronchioloalveolar carcinoma
AFP	Alpha fetoprotein	BAL	Bronchoalveolar lavage
AG	Anion gap	BCC	Basal cell carcinoma
AIDS	Acquired immunodeficiency syndrome	BID	Twice per day
AIN	Acute interstitial nephritis	Bili	Bilirubin
AJR	Abdominal jugular reflex	BIPAP	Bilevel positive airway pressure
AKI	Acute kidney injury	BM	Bone marrow
ALI	Acute lung injury	BL	Burkitt lymphoma
ALL	Acute lymphoblastic lymphoma	BMD	Bone mineral density
ALND	Axillary lymph node dissection	BMI	Body mass index
ALS	Amyotrophic lateral sclerosis	BMR	Basal metabolic rate
ALT	Alanine aminotransferase	BMT	Bone marrow transplant
ALP	Alkaline phosphatase	BNP	B-type natriuretic peptide
AMA	Antimitochondrial antibody	BOOP	Bronchiolitis obliterans organizing pneumonia
AMI	Acute myocardial infarction	BP	Blood pressure
AML	Acute myelogenous leukemia	BPPV	Benign paroxysmal positional vertigo
ANA	Antinuclear antibody		
ANC	Absolute neutrophil count		
ANCA	Anti-neutrophilic cytoplasmic antibody		

BRBPR	Bright red blood per rectum	CRF	Chronic renal failure
BRCA	Breast cancer gene	CRH	Corticotropin-releasing hormone
BSA	Body surface area	CRP	C-reactive protein
BSE	Breast self-examination	CRT	Cardiac resynchronization therapy
C&S	Culture and sensitivity	CSF	Cerebrospinal fluid
Ca	Calcium	CT	Computed tomography
CA 125	Cancer antigen 125	CVA	Cerebral vascular disease, costovertebral angle
CA 15.3	Cancer antigen 15.3	CVC	Central venous catheter
CA 19–9	Cancer antigen 19–9	CVD	Cerebral vascular disease
CABG	Coronary artery bypass graft	CVP	Central venous pressure
CAD	Coronary artery disease	CVVHD	Continuous veno-venous hemodialysis
CAH	Congenital adrenal hyperplasia	CXR	Chest X-ray
CAM	Confusion Assessment Method	DSW	5 % dextrose water
CA-MRSA	Community-acquired methicillin-resistant <i>Staphylococcus aureus</i>	DAT	Direct antiglobulin test
CAP	Community-acquired pneumonia	DBP	Diastolic blood pressure
CAPD	Continuous ambulatory peritoneal dialysis	DC	Direct current
CBC	Complete blood count	DCIS	Ductal carcinoma in situ
CBE	Clinical breast examination	DDAVP	Desmopressin acetate
Cbl	Cobalamin	DEXA	Dual-energy X-ray absorptiometry
CCB	Calcium channel blocker	DFA	Direct fluorescent antibody
CCP	Cyclic citrullinated peptides	DHEA	Dehydroepiandrosterone
CCS	Canadian Cardiovascular Society	DHEAS	Dehydroepiandrosterone sulfate
CEA	Carcinoembryonic antigen	DI	Diabetes insipidus
CHF	Congestive heart failure	DIC	Disseminated intravascular coagulation
Chol	Cholesterol	DIP	Distal interphalangeal joint
CIN	Cervical intraepithelial neoplasia	DKA	Diabetic ketoacidosis
CK	Creatine kinase	DLBCL	Diffuse large B-cell lymphoma
CKD	Chronic kidney disease	DLCO	Diffusion capacity of lung for carbon monoxide
CKMB	Creatine kinaseMB	DM	Diabetes mellitus
Cl	Chloride	DM1	Type 1 diabetes mellitus
CLL	Chronic lymphocytic leukemia	DM2	Type 2 diabetes mellitus
CMA	Canadian Medical Association	DMARDs	Disease-modifying agents of rheumatoid disease
CMC	Carpometacarpal joint	DNase	Deoxyribonuclease
CML	Chronic myelogenous leukemia	DOT	Directly observed treatment
CMML	Chronic myelomonocytic leukemia	DPI	Dry powder inhaler
CMV	Cytomegalovirus	DPT	Diphtheria, pertussis, tetanus
CN	Cranial nerve, cyanide	DS	Double strength
CNS	Central nervous system	dsDNA	Double-stranded DNA
CO	Carbon monoxide, cardiac output	DT	Delirium tremens
COP	Cryptogenic organizing pneumonia	DVT	Deep vein thrombosis
COPD	Chronic obstructive pulmonary disease	Dx	Disease
COX	Cyclooxygenase	EBV	Epstein–Barr virus
CPAP	Continuous positive airway pressure	ECG	Electrocardiogram
CPR	Cardiopulmonary resuscitation	ECOG	Eastern Cooperative Oncology Group
CR	Controlled release, complete remission	EEG	Electroencephalography
Cr	Creatinine	EF	Ejection fraction
CrCl	Creatinine clearance		

EGFR	Epidermal growth factor receptor	GN	Glomerulonephritis
EHEC	Enterohemorrhagic <i>Escherichia coli</i>	GPA	Granulomatosis with polyangiitis
EIEC	Enteroinvasive <i>Escherichia coli</i>	GU	Genitourinary
EMG	Electromyography	GVHD	Graft vs. host disease
ENA	Extractable nuclear antigen	GYN	Gynecological
EPO	Erythropoietin	H&N	Head and neck
ER	Estrogen receptor, emergency room	Hb	Hemoglobin
ERCP	Endoscopic retrograde cholangiopancreatography	HBV	Hepatitis B virus
ESAS	Edmonton symptom assessment scale	HCL	Hairy cell leukemia
ESBL	Extended spectrum β -lactamase	HCO ₃	Bicarbonate
ESR	Erythrocyte sedimentation rate	Hct	Hematocrit
ESRD	End-stage renal disease	HCV	Hepatitis C virus
ET	Essential thrombocytosis	HD	Hemodialysis
ETEC	Enteropathogenic <i>Escherichia coli</i>	HDL	High density lipoprotein
ETT	Endotracheal tube	HELLP	Hemolysis, elevated liver enzymes, low platelet count
EUS	Endoscopic ultrasound	HF	Heart failure
FAP	Familial adenomatous polyposis	HHS	Hyperosmolar hyperglycemic state
Fe	Iron	HHV8	Human herpes virus 8
FEV1	Forced expiratory volume (1 s)	HITT	Heparin-induced thrombocytopenia with associated thrombosis
FFP	Fresh frozen plasma	HIV	Human immunodeficiency virus
FH	Family history	HLA	Human leukocyte antigen
FHF	Fulminant hepatic failure	HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
FiO ₂	Fraction of inspired oxygen	HNPCC	Hereditary non-polyposis colorectal cancer
FISH	Fluorescence in situ hybridization	HPV	Human papillomavirus
FL	Follicular lymphoma	HR	Heart rate
FMC	First medical contact	hsCRP	High sensitivity C-reactive protein
FNA	Fine needle aspirate	HSIL	High-grade squamous intraepithelial lesion
FNH	Focal nodular hyperplasia	HSP	Henoch-Schönlein purpura
FOB	Fecal occult blood	HSV	Herpes simplex virus
FRC	Functional residual capacity	HTLV	Human T-cell lymphoma virus
FSGS	Focal segmental glomerulosclerosis	HU	Hounsfield unit
FSH	Follicle-stimulating hormone	HUS	Hemolytic uremic syndrome
FTA-ABS	Fluorescent treponemal antibody-absorption	IADL	Instrumental activities of daily living
FUO	Fever of unknown origin	IBD	Inflammatory bowel disease
FVC	Forced vital capacity	IBM	Inclusion body myositis
G6PD	Glucose-6-phosphate dehydrogenase deficiency	IBS	Irritable bowel syndrome
GBM	Glomerular basement membrane, glioblastoma multiforme	IBW	Ideal body weight
GBS	Guillain-Barre syndrome	ICD	Implantable cardioverter-defibrillators
GCS	Glasgow coma scale	ICH	Intracerebral hemorrhage
GCSF	Granulocyte colony-stimulating factor	ICHD	International Classification of Headache Disorders
GERD	Gastroesophageal reflux disease	ICP	Intracranial pressure
GFR	Glomerular filtration rate	ICS	Inhaled corticosteroid
GGT	Gamma-glutamyl transpeptidase	ICU	Intensive care unit
GI	Gastrointestinal	IDU	Injection drug use
Gm	Gram stain		

IE	Infective endocarditis	LR+	Positive likelihood ratio
IGRA	Interferon-gamma release assay	LSD	Lysergic acid diethylamide
IL	Interleukin	LSIL	Low-grade squamous intraepithelial lesion
ILAE	International League Against Epilepsy	LTBI	Latent tuberculosis infection
INF	Interferon	LUL	Left upper lobe
INH	Inhaler	LUQ	Left upper quadrant
INO	Internuclear ophthalmoplegia	LUSB	Left upper sternal border
INR	International normalized ratio	LV	Left ventricular
IPF	Idiopathic pulmonary fibrosis	LVEDD	Left ventricular end diastolic diameter
IPI	International prognostic index	LVEF	Left ventricular ejection fraction
IR	Immediate release	LVESD	Left ventricular end systolic diameter
ITP	Idiopathic thrombocytopenic purpura	LVH	Left ventricular hypertrophy
IV	Intravenous	LVOT	Left ventricular outflow tract
IVC	Inferior vena cava	MAC	<i>Mycobacterium avium</i> complex
IVP	Intravenous pyelogram	MAHA	Microangiopathic hemolytic anemia
JVP	Jugular venous pressure	MALT	Mucosa-associated lymphoid tissue
KOH	Potassium hydroxide	MAO	Monoamine oxidase
KPS	Karnofsky performance status	MAP	Mean arterial pressure
KUB	Kidney, ureter, and bladder X-ray study	MCA	Middle cerebral artery
LAA	Left atrial abnormality	MCD	Minimal change disease
LABA	Long acting beta agonist	MCL	Mantle cell lymphoma
LAD	Left anterior descending	MCP	Metacarpal joint
LAE	Left atrial enlargement	MCTD	Mixed connective tissue disease
LAHB	Left anterior hemiblock	MCV	Mean corpuscular volume
LAP	Leukocyte alkaline phosphatase	MDI	Metered dose inhaler
LBBB	Left bundle branch block	MDS	Myelodysplastic syndrome
LCIS	Lobular carcinoma in situ	MEDD	Morphine equivalent daily dose
LCX	Left circumflex artery	MELD	Model for end-stage liver disease
LDH	Lactate dehydrogenase	MEN	Multiple endocrine neoplasia
LDL	Low-density lipoprotein	MEP	Maximal expiratory pressure
LES	Lambert–Eaton syndrome, lower esophageal sphincter	MF	Myelofibrosis, mycosis fungoides
LFT	Liver function test	Mg	Magnesium
LH	Luteinizing hormone	MG	Myasthenia gravis
Li	Lithium	MGN	Membranous glomerulopathy
LLL	Left lower lobe	MGUS	Monoclonal gammopathy of uncertain significance
LLQ	Left lower quadrant	MHA-TP	Microhemagglutination assay for antibody to <i>Treponema pallidum</i>
LLSB	Left lower sternal border	MI	Myocardial infarction
LML	Left middle lobe	MIBG	Iodine-131-meta-iodobenzylguanidine
LMN	Lower motor neuron	MIBI	Methoxyisobutyl isonitrile
LMWH	Low molecular weight heparin	MIP	Maximal inspiratory pressure
LN	Lymph node	MM	Multiple myeloma
LOC	Level of consciousness	MMI	Methimazole
LP	Lumbar puncture	MMR	Measles, mumps, and rubella
Lp(a)	Lipoprotein a	MMSE	Mini-mental state examination
LPHB	Left posterior hemiblock	MoCA	Montreal Cognitive Assessment
LPL	Lipoprotein lipase		
LR–	Negative likelihood ratio		

MPA	Microscopic polyangiitis	PAC	Paroxysmal atrial contraction
MPGN	Membranoproliferative glomerulopathy	P _a CO ₂	Arterial carbon dioxide pressure
MPO	Myeloperoxidase	PAN	Polyarteritis nodosa
MPS	Myeloproliferative syndrome	P _a O ₂	Arterial oxygen pressure
MRCP	Magnetic resonance cholangiopancreatography	PAOP	Pulmonary artery occlusion pressure
MRI	Magnetic resonance imaging	PaP	Palliative prognostic score
MRSA	Methicillin-resistant <i>Staphylococcus aureus</i>	PAP	Pulmonary artery pressure
MS	Mitral stenosis, multiple sclerosis	PBC	Primary biliary sclerosis
MSI	Microsatellite instability	PCOS	Polycystic ovarian syndrome
MSK	Musculoskeletal	PCR	Polymerase chain reaction
MSM	Men who have sex with men	PCWP	Pulmonary capillary wedge pressure
MSSA	Methicillin-sensitive <i>Staphylococcus aureus</i>	PDA	Patent ductus arteriosus, posterior descending artery
MTC	Medullary thyroid cancer	PE	Pulmonary embolism
MTP	Metatarsophalangeal joint	PEA	Pulseless electrical activity
MVA	Mitral valve area, motor vehicle accident	PEEP	Positive end expiratory pressure
MZL	Marginal zone lymphoma	PEF	Peak expiratory flow
N&V	Nausea and vomiting	PET	Positron emission tomography
Na	Sodium	PFO	Patent foramen ovale
NAAT	Nucleic acid amplification test	PFT	Pulmonary function test
NCS	Nerve conduction studies	PIP	Proximal interphalangeal joint
NCSE	Non-convulsive status epilepticus	PJP	<i>Pneumocystis jirovecii</i> pneumonia
NE	Norepinephrine	PML	Progressive multifocal leukoencephalopathy
NEB	Nebulizer	PMN	Polymorphonuclear neutrophil
NG	Nasogastric	PMR	Polymyalgia rheumatica
NMDA	N-methyl-D-aspartic acid	PND	Paroxysmal nocturnal dyspnea
NMOU	Non-medical opioid use	PNH	Paroxysmal nocturnal hemoglobinuria
NMS	Neuroleptic malignant syndrome	PO	Oral
NNT	Number needed to treat	POEMS	Polyneuropathy, organomegaly, endocrinopathy, edema, M-protein, and skin abnormalities syndrome
NPH	Normal pressure hydrocephalus, insulin	PPS	Palliative Performance Scale
NPO	Nothing by mouth	PPV	Positive predictive value
NPV	Negative predictive value	PR	Progesterone receptor, partial remission
NS	Normal saline	PR3	Anti-proteinase-3
NSAID	Non-steroidal anti-inflammatory drug	PRES	Posterior reversible leukoencephalopathy syndrome
NSCLC	Non-small cell lung cancer	PRN	As needed
NSIP	Nonspecific interstitial pneumonia	PSA	Prostate-specific antigen
NSTE	Non-ST elevation	PSC	Primary sclerosing cholangitis
NYD	Not yet diagnosed	PSI	Pneumonia severity of illness score
NYHA	New York Heart Association	PSV	Pressure support ventilation
O&P	Ovum and parasites	PTCA	Percutaneous transluminal coronary angioplasty
OHS	Obesity hypoventilation syndrome	PTCL	Peripheral T-cell lymphoma
OHS	Obesity hypoventilation syndrome	PTH	Parathyroid hormone
OR	Odds ratio	PTLD	Post-transplant lymphoproliferative disease
OSA	Obstructive sleep apnea	PTP	Post transfusion purpura
Osmo	Osmolality		
PA	Posterior–anterior		

PTT	Partial thromboplastin time	SLL	Chronic lymphocytic lymphoma
PTU	Propylthiouracil	SNRI	Serotonin-norepinephrine reuptake inhibitor
PUD	Peptic ulcer disease		
PV	Polycythemia vera	Spc	Specificity
PVC	Paroxysmal ventricular contraction	SPN	Solitary pulmonary nodule
PVD	Peripheral vascular disease	SR	Slow release
QID	Four times per day	SSc	Systemic sclerosis
RA	Rheumatoid arthritis	SSEP	Somatosensory evoked potentials
RAA	Right atrial abnormality	SSRI	Selective serotonin reuptake inhibitor
RAE	Right atrial enlargement		
RAS	Renal artery stenosis	SS	Single strength
RBBB	Right bundle branch block	SSS	Sick sinus syndrome
RBC	Red blood cell	SSSS	Staphylococcal scalded skin syndrome
RCA	Right coronary artery		
RDW	Red blood cell distribution width	STE	ST elevation
RF	Rheumatoid factor	SV	Stroke volume
RFS	Relapse free survival	SVC	Superior vena cava
RLL	Right lower lobe	SVR	Systemic vascular resistance
RLQ	Right lower quadrant	SVT	Supraventricular tachycardia
RMR	Resting metabolic rate	TB	Tuberculosis
RMSF	Rocky Mountain Spotted Fever	TBI	Total body irradiation
RNP	Ribonucleoprotein	TCA	Tricyclic antidepressants
RPGN	Rapidly progressive glomerulonephritis	TD	Transdermal
		TEE	Transesophageal echocardiogram
RPR	Rapid plasma reagin	TEN	Toxic epidermal necrolysis
RR	Respiratory rate, relative risk	TGL	Triglyceride
RRR	Relative risk reduction	TIA	Transient ischemic attack
RSBI	Rapid shallow breathing index	TIBC	Total iron-binding capacity
RSV	Respiratory syncytial virus	TID	Three times per day
RSVP	Right ventricular systolic pressure	TIMI	Thrombolysis in myocardial infarction
RTA	Renal tubular acidosis		
RT-PCR	Reverse transcriptase polymerase chain reaction	TIPS	Transjugular intrahepatic portosystemic shunt
RUL	Right upper lobe	TLC	Total lung capacity
RUQ	Right upper quadrant	TMP/SMX	Trimethoprim-sulfamethoxazole
RUSB	Right upper sternal border	TNF	Tumor necrosis factor
SABA	Short acting beta agonist	TP-EIA	<i>Treponema pallidum</i> enzyme immunoassay
SAH	Subarachnoid hemorrhage		
SBP	Systolic blood pressure, spontaneous bacterial peritonitis	TPN	Total parenteral nutrition
SCC	Squamous cell carcinoma	TPO	Thyroid peroxidase
SCLC	Small cell lung cancer	TPPA	<i>Treponema pallidum</i> particle agglutination assay
SCT	Stem cell transplant	TRH	Thyrotropin releasing hormone
Sens	Sensitivity	TSH	Thyroid stimulating hormone
SIADH	Syndrome of inappropriate antidiuretic hormone	TST	Tuberculin skin test
		TTE	Transthoracic echocardiogram
SIRS	Systemic inflammatory response syndrome	TTP	Thrombotic thrombocytopenic purpura
SJS	Stevens-Johnson syndrome	TUR	Transurethral resection
SK	Streptokinase	TURP	Transurethral resection of prostate
SLE	Systemic lupus erythematosus	U/A	Urinalysis

UGI	Upper gastrointestinal	VF	Ventricular fibrillation
UIP	Usual interstitial pneumonia	VHL	Von Hippel–Lindau syndrome
UMN	Upper motor neuron	VLDL	Very low density lipoprotein
UNC	Urine net charge	VRE	Vancomycin-resistant enterococci
US	Ultrasound	VSD	Ventricular septal defect
UTI	Urinary tract infection	VT	Ventricular tachycardia
UV	Ultraviolet	vWD	Von Willebrand disease
V/Q	Ventilation/perfusion	VZV	Varicella zoster virus
VAP	Ventilator-associated pneumonia	WBC	White blood cell
VC	Vital capacity	WPW	Wolff–Parkinson–White
VDRL	Venereal Disease Research Laboratory		

Index

- A**
A-a gradient, 109, 111, 278
Abdominal aortic aneurysm, 74–76, 132
Abdominal bruits, 74
Abdominal mass, 71, 130, 134, 156, 159, 198, 217, 223, 227, 229, 382, 485
Abdominal pain
 acute pancreatitis, 132
 adrenal insufficiency, 166
 constipation, 143–145
 diabetic ketoacidosis, 132
 dyspepsia, 130, 132, 144
 hypercalcemia, 132
 irritable bowel syndrome, 144
 pancreatic cancer, 156
 renal colic, 132
 spontaneous bacterial peritonitis, 155
Abdominal wall pain, 132
Abdominal X-rays (AXR), 133
Abdominojugular reflux (AJR), 45, 54
ABO incompatibility, 182
Absolute neutrophil count (ANC), 165, 250
Absolute risk reduction (ARR), 478
Accelerated phase in CML, 185
Accuracy, 23, 95, 111, 177, 265, 325, 326, 366, 414, 478
ACE inhibitors, 16, 35, 60, 62, 72, 74, 83, 85, 89, 91, 92, 94, 96, 101, 371, 399, 412, 463, 467, 470, 490
Acetaminophen overdose, 121–122, 145
Achalasia, 128, 129, 215
Achilles tendonitis, 300, 302
Acid-base disorders, 47, 95
Acneiform lesions, 401–402
Acne vulgaris, 401, 402
Acquired immune deficiency syndrome (AIDS), 11, 138, 277–279, 286, 292, 423
 infections, 277
 malignancies, 278
ACR diagnostic criteria
 giant cell arteritis, 312, 313
 hand osteoarthritis, 309
 Henoch–Schonlein purpura, 314
 hip osteoarthritis, 309
 polyarteritis nodosa, 310, 313
 rheumatoid arthritis, 299, 315
 Takayasu’s aortitis, 84
Acromegaly, 23, 41, 70, 71, 90, 222, 304, 308, 360, 380, 381
Actinic keratosis, 410
Activated protein C (APC), 174, 177
Acute abdominal pain, 132–134, 138, 140
Acute chest syndrome, 164
Acute coronary syndrome (ACS), 30–38, 180
Acute diarrhea, 137–139, 301
Acute fatty liver of pregnancy, 467, 468
Acute hemolytic reaction, 162
Acute interstitial nephritis (AIN), 86, 166

- Acute labyrinthitis, 341, 343
Acute lymphoblastic leukemia (ALL),
189–190, 198
Acute lymphoblastic lymphoma,
197, 198
Acute mesenteric ischemia, 132, 134
Acute myelogenous leukemia (AML),
187–189, 203
Acute pancreatitis, 101, 112, 132,
157–158, 386, 449
Acute pericarditis, 32, 40, 80, 305
Acute promyelocytic leukemia
(APL), 188
Acute renal failure
multiple myeloma, 199–201
post-operative, 490
post-renal, 86
pre-renal, 83–84
renal, 84–86
Acute respiratory distress syndrome
(ARDS), 111–113
Acute stroke syndromes, 321–329
Acute tubular necrosis (ATN),
84, 86, 101
Acyclovir, 84, 85, 203, 259, 405, 470
Addiction, 491
nicotine, 491–492
Addison's disease, 96, 194, 383, 442
Admission, 1, 2, 4, 9, 10, 33, 72, 107,
109, 136, 142, 157, 158, 247,
285, 289, 355, 357, 405, 429,
445, 457, 466, 469, 496–497
Adrenal incidentaloma, 71, 382–383, 386
Adrenal insufficiency, 98, 101, 127, 144,
166, 322, 372, 374, 376, 380,
383–384, 393, 438, 468, 484
Advanced cardiovascular life support
(ACLS), 52, 461
Advance directive, 418, 495
Adynamic bone disease, 90
Aggressive lymphomas, 197, 244
Airborne isolation, 290
Airflow limitation, 1, 5, 6, 8
Airway
artificial, 113, 114
assessment, 109, 112, 114, 285
Albuminuria, 90, 91
Alcoholic liver disease, 145, 146
Alcohol intoxication, 422
Alcohol-related dementia, 134
Alcohol withdrawal, 257, 337, 424,
478–481, 490
Aldosterone, 71, 95–97, 100, 101, 382,
383, 460, 467
Alkylating agents, 187, 245, 319
Allergic bronchopulmonary aspergillosis
(ABPA), 4, 21, 286
Allergic reactions, 274
Allogeneic stem cell transplant, 186, 188,
189, 197, 198, 252
Allopurinol, 103, 144, 166, 244, 296, 412
Alpha fetoprotein (AFP), 145,
235–237, 280
Alpha-1-antitrypsin deficiency, 8, 151
Alport's syndrome, 87, 92, 93
Altered level of consciousness
alcoholism, 480
diabetic ketoacidosis, 367
hepatic encephalopathy, 152–153
hypercalcemia, 481
hyponatremia, 422
hypoglycemia, 119, 254, 374–375
hyponatremia, 97–99
meningitis, 257–259
non-ketotic hyperosmolar, 99
overdose, 120–121
seizures, 254, 320, 462, 480, 481
stroke, 462
syncope, 52–53
Alzheimer's disease, 341, 422
Amantadine, 121, 282, 346, 482
Amenorrhea, 90, 392–393, 452
American Society of Anesthesiologists
class, 10
Aminoglycosides, 11, 84, 86, 101,
272, 490
dosing, 84, 341
Amino-Penicillins, 270
Amiodarone toxicities, 51
Amniotic fluid embolism, 465–466
Amphotericin B, 84, 85, 96, 99, 101, 102,
251, 252, 287–289
Amyloidosis, 23, 41, 42, 47, 49, 79, 85,
87, 90, 127, 128, 141, 143,
151, 184, 194, 199–201, 228,
298, 301, 311, 357, 361, 383,
411, 482–484
Amyotrophic lateral sclerosis (ALS),
110, 362
Anal cancer, 236

- Anaphylaxis, 1, 116, 117, 125, 137, 274, 292, 413
- Anasarca, 155, 447
- Anastrozole, 214
- Anemia
 of chronic disease, 160, 161, 298, 305
 macrocytic, 161, 163, 164, 453, 479
 microcytic, 160
 normocytic, 90, 160–163
- Angina, 29–35, 53, 60, 73, 76, 125, 134, 201, 314, 464
- Angiodysplasia, 59, 134, 137
- Angioedema, 72, 274, 413
- Angioplasty, 36, 69, 74, 134
- Angiotensin receptor blockers, 72
- Anion gap (AG), 95, 96, 123, 367, 369
- Ankle brachial index (ABI), 67, 69, 265, 366, 398, 405
- Ankle examination, 67
- Ankylosing spondylitis (AS), 21, 22, 24, 26, 42, 61, 293, 296, 297, 300–303, 308
- Ann Arbor staging, 193
- Anterior pituitary deficiency, 375, 380, 381, 395
- Antibiotic resistance, 11, 469
- Antibiotics
 associated diarrhea, 138
 empiric choices, 66
 in pregnancy, 174, 176, 376, 470
- Anticentromere, 20, 21, 307, 315
- Anticholinergic overdose syndromes, 121
- Anticoagulation
 bleeding risks, 36, 168
 contraindications, 13, 32, 84, 178
 hospitalized patients, 118, 423
 pathway, 172
 reversal, 115
 therapies, 13, 175, 179–181
- Anti-cyclic citrullinated peptides, 21, 315
- Antidotes, 121
- Anti-double stranded DNA, 316
- Anti-fungal agents, 105
- Anti-glomerular basement membrane (anti-GBM), 17, 18, 89
- Anti-histone, 306, 316
- Anti-Jo 1, 308, 316, 361
- Anti-La (SS-B), 316
- Anti-metabolites, 213
- Anti-Mi–2, 316
- Anti-neoplastic agents, 412
- Antinuclear antibodies (ANA), 315
- Antiphospholipid antibody syndrome, 12, 168, 169, 172, 411, 475
 in pregnancy, 475
- Anti-pseudomonal penicillins, 271
- Anti-retrovirals, 157, 278, 280
- Anti-RNP, 305
- ANTI-RO (SS-A), 316
- Anti-Smith, 305, 306, 316
- Anti-SRP, 307, 316, 361
- Anti-topoisomerase I (anti-Scl–70), 20, 21, 307, 315, 316
- Antiviral agents, 198, 282–283
- Aortic aneurysm, 69, 303, 486
- Aortic dissection, 13, 29, 30, 32, 36–38, 61, 62, 70, 71, 74, 80
- Aortic insufficiency, 117, 139, 201, 264, 486
- Aortic regurgitation, 5, 29, 36, 41, 42, 46, 53–57, 61–62, 66, 71, 300, 302
- Aortic sclerosis, 55, 56, 59, 75
- Aortic stenosis, 5, 29, 30, 32, 41–43, 46, 52–56, 58–60, 439, 486
- Aortic valve replacement (AVR), 29, 60, 62
- APACHE II score, 109
- Apathetic hyperthyroidism, 378
- Aphasia, 259, 323, 324, 328, 421
 stroke/TIA, 327, 365, 487
- Aplastic anemia, 149, 168, 171, 187, 402
- Apnea test, 110
- Appendicitis, 132, 138
- Aromatase inhibitors (AIs), 213, 214, 245
- Arrhythmia, 3, 23, 31–33, 36–39, 42, 46–49, 52, 53, 64, 78, 81, 100, 101, 110, 121, 124, 134, 284, 285, 322, 429, 459, 467, 479, 482–485
 atrial fibrillation, 36, 134, 377, 378
- Arrhythmogenic right ventricular dysplasia, 41
- Arterial blood gas (ABG), 95, 369
- Arthralgias, 149, 250, 269, 307, 311, 403
- Arthritis, 1, 39, 67, 141, 248, 250, 287, 296, 297, 299, 301, 302, 305
- Arthrocentesis, 294, 295, 297, 299, 301, 306, 487

- Asbestos exposure, 237
 Ascending cholangitis, 133, 158, 468
 Ascites, 16, 20, 134, 151, 152, 154, 155, 184, 202, 225, 452, 468
 Aseptic necrosis, 309
 Aspergillosis, 251, 286–288, 482
 Aspiration pneumonia, 9, 11, 275, 322, 422, 465
 Asplenia, 183
 Asthma, 1, 2, 4, 24, 284, 397, 465
 exacerbation, 1, 5, 464
 in pregnancy, 144
 Asystole, 37, 48, 109, 122, 124
 Ataxia, 42, 52, 151, 152, 187, 224, 321, 323, 324, 341, 344, 347, 425, 452, 482
 Ataxic breathing, 440
 Atherosclerotic ulcers, 406
 Athetosis, 345, 346
 Atrial fibrillation, 6, 12, 20, 35–36, 44, 46–54, 61–65, 69, 78, 80, 179–181, 325, 327, 467, 487
 Atrial flutter, 49, 78, 81
 Auer rods, 188, 189
 Aura, 336, 337
 Auscultatory gap, 54
 Austin Flint murmur, 56, 57, 61
 Autoimmune diseases, 315, 475
 Autoimmune hemolytic anemia
 cold agglutinins, 162, 163
 warm agglutinins, 161, 162
 Autoimmune hepatitis, 144, 146, 149, 151
 Autologous stem cell transplant, 194, 197, 202, 307
 Autonomic neuropathy, 143, 357, 366, 441, 485
 Avascular necrosis, 164, 293, 305, 385
 AV block, 34, 38, 48, 52, 78, 100, 250
 AV dissociation, 54, 78
 AV nodal blocking agents, 49
 Axillary lymph node dissection, 212, 213
 Axillary nerve, 359
 Azoles, 144, 287
- B**
 Babesiosis, 165, 250, 469
 Bacillus Calmette-Guerin (BCG), 230, 268
 Back examination, 300, 303
 Back pain, 197, 254, 266, 301–308, 347
 Bacteremia, 11, 66, 67, 219, 251, 260, 267, 289
 Balloon pump, 36, 62
 Band cell, 118
 Barbiturate overdose, 121, 123
 Barrett's esophagus, 130, 131, 216
 Bartter's syndrome, 97
 Basal cell carcinoma (BCC), 279, 398, 407, 409
 Basic calcium phosphate crystals (BCPC), 296
 Basophilic stippling, 183
 Battery, 417, 495
 B-cell lymphomas, 194, 196, 197, 199
 Beck's triad, 57, 61
 Behcet's disease, 248, 296, 297, 300, 310–312, 333
 Bell's palsy, 330, 333
 Bence Jones proteinuria, 200
 Benign positional vertigo, 336, 341
 Benzodiazepines overdose, 121, 122, 337, 424
 Bernard-Soulier syndrome, 171, 173
 β -blocker overdose, 122
 β -blockers, 35, 45–47, 50, 60, 63, 71, 72, 74, 75, 81, 121, 340, 399, 466, 467, 480
 β -Lactamase resistance, 270
 Bilevel Positive Airway Pressure (BIPAP), 115
 Biliary tract disease, 133
 Binet staging, 191
 Biological anticancer therapy, 163
 Bioprosthetic heart valve, 49, 487
 Bitemporal hemianopia, 330
 Bladder cancer, 86, 229–230, 246
 Blast crisis in CML
 bleeding, 185
 post-operative, 488
 Bleeding diathesis, 37, 111, 171–173, 178
 Bleomycin toxicity, 193, 306
 Blood pressure, 30, 35, 36, 45, 54, 61, 69, 71–74, 85, 87, 91, 92, 94, 103, 104, 117, 135, 313, 461
 BODE index, 6
 Body mass index (BMI), 401, 449
 Bone density testing, 232, 443

- Bone marrow transplant, 8, 192
 Bone metastases, 232, 435
 blastic, 237
Borrelia burgdorferi, 195, 248, 293
 Bouchard's nodes, 308, 317
 Brachytherapy, 217, 231, 246
 Bradycardia, 31, 48, 51, 53, 70, 73, 78,
 100, 109, 122, 124, 163,
 375, 473
 Bradykinesia, 345, 346
 Brain death, 109–110
 Brain metastasis, 228
 Brain tumors, 319–321, 339, 344,
 361, 362
 BRCA syndromes, 242
 Break-bone fever, 255
 Breaking bad news, 444
 Breast cancer, 210–215, 230, 236–238,
 241–243, 245, 381
 Breast examination, 239
 Broca's aphasia, 330
 Bronchiectasis, 1, 4, 5, 8, 9, 11, 16, 17,
 22, 26, 41, 267, 299, 414,
 439, 442
 Bronchiolitis obliterans, 8, 26, 203, 299
 Bronchiolitis obliterans organizing
 pneumonia (BOOP), 8, 22
 Bronchogenic carcinoma, 18
 Brucellosis, 149, 194, 254, 256
 Brudzinski sign, 257, 258
 Brugada syndrome, 81
 Bruit
 abdominal, 71, 74
 carotid, 325, 370
 B-type natriuretic peptide, 45
 Budd-Chiari syndrome, 467
 Buerger's disease, 311, 406, 490
 Buerger's test, 68
 Bullous lesions, 403
 Bullous pemphigoid, 397, 403, 404
 Bundle branch blocks, 12, 37, 55, 78, 79
 Burkitt's lymphoma (BL), 194, 195,
 197, 198
 Burr cells, 184
 Bursitis, 293, 296, 308
- C**
 CA 15-3, 211, 236–238
 CA 19–9, 218, 224, 235, 236, 238
 CA 125, 235–239, 241
 Cachexia, 5, 56, 64, 143, 225, 357, 361,
 438, 439, 441–443, 445,
 451, 453
 pancreatic cancer, 144, 156–158, 225
 CAGE questionnaire, 432, 434
 Calcium channel blockers, 20, 21, 34, 35,
 47, 50, 63, 72–74, 121, 122,
 130, 143, 152, 307, 340, 413,
 429, 441, 467, 489
 Calcium channel blockers overdose, 20,
 21, 34, 35, 47, 50, 63, 72–74,
 121–123, 130, 143, 152, 307,
 340, 413, 429, 441, 467, 489
 Calcium oxalate stone, 84, 93, 102, 296
 Calcium pyrophosphate deposition
 disease (CPPD), 296
 Caloric testing, 109, 342
 Campylobacter, 137–139, 195, 253, 270,
 275, 278, 296, 302, 357
 Canadian Cardiac Society (CCS)
 classification, 31, 486
 C ANCA, 17, 85, 88, 89, 297, 311, 312,
 314, 443
 Cancer of unknown origin, 235–237
 Candidiasis, 130, 251, 277, 286, 288,
 400, 442
 Capacity, 23, 26, 112, 114, 119, 173, 284,
 380, 381, 418, 419, 449, 451,
 455, 494, 495
 Capecitabine, 163, 213, 214, 216, 218,
 220, 222, 225, 246
 Carbapenems, 266, 270, 271
 Carbon monoxide poisoning, 119
 Carboplatin, 197, 208, 210, 213, 214,
 216, 218, 234, 320, 409
 Carcinoembryonic antigen (CEA), 207,
 216, 218, 220, 224,
 235–239, 245
 Carcinoid heart disease, 222
 Carcinoid syndrome, 205, 221, 222, 397
 Cardiac output, 24, 36, 40, 53, 59, 108,
 116, 118, 119, 124, 152, 164,
 459, 464
 Cardiac resynchronization therapy, 46
 Cardiomyopathy, 33, 41, 42, 47, 48, 54,
 55, 58, 80, 111, 202, 209, 307,
 466, 467, 482, 484
 in pregnancy, 145, 176, 339, 376,
 378, 472–473

- Cardiopulmonary resuscitation (CPR),
13, 37, 39, 109, 123, 133, 285,
445, 495
- Cardioversion, 48–50, 461, 467
- Carnett's test, 132
- Carotid bruit, 325, 370
- Carotid endarterectomy, 327
- Carpal tunnel syndrome, 298, 350, 355,
359, 380, 484
- Casopfungin, 251, 286–289
- Castleman's disease, 194, 195, 199
- Catheter-associated bacteriuria, 260, 261
- Cauda equina syndrome, 243–244, 303
- Cavernous sinus lesions, 330
- CD4 count, 276, 277, 279, 280, 470
- Celiac disease, 89, 139, 142, 143, 149,
160, 198, 389, 398, 414, 451
- Cellulitis, 68, 166, 260, 263, 275
- Central venous catheterization, 108, 118,
286, 289
- Central venous pressure (CVP), 45, 116,
117, 244
- Central venous saturation, 108
- Cephalosporins, 22, 84, 85, 119, 138,
166, 248, 261, 270, 271, 274,
335, 403, 405, 412, 413,
470, 490
- Cerebellar disorders, 333
- Cerebellopontine angle lesions, 330
- Cerebrospinal fluid analysis, 119, 420
- Cervical radiculopathy, 348
- Cervicitis, 300–302
- CHADS₂ criteria, 51, 487
- Chemotherapeutic agents, 409
- Chemotherapy-induced diarrhea, 245
- Chemotherapy-induced nausea and
vomiting, 127, 440
- Chest pain
acute coronary syndrome, 30–38,
47, 48, 180
aortic dissection, 13, 29–30, 32,
36–38, 62, 74, 80
aortic stenosis, 5, 29, 30, 32, 41–43,
46, 52–56, 58–60, 439
pericarditis, 29, 30, 32, 37, 40, 80,
151, 153, 155, 184, 202, 307
pneumonia, 5, 6, 8–11, 14–17, 21, 22,
25, 29, 30, 41, 46, 52, 66, 98,
107, 110, 112, 116, 119, 121,
124, 127, 130–132, 152, 157,
163, 164, 166, 167, 208, 299,
322, 336, 422, 425, 439, 451,
456, 465, 490
- pulmonary embolism, 5, 12, 13, 110,
111, 116, 174, 177, 178,
181, 322
- Chest radiography (CXR), 2, 4, 6, 10,
12–22, 25, 30, 32, 33, 40, 42,
44, 45, 49, 52, 60–64, 66, 85,
110, 112, 117, 119, 120, 124,
125, 127, 133, 135, 166, 174,
178, 183, 193, 196, 207, 209,
210, 216, 218, 220, 224, 226,
228, 231, 234, 244, 248, 251,
254, 258, 267, 268, 276, 278,
280, 281, 284, 297, 311, 314,
337, 355, 369, 388, 406, 408,
414, 439, 440, 443, 464, 465,
479, 483, 486, 489
- Cheyne-Stokes breathing, 433, 440
- Child-Pugh classification, 150
- Chlamydia, 9, 22, 58, 65, 195, 259, 261,
262, 270, 272, 273, 276, 281,
283, 296, 301, 302, 414
- Chloromas, 187
- Cholangitis, 132, 133, 141, 144, 149,
157, 244, 278, 315, 468
- Cholecystitis, 29, 31, 119, 132, 133, 227,
303, 468
- Choledocholithiasis, 133, 144, 468
- Cholelithiasis, 222, 449, 467, 468
- Cholestasis, 94, 144, 156, 397, 447, 451,
457, 468
- Cholesterol emboli syndrome, 85, 166,
174, 490
- Cholinergic syndromes, 121
- Chronic bronchitis, 5, 16, 27
- Chronic cough, 16–17, 130, 267,
468, 485
- Chronic daily headaches, 340
- Chronic diarrhea, 102, 138–140, 221,
246, 449
- Chronic fatigue syndrome, 310
- Chronic kidney disease (CKD), 31, 33,
50, 51, 70, 73, 75, 76, 83,
89–91, 94, 162, 284, 287, 293,
296, 371, 380, 387, 395, 431,
462, 484
- Chronic liver disease, 146, 147, 149–153,
156, 163, 184, 227, 291

- Chronic lymphocytic leukemia (CLL),
88, 162, 163, 168, 170, 184,
187, 190–192, 194, 196, 199,
202, 484
- Chronic mesenteric ischemia, 69,
132, 134
- Chronic myelogenous leukemia (CML),
159, 167, 184–187, 237
- Chronic myelomonocytic leukemia
(CMML), 185
- Chronic obstructive pulmonary disease
(COPD), 1, 4–9, 11, 24, 26,
33, 41–43, 49, 54, 75, 79, 81,
109, 110, 113, 115, 159, 284,
422, 431, 442, 457, 490, 494
- Chronic phase in CML, 185, 186, 202
- Chronic renal failure (CRF), 58, 70, 87,
109, 123, 176, 267, 295, 367,
374, 386
- Chvostek's sign, 387
- Cidofovir, 283
- Cirrhosis, 8, 14, 16, 20, 52, 74, 83, 89,
96, 98, 109, 134–136,
144–153, 155–157, 184, 225,
226, 236–238, 256, 287, 386,
389, 395, 396, 414, 449, 455,
457, 478, 479, 482
- Cisplatin, 101, 197, 208, 210, 213, 216,
218, 222, 225, 230, 233, 234,
278, 320, 355
- Clark's levels, 408
- Claudication, 304
neurogenic, 52, 53, 70, 85, 86, 99,
112, 116, 199, 259, 336
vascular, 5, 29, 30, 37, 41, 50, 52, 53,
66–70, 73, 74, 99, 118, 122,
134, 152, 171, 176, 178, 212,
226, 227, 233, 254, 257,
264–266, 311–314, 321, 330,
365, 377, 411, 414, 419, 421,
460, 462, 464, 484, 486, 487,
489, 490
- Clindamycin, 11, 67, 138, 249, 251, 261,
263, 264, 270, 273, 275, 277,
278, 398, 401, 404, 470, 489
- Clostridium difficile* colitis, 137
- Clotting disorders, 104, 169, 417, 465
- Clubbing, 14, 17–19, 21, 66, 150, 151,
163, 205, 301, 377, 414, 415
- Cluster headaches, 340
- Coagulation pathway, 172
- Coagulopathies, 468
- Coarctation of aorta, 29, 70, 71, 311
- Coccidioidomycosis, 21, 166, 194, 253,
277, 287–288, 383, 414
- Cockcroft-Gault formula, 83
- Code status, 445
- Cognitive impairment, 38, 151, 245, 417,
419–422, 436, 437, 472
- Colonoscopy, 134, 137, 138, 140, 141,
144, 157, 160, 220, 235, 236,
239, 240, 243, 246, 252,
406, 452
- Colorectal cancer, 137, 141, 218–221,
237, 238, 240, 242, 243,
245–246, 279
- Coma, 325
- Communication skills, 245, 418, 431,
432, 443–445, 495, 496
- Community acquired pneumonia, 9, 10,
119, 260, 275, 277
- Compartment syndrome, 67, 124,
264, 481
- Competency, 418, 419
- Complements, 88, 305
- Conditioning, 202, 203
- Conductive hearing loss, 343
- Confidentiality, 492, 495
- Conflict of interest, 496
- Confusion, 425
- Confusion assessment method (CAM),
418, 423, 425, 432
- Congenital adrenal hyperplasia, 96, 383,
392–395, 401
- Congestive heart failure (CHF), 16, 21,
33, 43, 51, 67, 155, 174, 175,
284, 405, 422, 485, 486
- Connective tissue disease, 14, 17, 20, 22,
39, 42, 62, 85
- Conn's syndrome, 97, 100, 382
- Consent, 419, 424, 494–496
for procedures, 494
- Constipation, 73, 76, 105, 143–144, 153,
223, 244, 255, 307, 345, 357,
365, 375, 388, 427, 428, 436,
440, 441, 443, 457, 460,
485, 492
- score, 441

- Constrictive pericarditis, 40, 41, 54, 151, 153, 155, 184, 298
- Contact dermatitis, 274, 397, 403, 412, 413
- Contact isolation, 249
- Continuous positive airway pressure (CPAP), 23, 24, 46, 112, 113, 115, 160, 488
- Contrast nephropathy, 37, 86
- Coomb's test, 151, 162, 168, 170, 183
- COPD exacerbation, 5, 33, 41, 113, 283, 439
- Cornell criteria, 79
- Coronary artery bypass graft surgery, 38
- Coronary artery calcium score, 75, 370
- Coronavirus (COVID-19), 9, 10, 248, 253, 281, 283–285, 290, 469
- Cotswolds staging, 193
- Cough, 2, 4, 6, 9, 12, 14, 16–18, 20–23, 39, 43, 45, 46, 72, 109, 110, 114, 115, 130–132, 164, 166, 205, 210, 215, 233, 244, 247, 249, 251, 253, 254, 267, 281, 284, 287, 339, 379, 409, 427, 447, 468, 483, 485, 492
- Coumadin-induced skin necrosis, 179
- Cranial nerves, 197, 330–332, 334, 357
- C-reactive protein (CRP), 10, 18, 31, 141, 142, 167, 248, 249, 284, 294, 297–301, 306, 310, 311, 313, 315, 347, 377, 442, 445, 484
- CREST syndrome, 156, 296, 307, 316, 318
- Critical illness neuromuscular disorders, 361
- Crohn's disease, 134, 137, 139, 140, 142, 198, 219, 240, 301, 406, 415, 451, 453
- Cross-leg palsy, 360
- Cryoglobulinemia, 22, 84, 85, 88, 89, 149, 174, 191, 195, 199, 247, 306, 310–312, 315, 411, 482, 484
- Cryptococcosis, 41, 194, 277, 287
- Cryptogenic organizing pneumonia (COP), 5, 8, 9, 11, 21, 22, 41, 52, 283
- CT chest, 9, 22, 110, 112, 151, 166, 207, 210, 211, 216, 228, 234–237, 239, 244, 245, 311, 354, 385, 464, 483
- CT head, 52, 99, 120, 124, 127, 153, 207, 234, 258, 277, 320, 322, 325–327, 332, 337, 340, 342, 346, 362–363, 420, 423, 425, 465
- Cushing's disease, 380, 381, 384, 385, 393, 401
- Cushing's syndrome, 70, 71, 75, 97, 128, 159, 205, 304, 308, 365, 366, 380, 382, 384–386, 389, 392, 395
- Cutaneous lupus erythematosus, 411, 412
- Cyanide poisoning, 125
- Cyclophosphamide, 18, 88, 89, 162, 163, 187, 190, 191, 194, 196–198, 202, 203, 210, 213, 214, 229, 299, 306, 307, 314, 320, 395, 483
- Cystic kidney diseases, 93–94
- Cystine stones, 102, 103
- Cystitis, 132, 166, 259, 289, 469
- Cytomegalovirus (CMV), 22, 41, 129, 130, 134, 138, 139, 144, 145, 157, 163, 168, 170, 183, 194, 203, 248–250, 253, 276–278, 282, 298, 306, 311, 313, 335, 357, 360, 365, 383, 469, 482
- D**
- Dactylitis, 300–302, 399
- Daptomycin, 66, 264, 274
- Death
 - brain death criteria, 109–110
 - post myocardial infarction, 36
- DeBaKey classification, 29
- Decontamination, 120
- Deep vein thrombosis (DVT), 7, 12–14, 17, 49, 67, 68, 119, 141, 159, 174, 175, 177–181, 301, 322, 405, 406, 464, 488, 490
- Dejerine syndrome, 331
- Delirium, 38, 48, 121–124, 142, 153, 169, 255, 260, 305, 335, 377, 388, 417–419, 421–426, 428, 429, 431–433, 435, 436, 438,

- 439, 441, 445, 446, 479, 480,
485, 488, 490
- alcoholism, 51, 75, 102, 124, 154,
163, 184, 257, 264, 344, 374,
386, 411, 415, 419, 453,
458, 478–481
- hepatic encephalopathy, 151–153
- hypercalcemia, 127, 132, 143, 152,
157, 191, 195, 199, 201, 381,
388–389, 481
- hyperglycemia, 99, 105, 123, 279,
366, 370, 385, 457, 488
- hypernatremia, 360, 370
- hypoglycemia, 119, 122–124, 145,
146, 322, 335–337, 365, 366,
370–372, 374–375, 384
- hyponatremia, 9, 74, 75, 97–99, 104,
136, 152, 335, 338, 360, 382,
422, 485
- meningitis, 98, 99, 116, 152, 164,
197, 253, 256–261, 275, 277,
281, 286–288, 305, 314, 330,
335, 337, 339, 341, 343, 419,
422, 424, 483, 485
- overdose, 47, 78, 113, 120–123, 145,
146, 277, 360, 375, 424, 436,
480, 482
- post-operative, 127
- seizures, 23, 52, 90, 98, 99, 119–124,
145, 202, 205, 254, 256–259,
305, 320–322, 325, 326,
335–339, 360, 387, 421–424,
426, 458, 462–464, 474, 475,
479–481, 485, 493
- Delirium tremens, 479, 480
- Delta-delta, 95
- Dementia, 9, 37, 53, 128, 197, 206, 250,
262, 321, 335, 341, 344, 345,
347, 357, 419–424, 426, 452,
453, 485, 488
- Dengue fever, 194, 254, 255
- Depression, 2, 22, 24, 32, 38–40, 70,
73, 78, 80, 120, 122, 124, 143,
149, 190, 199, 224, 245, 305,
309, 310, 322, 326, 331, 334,
345, 346, 353, 361, 367, 375,
384, 386, 388, 409, 419,
422–424, 431, 432, 435,
436, 438, 440–442, 449, 450,
452, 459, 463, 464, 473,
479, 491
- palliative setting, 128,
432–434, 440–442
- Dermatitis herpetiformis, 89, 143, 397,
398, 403
- Dermatomes, 348
- Dermatomyositis, 22, 42, 128, 194, 224,
248, 306, 307, 309, 316, 360,
361, 394, 397, 407, 411,
442, 481
- Dermatophyte infections, 400
- DeWeese's test, 68
- Dexamethasone suppression test, 71, 381,
382, 385, 394
- Diabetes insipidus, 85, 99, 100, 123, 381,
382, 426, 467, 484
- Diabetes mellitus, 37, 73, 75, 76, 86, 91,
119, 222, 260, 266, 284, 287,
348, 356, 360, 365–371, 386,
389, 395, 406, 426, 451,
462, 490
- complications, 9, 11, 16, 23, 31, 34,
36, 38, 47, 58, 59, 62, 63, 66,
71, 87, 91, 93, 102, 104, 108,
117, 121, 124, 130, 133, 136,
141, 145, 157, 169, 171,
176–182, 188, 203, 245, 246,
252, 254, 257, 262, 264, 267,
277, 279, 281, 282, 284, 289,
293, 299, 313, 322, 326, 336,
365, 366, 370, 374, 386, 392,
404, 417, 422–425, 428, 431,
434, 441, 449, 451, 452,
456–458, 462, 466, 471–475,
478–481, 486–490, 494, 496
- insulin, 119, 122, 123, 365–368,
370–375, 380, 381, 385,
393, 394
- oral hypoglycemics, 338, 366, 374
- Diabetes, pregnancy in, 145, 169, 176,
306, 339, 376, 378, 459–461,
463–475, 492
- Diabetic foot ulcer, 265
- Diabetic ketoacidosis (DKA), 95, 96,
102, 365–368, 370, 371, 488
- Diabetic nephropathy, 87, 91, 96
- Diabetic neuropathy, 24, 31, 139,
263, 357

- Diabetic retinopathy, 471
- Dialysis
 acute indications, 84
 chronic indications, 37
 continuous renal replacement therapy (CRRT), 104
 hemodialysis, 84–86, 90, 91, 103, 104, 122, 455, 481, 484
 peritoneal dialysis (PD), 14, 84–86, 91, 104–105, 455
- Diarrhea
 acute, 137–139
 antibiotics-associated, 138
 carcinoid tumors, 139
 chronic, 138–140
 inflammatory bowel disease, 139
 irritable bowel syndrome, 139, 143, 144, 253
- Diastolic dysfunction, 42, 45, 47, 73
- Diastolic murmurs, 56, 58
- Dieulafoy lesion, 134
- Diffuse alveolar hemorrhage, 17, 110, 305
- Diffuse body pain, 309
- Diffuse idiopathic skeletal hyperostosis (DISH), 308
- Diffuse large B cell lymphoma, 191, 194, 196, 278
- Digibind, 48, 121
- Digoxin intoxication, 47–48
- Dilated cardiomyopathy, 49, 64, 79, 250, 467, 479
- Diplopia, 210, 313, 323, 329–332, 334, 342, 354, 377, 494
- Dipyridamole/adenosine MIBI, 33
- Direct thrombin inhibitors, 13, 34, 181
- Discharge, 4, 11, 34, 109, 136, 211, 213, 247, 249, 251, 253, 261, 262, 285, 289, 293, 336, 396, 432, 486, 493, 496–497
- Disc herniation, 304
- Discord lupus, 80, 143
- Disposition, 497
- Disseminated gonococcus, 248
- Disseminated intravascular coagulation (DIC), 168, 169
- Diuretics, 21, 35, 45, 47, 53, 62, 63, 72–74, 84, 86, 91, 96, 97, 99–101, 151, 152, 155, 157, 182, 295, 343, 371, 383, 386, 387, 406, 411, 412, 422, 426, 427, 439, 451, 463, 467, 489
- Diverticular disease
 diverticulitis, 132, 134
 diverticulosis, 137
- Dizziness, 16, 20, 48, 49, 53, 73, 135, 160, 161, 163, 223, 341–343, 375, 425, 427
- Dobutamine echocardiography, 33
- Docetaxel, 208, 213, 214, 216, 218, 231, 232
- Doll's eyes response, 109
- Donor, 162, 182, 183, 188, 190, 197, 202, 203
 stem cell transplant, 171, 176, 183, 186, 188, 189, 194, 195, 197, 198, 202–203
- Do not resuscitate orders, 109, 367
- Doxorubicin, 190, 193, 194, 196–198, 210, 213, 222, 278
- Driving limitations, 23, 36, 69, 321, 336, 338, 371, 417, 492–494, 496
- Drop attacks, 425
- Drop head syndrome, 362
- Droplet isolation, 284
- Drug eruptions, 402, 412, 413
- Drug-induced systemic lupus, 306
- Drug-related exanthems, 299, 424
- Ductal carcinoma in situ (DCIS), 211
- Dupuytren's contracture, 150, 163, 415
- Dysarthria, 99, 151, 323, 324, 328, 330, 342, 345, 485
- Dysbetalipoproteinemia, 75, 77
- Dyslipidemia, 31, 32, 36, 43, 69, 71, 75, 77, 87, 90, 133, 146, 214, 322, 449, 451, 464
- Dyspepsia, 130–132, 136, 144, 218, 468, 492
- Dysphagia, 99, 102, 128–131, 134, 205, 210, 215–217, 307, 322–325, 331, 342, 379, 433, 442, 443, 445, 456, 485
 esophageal cancer, 129, 131, 215
- Dysphonia, 328, 379, 485
- Dysplastic nevi, 407, 409
- Dysplastic nevus syndrome, 407, 409
- Dyspnea
 acute coronary syndrome, 439

- acute respiratory distress syndrome, 111–113
- aortic stenosis, 41
- asthma exacerbation, 5, 41
- congestive heart failure, 21, 43
- COPD exacerbation, 41
- flash pulmonary edema, 47
- hypoxemia, 110
- interstitial lung disease, 5
- metabolic acidosis, 5, 25, 41, 90, 91, 95, 96, 100
- palliative setting, 432, 439–442
- pleural effusion, 5, 14–16, 44, 49, 209, 215, 256, 267, 439
- pneumonia, 5
- pulmonary embolism, 5
- pulmonary hypertension, 5, 110
- respiratory alkalosis, 25–27, 95, 102, 122, 459
- tamponade, 5–9, 39, 41, 43, 56
- Dystonia, 151, 345, 346
- Dysuria, 92, 229, 247, 249, 251, 253, 256, 259, 260
- E**
- Eaton–Lambert syndrome, 361
- Echinocandin, 286, 289
- Echocardiogram, 6, 12, 20, 21, 30, 32, 33, 36, 40, 45, 47, 49, 52, 58, 60, 62–64, 66, 85, 110, 112, 116, 117, 145, 152, 193, 196, 201, 222, 248, 326, 381, 415, 467, 475, 484, 486, 488
- Eclampsia, 70, 335, 461–463, 467, 474, 475
- ECOG performance status, 196, 228, 432
- Eczema, 397
- Ehrlichia*, 249, 250, 270
- Eisenmenger syndrome, 64, 466
- Elderly, 51, 428–429
- Electrocardiogram (ECG), 3, 6, 12, 21, 30–33, 36, 37, 39, 40, 44, 45, 48, 49, 52, 60, 61, 63, 64, 66, 69, 71, 78, 80, 100, 101, 110, 112, 117, 120, 121, 124, 125, 133, 248, 276, 323, 342, 369, 370, 377, 387, 388, 415, 424, 426, 436, 439, 449, 459, 479, 483, 484, 486
- exercise stress test, 32
- Elevated liver enzymes, 461, 462, 480, 482
- Elliptocytosis, 155, 184
- Embolic stroke, 322, 326
- Emesis, 121, 128, 134
- Emphysema, 8, 18, 27, 483
- Empiric antibiotics, 133, 182, 248, 259, 266, 275
- Empyema, 9–11, 16, 98, 256, 414
- Encephalitis, 281, 322, 335, 337, 339, 362, 422
- Endocarditis, 5, 14, 41, 43, 47, 49, 59–62, 64–67, 84, 85, 88, 89, 117, 174, 178, 184, 247, 248, 250, 256, 257, 260, 270, 274, 275, 286, 293, 296, 297, 300, 305, 306, 311, 315, 322, 414, 439, 466, 482, 485, 489
- Endocarditis prophylaxis, 67, 466, 489
- Endoscopy, 120, 129–133, 136–138, 140, 141, 160, 163, 217, 218, 223, 231, 236, 237, 240, 243, 278
- Endotracheal tubes, 114
- Engraftment, 202, 203
- Enthesitis, 300–302
- Enterofeeding/enteral feeding/feeds, 119, 443
- Enteropathic arthritis (EA), 300, 301
- Eosinophilia, 1, 4, 15, 21, 85, 166, 167, 192, 224, 253, 312, 314, 397
- Epilepsy, 152, 335–338, 362, 474, 493
- Epirubicin, 216, 218
- Erlotinib, 208, 225, 401
- Eruptive xanthoma, 75, 77
- Erysipelas, 263, 264
- Erythema migrans, 248, 250
- Erythema multiforme, 192, 287, 403, 404, 412
- Erythema nodosum, 138, 141, 192, 248, 267, 287, 299, 301, 314, 414, 483
- Erythrocyte sedimentation rate (ESR), 315
- Erythromelalgia, 159
- Esophageal cancer, 29, 31, 129, 131, 215–217, 414

- Esophageal dysphagia, 215
Esophageal ring, 128–129
Esophageal spasm, 31, 73, 128, 129, 176
Esophageal web, 161
Esophagitis, 29, 31, 128–131, 134, 136,
166, 278, 286
Essential thrombocytosis (ET), 185
Essential tremor, 74
Ethics, 439, 495, 496
Ethnic neutropenia, 165
Ethylene glycol overdose, 121, 480
Etoposide, 187, 194, 197, 203, 208, 210,
222, 234, 320
Euthanasia, 439
Evans syndrome, 168, 170
Exanthematous lesions, 250, 402–403
Exanthems
 drug-related, 412–413
 viral, 248
Exemestane, 213, 214
Exercise-induced asthma, 2, 4
Extended spectrum β -lactamase
 (ESBL), 270
Extraocular eye movements, 331,
332, 354
Eye lymphoma not found
- F**
Facial droop, 332
 stroke/TIA, 327, 365, 487
Facial nerve lesions, 332
Facial nerve palsy, 250
Facial telangiectasia, 134, 401, 411
Factor V Leiden, 12, 174, 175, 177,
178, 465
Falls, 53, 102, 260, 322, 324, 341, 344,
367, 417, 419, 420, 425, 428,
429, 432, 433, 453
Famciclovir, 282, 405
Familial adenomatous polyposis
 (FAP), 243
Familial hypocalciuric hypercalcemia
 (FHH), 388, 389
Familial combined hyperlipidemia, 75, 77
Familial dyslipidemia, 77
Fanconi's anemia, 168, 170, 171
Fanconi's syndrome, 91, 96, 102,
187, 386
Fat embolism, 14, 111, 164
Fatigue, 8, 31, 43, 53, 64, 67, 90, 149,
156, 160, 161, 163, 187,
189–192, 195, 199, 201, 205,
209–211, 215, 217, 219, 223,
224, 228–230, 232–233, 245,
250, 267, 281, 284, 298, 305,
310, 311, 313, 334–335, 346,
366, 375, 377, 380, 384, 388,
393, 431, 432, 436, 438, 442,
443, 483–485
Febrile neutropenia, 165, 188, 190, 202,
203, 244, 250–252, 288
Fecal osmotic gap, 140
Feltz syndrome, 184, 298
Femoral nerve, 352, 360
Ferritin, 141, 145, 151, 156, 160–162,
164, 167, 297, 395, 412, 452,
479, 482
Fever
 endocarditis, 62
 neurological symptoms, 257
 neutropenic, 165, 247, 252
 NYD, 247
 polyarthritis, 63, 297, 402
 rash, 14, 166, 248, 250, 253, 256,
257, 259, 261, 293, 297,
402, 403
 sepsis, 25, 46, 54, 109
 skin infections, 263
 of unknown origin (FUO), 247
 urinary symptoms, 84, 144, 232
 with travel, 253–256
Fibrates, 76, 77, 156, 360, 370, 489
Fibromyalgia, 24, 144, 309, 310, 361
5-Flucytosine, 289
5-Fluorouracil, 216, 218–222,
225, 410–412
5-hydroxyindoleacetic acid (5-HIAA),
221–223, 238
Fixed drug eruption, 412, 413
Flaccidity, 328
Flash pulmonary edema, 46, 71, 74
Fluconazole, 203, 251, 261, 277, 278,
286–289, 400, 429
Fludarabine, 155, 162, 191, 196, 198, 202
Fluoroquinolones, 11, 104, 144, 255,
261, 272, 275, 374, 470
Flushing, 73, 99, 222, 401, 402, 411

- Focal liver lesion, 225
- Focal neurological deficits, 30, 314, 320, 419
- stroke, 30
- Focal nodular hyperplasia (FNH), 227
- Focal segmental glomerulosclerosis (FSGS), 88
- Follicular lymphoma international prognostic index (FLIPI), 196
- Fondaparinux, 13, 34, 107, 119, 170, 175, 180
- Foot examination, 366
- Foscarnet, 283
- Fournier's gangrene, 264
- Fractional excretion of sodium, 295
- Fracture index for postmenopausal women, 295
- Fragmented cells, 184
- Frailty, 284, 285, 417, 427
- Frontotemporal dementia, 419, 421
- Functional dyspepsia, 130, 144
- Fungal infections, 203, 244, 249, 251, 259, 285, 286, 405, 414
- Futility, 495
- G**
- Gail model, 211
- Gait assessment, 347
- Gallavardin phenomenon, 57, 59
- Gallstone ileus, 133
- Gallstone pancreatitis, 133, 158
- Gallstones, 75, 76, 133, 141, 146, 156, 157, 223, 460
- Ganciclovir, 282
- Gastric cancer, 130–132, 136, 163, 211, 215–218, 237, 238
- Gastric ulcer, 132, 136
- Gastritis, 90, 134, 160, 163, 198, 217, 221, 385, 398, 435, 453
- Gastroesophageal reflux disease (GERD), 2, 16, 29, 31, 128–131, 134, 216, 278, 283, 307, 442, 450, 460, 464, 468
- Gastrointestinal bleeding (GIB)
- Gastroparesis, 127, 130, 131, 365, 366, 370, 442
- Gemcitabine, 197, 208, 210, 213, 225, 360
- Geriatrics, 417–429
- Germ cell tumor, 233, 236–238, 244
- Gestational diabetes, 365, 366, 460, 470–472
- Gestational hypertension, 70, 75, 462, 463, 471, 472
- Gestational thrombocytopenia, 474
- Get up and go test, 425
- GI bleed
- lower, 137, 140
- upper, 134–136, 151
- Giant cell arteritis (GCA), 29, 247, 297, 312, 313
- Gitelman's syndrome, 97, 100
- Glabellar tap reflex, 329
- Glanzmann's thrombasthenia, 171, 173
- Glasgow coma scale (GCS), 109, 113, 120, 124, 125
- Gleason score, 230–232
- Glioblastoma multiforme, 319, 320
- Global aphasia, 324
- Glomerulopathies, 87
- Glucagonoma, 221, 365
- Glucocorticoids, 4, 8, 22, 75, 130, 131, 141, 190, 268, 293, 301, 302, 309, 378, 383–387, 389, 391, 394, 400, 405, 411, 413, 464
- complications, 386
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency, 155, 161, 183, 278, 296
- Gluten, 142, 143, 398, 455
- Glycemic control, 77, 119, 131, 370, 374, 450, 456, 458, 470, 471
- Goals of care, 285, 432, 443–444
- Goiter, 1, 23, 51, 71, 123, 163, 375–379, 472, 473
- GOLD classification, 6
- Gonadal failure, 392
- Goodpasture disease, 18
- Gottron's papules, 307
- Gout, 74, 85, 94, 102, 293, 295–296, 300, 449
- Graft versus host disease (GVHD), 183, 202, 203, 397
- Graft versus leukemia (GVL) effect, 202
- Graham Steell murmur, 20, 57, 61
- Gram negative bacilli, 65, 248, 257, 264, 269–270, 277, 293

- Gram negative cocci, 248, 269
- Gram positive bacilli, 9, 269
- Gram positive cocci, 248, 269
- Gram stain, 2, 6, 10, 15–17, 66, 105, 112, 153–155, 164, 248, 249, 251, 254, 258, 261, 263, 267, 269–274, 281, 284, 293–295, 297, 299, 301, 306, 405, 439
- Granulomatosis with polyangiitis (GPA), 17, 18, 84, 89, 111, 247, 248, 296, 297, 300, 310–312, 314, 316, 333
- Grasping reflex, 329
- Grave's disease, 51, 376, 377, 473
in pregnancy, 473
- Groin skin lesions, 400
- Guardianship, 418
- Guillain–Barre syndrome (GBS), 24, 26, 98, 108, 110, 128, 138, 258, 281, 333, 357
- H**
- HACEK organisms, 270
- Hairy cell leukemia (HCL), 95, 97, 184, 185, 190, 192, 194
- Hand examination, 317
- Hasenclever score, 193
- Headache, 16, 23, 48, 53, 73, 125, 159, 186, 189, 197, 211, 214, 223, 233, 247, 249–251, 253–258, 276, 281, 284, 310, 312, 313, 319, 320, 325, 326, 331, 339–342, 344, 375, 380, 382, 392, 393, 409, 421, 462, 468, 479, 480, 484, 485, 492
meningitis, 339
- Hearing impairment, 343, 421, 427
- Heartburn, 128, 130, 131
- Heart disease, 20, 41, 42, 45, 46, 49, 50, 52, 53, 61–66, 70, 75, 78, 79, 134, 135, 189, 222, 366, 376, 414, 459, 466, 467, 479, 487, 489
in pregnancy, 466–467
- Heart failure, 10, 31, 32, 35, 36, 41–44, 46–49, 52, 54, 55, 60–62, 64, 69, 72, 73, 83, 85, 110, 117, 118, 133, 149, 151, 153, 154, 184, 214, 222, 238, 283, 428, 429, 431, 449, 455, 458, 462, 466, 482, 486, 493
left sided, 43–44, 61, 67, 222
- Heart sounds, 39, 40, 54–55, 57
- Heavy chain deposition disease, 85, 199
- Heberden's nodes, 308
- Heinz bodies, 183
- Helicobacter pylori*, 132, 195
- Heliotrope rash, 307
- Hemangioma, 201, 225–227
hepatic, 225–227
- Hemangiomas, 20
- Hematemesis, 17, 128, 134, 217
- Hematochezia, 134, 219, 220
- Hematopoietic stem cell
transplant, 202–203
- Hematuria, 18, 84, 87–89, 92–94, 227, 229, 247, 256, 260, 484
- Hemochromatosis, 41, 42, 49, 79, 144, 145, 149–152, 225, 296, 308, 309, 365, 375, 380, 395, 412, 482–483
- Hemodialysis, 9, 65, 84–86, 90, 91, 103–104, 109, 121–123, 266, 286, 397, 412, 455, 481, 484
- Hemodynamic instability, 8, 36, 48, 100, 107, 113, 120, 136, 457
- Hemolysis, 101, 102, 133, 155, 160, 162, 164, 169, 170, 176, 305, 452, 461, 462
- Hemolytic uremic syndrome (HUS), 84, 156, 161, 162, 168, 169, 174, 184, 257, 475
- Hemoptysis, 12–14, 17–18, 20, 21, 61, 62, 84, 92, 134, 205, 208, 209, 247, 267, 284, 287, 312, 314
pulmonary embolism, 314
- Hemorrhagic stroke, 13, 321, 324–326
- Hemostasis, 136, 171, 180, 294
- Henoch–Schonlein purpura (HSP), 311, 312, 316
- Heparin, 7, 13, 34, 35, 50, 104, 107, 119, 136, 137, 168–172, 175, 179–181, 389, 390, 465, 466, 487, 490
- Heparin-induced thrombocytopenia and thrombosis (HITT), 104, 168, 169, 174, 179–181, 490

- Heparinoids, 180
- Hepatic adenoma, 225, 227
- Hepatic disease, 135, 315
in pregnancy, 467–468
- Hepatic encephalopathy, 151–153,
419, 455
- Hepatic hydrothorax, 14, 151
- Hepatitis, 41, 132, 144, 146, 147,
149–151, 154, 156, 168, 170,
183, 184, 191, 237, 247, 269,
278–280, 292, 305, 316, 406,
467, 468, 479
- Hepatitis B vaccination, 145–148, 152,
164, 227, 254, 276, 279, 280,
290, 468, 475
- Hepatitis C, 145, 148–149, 152, 227, 276,
279, 280, 468, 475
HIV coinfection, 280
- Hepatocellular carcinoma (HCC),
146–148, 151, 153, 156,
225–227, 237, 280, 482, 485
- Hepatomegaly, 18, 39, 43, 62–64, 146,
151, 159, 189, 191, 202, 215,
217, 297, 482, 483
- Hepatopulmonary syndrome, 151
- Hepatorenal syndrome, 151, 152
- Hereditary cancer syndromes, 240,
245, 246
- Hereditary non-polyposis colorectal
cancer (HNPCC), 217, 219,
224, 240, 242–243, 246
- Herniation syndromes, 320, 321
- Herpes simplex virus (HSV), 129, 130,
134, 144–146, 157, 194, 203,
250, 257–259, 261, 275–278,
282, 362, 403–405, 467, 469
- Herpes zoster, 291, 333, 341, 405
- Highly active antiretroviral therapy
(HAART), 279, 280
- Hip examination, 318
- Hirsutism, 382, 385, 393–395, 449
- Histoplasmosis, 9, 18, 21, 39, 41, 144,
194, 253, 277, 279, 287, 380,
383, 414, 482
- History
geriatrics, 417
taking, 327, 470
- Hives, 400
- HMG-CoA reductase inhibitors, 76
- Hodgkin's lymphoma, 166, 183, 187,
192–195, 202, 353, 414
- Home oxygen, 8
- Homonymous hemianopia, 323, 324, 330
- Hormonal agents, 214, 435
- Horner syndrome, 14, 17–19, 205,
340, 353–355
- Hospital admission and
discharge, 496–497
- Howell Jolly bodies, 164, 183
- HSV encephalitis, 259, 277, 362
- Human immunodeficiency virus (HIV)
CNS involvement, 277
GI involvement, 287
in pregnancy, 279
prophylaxis, 279
pulmonary involvement, 278
- Hungry bone syndrome, 101, 102, 386
- Hydromorphone, 107, 133, 435–437
- Hyperaldosteronism, 71, 74, 97, 99,
100, 383
- Hyperbilirubinemia, 144, 155–156, 471
- Hypercalcemia, 47, 81, 83, 85, 94, 99,
101, 123, 127, 132, 143, 152,
157, 191, 192, 195, 199, 201,
205, 226, 228–230, 244, 381,
388–389, 407, 422, 424, 426,
432, 435, 436, 440, 441,
481, 483
cancer, 94, 132, 143, 157, 158,
205–209, 226, 229, 231, 244,
383, 389, 426, 432, 435,
440, 441
- Hypercapnia, 8, 23, 42, 97, 112, 113,
120, 422, 439, 489
- Hypercarbic respiratory failure, 111
- Hypercholesterolemia, 75–77, 157
- Hyperchylomicronemia, 77
- Hypercoagulable states
deep vein thrombosis, 177–178
pulmonary embolism, 13, 177,
178, 181
recurrent thrombosis, 177
- Hyperemesis gravidarum, 127, 467,
468, 473
- Hyperglycemia
diabetic ketoacidosis, 488
- Hyperkalemia, 37, 46–48, 72, 74, 78, 80,
84, 90, 91, 100–101, 107, 244,
336, 382

- Hyperkinetic movement disorders, 346–347
- Hyperlipidemia, 37, 75–78, 85, 87, 123, 146, 156, 157, 295, 327, 366, 392, 399, 451
- Hyperosmolar hyperglycemic state, 366, 370
- Hypernatremia, 47, 99–100, 360, 370, 422
- Hyperprolactinemia, 380, 381, 392, 393, 395, 396
- Hypersensitivity pneumonitis, 21, 22, 283
- Hypersensitivity reactions, 274, 400, 403, 404, 413
- Hypersensitivity vasculitis, 412, 413
- Hypersomnolence, 22–24
- Hypersplenism, 165, 168, 170, 298, 475, 483
- Hypertension
aortic dissection, 70
Conn's syndrome, 382
Cushing's syndrome, 70, 71, 75, 97
pheochromocytoma, 71
post-operative, 490
- Hypertensive cardiomyopathy, 41
- Hypertensive emergency, 70, 72, 84
- Hypertensive retinopathy, 70, 366
- Hypertensive urgency, 70–72
- Hyperthyroidism, 25, 48, 51, 55, 70, 71, 80, 109, 127, 139, 247, 335, 353, 360, 365, 366, 376–378, 381, 388, 389, 392, 393, 396, 397, 414, 460, 473, 482
in pregnancy, 378, 468, 473
- Hypertrichosis, 201, 394, 485
- Hypertriglyceridemia, 75–77, 99, 157
- Hypertrophic cardiomyopathy, 49, 52–54, 56, 58, 59, 65, 79
- Hypertrophic obstructive cardiomyopathy (HOCM), 47, 51, 55, 59
- Hypertrophic osteoarthropathy, 205, 414, 415
- Hypertrophy criteria, 79
- Hyperventilation, 25, 95, 102, 113, 341
- Hyperviscosity syndrome, 199, 201, 484
- Hypnic headache, 339, 340
- Hypoadosteronism, 96, 101
- Hypocalcemia, 81, 102, 108, 157, 244, 335, 360, 386–387, 399, 471, 481
- Hypogammaglobulinemia, 9, 11, 191, 210
- Hypoglycemia, 48, 73, 101, 119, 122–124, 145, 146, 223, 226, 254, 335, 336, 365, 366, 370–372, 374–375, 384, 428, 429, 467, 471, 473, 479, 494
- Hypokalemia, 24, 47, 71, 79, 81, 96, 97, 100, 102, 105, 108, 121, 123, 124, 143, 153, 360, 381, 382, 441, 454, 479
- Hypokinetic movement disorders, 345
- Hypomagnesemia, 47, 79, 97, 100–102, 108, 143, 152, 335, 387, 422, 441, 479
- Hyponatremia
acute, 99
chronic, 99
hyperosmolar, 99
hypoosmolar, 97–98
isoosmolar, 99
pseudo, 99
- Hypophosphatemia, 24, 102, 108, 122, 360, 387, 479
- Hypotension, 10, 12, 29, 32, 34–36, 39, 40, 60, 73, 74, 107, 109, 116, 118, 121–125, 134–136, 139, 142, 146, 153, 155, 157, 158, 163, 166, 222, 247, 249, 251, 252, 254, 264, 274, 340, 365, 377, 383, 384, 387, 413, 425, 428, 463, 465, 480, 483, 485
- Hypothermia, 80, 100, 110, 122–124, 375, 422
- Hypothyroidism, 14, 23, 38, 41, 47, 51, 70, 75, 77, 98, 123, 124, 131, 143, 152, 153, 155, 161, 163, 194, 201, 202, 223, 237, 306, 309, 356, 360, 375–376, 380, 392–394, 397, 422, 432, 438, 441, 472, 473, 482, 484
in pregnancy, 376, 472
- Hypoventilation, 24–25, 95, 110–112, 163
- Hypovolemia, 87, 98, 100, 135, 137, 139, 244

- Hypoxemia, 7, 10, 12, 20–25, 42, 47,
110–113, 115, 119, 120, 124,
125, 151–153, 157, 159, 164,
247, 249, 251, 254, 415, 439
- Hypoxemic respiratory failure, 111
- I**
- Ideal body weight (IDW), 112, 114, 268,
370, 376, 465
- Idiopathic hirsutism, 393, 395
- Idiopathic/immune
thrombocytopenic purpura
(ITP), 8, 15, 20–22, 39–41, 49,
79, 84, 97, 99, 116, 127, 130,
131, 157, 158, 165–168, 170,
178, 251, 253, 258, 278, 309,
316, 336, 339, 340, 345, 384,
387, 392, 394, 396, 397, 400,
411, 414, 422, 426, 428
- Idiopathic pulmonary fibrosis (IPF), 22,
26, 284, 414
- IgA nephropathy, 87–89, 92, 93, 311, 398
- IgG4 disease, 315, 375
- Ileus, 97, 102, 133, 134, 139, 155, 157,
456, 457
- Imaging
abdominal X-rays (AXR), 117, 120,
127, 133, 135, 141, 143, 440,
441, 465
chest radiography, 10
CT chest, 4, 6, 9, 10, 12, 14–21, 25,
30, 52, 66, 110, 112, 166, 193,
196, 209, 222, 248, 267, 284,
286, 354, 465
neurology, 319–363
- Imatinib, 167, 186, 187, 190, 223,
409
- Immune Reconstitution Inflammatory
Syndrome (IRIS), 280
- Immunization, 164, 249, 251, 254, 279,
284, 290–292, 403, 467, 469
- Immunizations, 165, 247
- Immunocompromised patients, 260, 287
- Impetigo, 263, 403, 404
- Implantable cardioverter defibrillators
(ICD), 36, 46, 47, 494
- Incidentaloma, adrenal, 71, 380,
382–383, 386
- Inclusion body myositis (IBM), 307,
360, 361
- Incontinence, 16, 52, 84, 121, 243, 260,
336, 348, 419, 421, 427,
428, 449
- Incoordination, 152, 334, 344, 345, 425
- Indirect factor Xa inhibitors, 179, 180
- Indolent lymphomas, 195, 202
- Infection control, 284, 285, 289–290,
404
- Inferior vena cava (IVC) obstruction, 13,
150, 151, 175, 178, 184, 226,
227, 459, 465
- Inflammatory arthritis, 142, 302,
308, 399
- Inflammatory back pain, 301
- Inflammatory bowel disease (IBD), 9, 12,
132, 134, 137–143, 145, 156,
157, 175, 195, 232, 237, 240,
248, 254, 293, 296, 297, 300,
301, 389, 406, 414, 415, 451,
453, 482
extra-intestinal manifestations,
134, 195
- Inflammatory cardiomyopathy, 41
- Inflammatory myopathies, 306–308,
315, 316
- Influenza vaccination, 2, 7, 11
- Infusion reactions, 288
- Inhaled medications, 3, 8
- Inotropes, 34–36, 116–119, 445, 467, 493
- Insomnia, 16, 23, 52, 384, 432, 479,
491, 492
- Insulin, 73, 77, 100, 101, 119, 122, 123,
222, 279, 365–368, 370–375,
380, 381, 385, 393, 394, 401,
442, 449, 457, 458, 460, 470,
471, 486, 488, 494
principles of use, 371–374
- Insulin resistance syndrome, 77
- Intensive care
admission criteria, 107
general issues, 112
mechanical ventilation, 107, 112
preventative strategies, 107, 112
procedures, 108
prognosis, 109
sedation, 107
weakness, 108

- International prognostic index
 follicular lymphoma, 196
 Hodgkin's lymphoma, 192–194
 non-Hodgkin's lymphoma, 194–199
- Internuclear ophthalmoplegia (INO), 331, 332, 334
- Interstitial lung disease, 5, 9, 16, 21–22, 26, 27, 41, 110, 166, 307
- Intoxication, 84, 110, 122, 152, 322, 388, 422, 479, 481
- Intracerebral hemorrhage, 112, 164, 258, 479
- Intraductal papillary mucinous neoplasm (IPMN), 224
- Intrahepatic cholestasis, 144, 468
 of pregnancy, 467, 468
- Intubation, 2, 7, 17, 25, 96, 107, 109, 114, 117, 119, 120, 122, 124, 125, 146, 259, 285, 367, 413, 445, 459, 460
 impending, 8
- Iodine uptake study, 377
- Irinotecan, 208, 216, 218, 220, 225
- Iron deficiency anemia, 137, 143, 161, 219
- Iron index, 24
- Irritable bowel syndrome (IBS), 130, 139, 143, 144, 253, 441
- Ischemia criteria, 33
- Ischemic cardiomyopathy, 41, 111
- Ischemic colitis, 132, 134, 137, 142, 451
- Ischemic stroke, 13, 37, 164, 321, 326, 327, 339
- Isolations, 44, 50, 165, 255, 268, 284, 286, 287, 289, 290
- Isometric exercises, 56
- Isoniazid, 355
- Isopropyl alcohol overdose, 123
- Itraconazole, 4, 251, 279, 287, 288, 400, 429
- J**
- Janeway lesions, 66
- Jaundice, 56, 64, 133, 134, 144, 146, 147, 149, 150, 152, 155–158, 162, 163, 184, 202, 205, 211, 223–225, 228, 229, 256, 301, 377, 467, 468
- Joint aspirations, 294
- Joint pain
 crystal arthropathy, 293
 osteoarthritis, 296, 309
 rheumatoid arthritis, 296, 298, 309
 septic arthritis, 266, 293–294
 systemic lupus erythematosus, 305
- Jones criteria, 63
- Jugular venous pressure (JVP), 20, 36, 39, 40, 42, 43, 45, 54, 57, 62, 64, 80, 85, 87, 116, 460, 468
- K**
- Kaposi's sarcoma, 195, 199, 277, 278, 405
- Karnofsky performance status, 207, 320, 446
- Keratoconjunctivitis sicca, 293, 298
- Keratoderma blennorrhagica, 302
- Kernig sign, 257, 258
- Ketoacidosis, 123, 152, 368, 374, 422
- Kidney mass, 14, 18, 22, 74, 85, 88–90, 92–94, 99, 100, 102, 103, 131, 133, 136, 145, 150, 159, 169, 176, 184, 191, 217, 228, 242, 267, 286, 295, 304, 307, 311, 312, 314, 322, 387, 437, 449, 460, 475, 490
- Killip class classification, 32–34, 36
- King's College criteria, 122, 146
 acetaminophen overdose, 121–122
- Knee examination, 318
- Korsakoff's amnesia, 452, 480
- Krukenberg tumor, 217
- Kussmaul breathing, 440, 480
- Kwashiorkor syndrome, 452
- L**
- Labral tear, 317
- Lactic acidosis, 95, 96, 116, 119–120, 123, 125, 254, 279, 336, 371
- Lacunar stroke, 322
- Lambert–Eaton syndrome (LES), 353, 355, 357
- Langerhans cell histiocytosis, 20
- Latent tuberculosis, 268
- Left ventricular hypertrophy, 41, 60, 70

- Leg pain, 68
 Leg swelling, 12, 14, 227
 unilateral, 12
 Leptomeningeal meningitis, 197
 Leptospirosis, 41, 194, 247, 253, 256
 Leser–Trelat sign, 217, 410
 Lesions
 acneiform, 401
 exanthematous, 250, 402, 403
 nodules, 411
 papulosquamous, 398
 pigmented, 407
 pruritic, 398
 ulcers, 406
 vesicular/bullous, 403, 411
 Letrozole, 214, 394
 Leukemia
 acute lymphoblastic leukemia,
 187, 198
 acute myelogenous leukemia,
 187–189, 203
 chronic lymphocytic leukemia, 187,
 190, 194, 199, 202
 chronic myelogenous leukemia, 167,
 185, 186
 definition, 119, 161, 165, 167, 168,
 187, 245, 247, 388, 389
 Leukemic cutis, 187
 Leukocyte alkaline phosphatase
 (LAP), 159
 Leukocytoclastic vasculitis, 311
 Lewy body dementia, 53, 345, 357, 419,
 421, 424
 Lhermitte’s sign, 243, 321, 334, 348, 453
 LHRH agonists, 212, 213, 232, 389
 Libman–Sacks endocarditis, 65, 305
 Lichen planus, 149, 398–400
 Li–Fraumeni syndrome, 211, 224, 319
 Ligament tear, 293
 Light chain deposition disease, 85, 87,
 199, 484
 Light’s criteria, 15
 Likelihood ratio, 415, 433, 477, 478
 Linitis plastica, 217
 Lipase, 30, 32, 112, 124, 130, 133, 145,
 154, 157, 216, 218, 220, 224,
 234, 276, 278, 369, 451
 Lithium toxicity, 123
 Livedo reticularis, 176, 284, 305, 311,
 313, 411, 484
 Liver enzymes, 142, 144–145, 147, 156,
 297, 400
 Liver failure
 acute, 145–146, 151, 468
 chronic, 374
 encephalopathy, 122
 fulminant, 145, 146, 467
 hepatitis B, 145, 146, 152, 227,
 280, 467
 hepatitis C, 145, 152, 277, 280, 468
 jaundice, 222
 Liver metastases, 222, 223, 228, 434
 Liver transplant, 136, 146, 149, 151–153,
 155, 157, 226
 Lobular carcinoma in situ (LCIS), 211
 Lofgren’s syndrome, 296, 297, 299,
 300, 483
 Long thoracic nerve, 359
 Lower GI bleed, IBD, 137, 140
 Lower motor neuron, 243, 303, 328,
 332, 362
 Low molecular weight heparins
 (LMWH), 104, 179
 Lumbar puncture, 119, 188, 190, 197,
 249, 254, 258, 277, 281, 284,
 287, 333, 334, 337, 339–341,
 347, 356, 357, 422, 424
 Lumbosacral radiculopathy, 303
 Lung abscess, 9, 12, 16, 414
 Lung cancer, 17–20, 128, 205–209,
 237–239, 243, 245, 279, 414,
 415, 439, 466, 491
 Lung cavities, 9
 Lung metastases, 382
 Lung resection assessment, 12, 17,
 487, 489
 Lupus, 347
 anticoagulant, 12, 171, 172, 174–176,
 305, 306, 475
 pernio, 483
 in pregnancy, 176
 Lyme disease, 41, 128, 194, 249, 250,
 254, 296, 297, 300, 333, 419
 Lymphadenopathy, 14, 17–19, 66, 160,
 163, 166, 168, 188, 189,
 191–196, 198, 199, 220, 236,
 247, 249–251, 254–256, 261,
 267, 276, 280, 287, 297, 299,
 305, 379, 396, 483–485
 Lymphoblastic lymphoma, 187, 197

- Lymphocytosis, 22, 190–192, 195, 334
- Lymphoma
 definition, 187, 319
 Hodgkin's, 88, 166, 183, 184, 187,
 192–194, 199, 202, 279,
 353, 397
 non-Hodgkin's, 166, 187, 191, 192,
 194–199, 243, 277, 278, 299,
 321, 398, 449, 484
 small lymphocytic, 187, 191, 194
- Lymphoplasmacytic lymphoma, 190,
 194, 199
- M**
- Macrocytic anemia, 163, 479
- Macrolides, 10, 272, 275, 403
- Malabsorption, 101, 139, 141, 184, 355,
 386, 387, 451–454, 456, 457,
 484, 485
- Malaria, 155, 161, 169, 184, 185,
 250, 253–255
- Malar rash, 305, 411
- Malignant hypertension, 84, 169, 331
- Malignant pleural effusion, 209, 237
- Mallory–Weiss tear, 134, 136
- Malnourishment, 451, 455
- Mammogram, 211, 236, 241, 242, 245
- Management, 4, 5, 7, 10, 24, 33, 36, 40,
 48, 60, 62, 63, 74, 91, 94, 120,
 124, 128, 134, 136, 141, 158,
 173, 176, 188, 190, 192, 194,
 201, 208, 210, 212, 216–218,
 220–222, 225, 226, 229, 232,
 235–237, 245, 251, 277,
 281–283, 285, 295–297, 299,
 309, 321, 323, 326, 327, 335,
 337, 338, 340, 341, 371, 376,
 381, 384, 389, 393, 404, 409,
 415, 418, 422, 424, 426, 428,
 435, 436, 438–443, 447, 450,
 451, 458, 461, 463–469, 471,
 472, 483, 487, 488
 principles, 466
- Mantle cell lymphoma (MCL), 190, 194,
 195, 197
- Marantic endocarditis, 65
- Marasmus syndrome, 452
- Marfan's syndrome, 9, 29, 61, 466
- Marginal zone lymphoma (MZL), 190,
 194, 195
- Mastectomy, 212, 213, 215, 236, 242,
 245, 474
- McDonald criteria, multiple
 sclerosis, 334
- Mechanical, 2, 6, 10, 16, 25, 36, 49, 50,
 60, 105, 107, 108, 111, 113,
 117, 156, 176, 178, 285, 302,
 303, 308, 309, 322, 353, 357,
 442, 445, 466, 467, 487,
 488, 490
- Mechanical back pain, 303
- Mechanical heart valve, 50, 176
- Mechanical ventilation, 2, 6, 7, 10, 25,
 107, 111–116, 133, 289, 490
- Median nerve, 350, 351, 353, 356, 359
- Mediastinal lymphoma, 194
- Mediastinal masses, 192
- Medical fitness to drive, 336,
 338, 492–494
- Medication-induced headaches, 167
- Medications, pregnancy in, 474
- Mediterranean fever, 256
- Medullary cystic kidney disease, 92–94
- Medullary sponge kidney, 92–94, 102
- Medullary syndromes, 331
- Melanoma, 39, 178, 194, 203, 215, 235,
 321, 382, 388, 405, 407–410
- MELD score, 146, 150
- Melena, 134, 135, 137, 217
- Membranoproliferative
 glomerulonephritis
 (MPGN), 147
- Membranous glomerulonephritis
 (MGN), 305
- Meniere's disease, 343
- Meningitis, 250
 leptomeningeal, 197
- Meniscal tear, 309
- Mesothelioma, 39, 209–210, 237,
 244, 414
- Metabolic acidosis, 5, 25, 41, 90, 91,
 94–96, 100, 115, 120, 122,
 123, 424, 439, 440, 480, 481
 diabetic ketoacidosis, 132
- Metabolic alkalosis, 24, 97, 100, 153
- Metabolic cardiomyopathy, 41
- Metabolic syndrome, 31, 76, 77, 295,
 394, 471

- Methadone conversion, 437
 Methanol overdose, 121
 Methemoglobinemia, 119
 Methicillin resistant *Staphylococcus aureus* (MRSA), 9, 11, 67, 116, 119, 251, 261, 263, 264, 266, 270, 272–275, 281, 290, 293, 398, 402
 Methotrexate, 84, 149, 163, 190, 197, 203, 278, 297, 299, 301, 302, 306, 307, 312–314, 321, 399, 405, 411, 412, 474, 483
 Metronidazole, 11, 130, 133, 138, 139, 142, 261, 263, 273, 275, 401–402, 429, 470
 Micafungin, 286, 288, 289
 Microangiopathic hemolytic anemia (MAHA), 84, 168, 169, 184, 475
 Microcytic anemia, 160–161
 Microscopic polyangiitis (MPA), 89, 310, 312, 314, 316
 Mid-systolic click, 55, 57, 65
 Migraines, 322
 Migrainous vertigo, 342
 Milk alkali syndrome, 388
 Minimal change disease (MCD), 86–88, 192
 Mitral regurgitation, 31, 36, 41, 42, 46, 47, 53–59, 63–66
 Mitral stenosis, 5, 17, 43, 46, 49–52, 54–57, 61–64, 466
 Mitral valve prolapse, 56–58, 64, 65, 94
 Mixed connective tissue disease, 306, 315, 316
 Mixed hypertriglyceridemia, 75, 77
 Model for end-stage liver disease (MELD), 150
 Modified Duke's criteria, 66
 Monoarthritis
 gout, 293, 297
 septic arthritis, 293, 294
 Monobactam, 271
 Monoclonal antibodies, 255
 Monoclonal gammopathy, 191
 Monoclonal gammopathy of undetermined significance (MGUS), 199–201, 355
 Mononeuritis multiplex, 311, 313, 355, 357, 365
 Mononeuropathy, 313, 355, 361, 365
 Morphine, 16, 34, 35, 40, 45, 98, 99, 103, 107, 133, 158, 164, 171, 435–437, 447
 Motor cortex, 337, 361
 MR angiography, 69, 362
 MRI head, 14, 99, 197, 320, 326, 333, 334, 337, 340, 342, 346, 362
 MR venography, 362
 Mucosa associated lymphoid tissue (MALT), 197
 Mucositis, 443
 treatment, 442, 443
 Multiple endocrine neoplasia (MEN) syndromes, 401
 Multiple myeloma, 85, 86, 89, 91, 96, 161, 199–202, 237, 243, 247, 279, 303, 311, 388, 389, 449, 484
 Multiple sclerosis, 123, 127, 128, 143, 258, 309, 331–335, 341, 343, 344, 357, 361, 362, 397, 441
 Multisystem disorders, 482–486
 Murmurs
 diastolic murmurs, 56, 58
 innocent, 58
 maneuvers, 56
 systolic murmurs, 56, 58, 62
 Muscle strength grading, 361
 Myalgias, 10, 76, 249, 250, 256, 284, 313, 339, 403
 Myasthenia gravis (MG), 24, 26, 108, 128, 210, 328, 331–333, 353–355, 361, 362, 463
 thymoma, 210
 Mycobacterium avium complex (MAC), 253, 278
 Mycosis fungoides, 195, 198, 397, 398
 Myelodysplastic syndrome (MDS), 163, 185, 188, 189, 202, 203, 245, 247
 Myelofibrosis (MF), 159, 160, 167, 184–186
 Myelopathy, 108, 298, 321, 348, 485
 Myeloproliferative disorders
 chronic myelogenous leukemia, 118–119
 essential thrombocytosis, 185
 polycythemia rubra vera, 186

- Myocardial infarction
 peri-operative, 216
 posterior infarction, 36
 right ventricular infarction, 36
 territory, 80
- Myoclonus, 345, 346, 436, 482
- Myopathy, 24, 76, 102, 108, 309,
 362, 443
- Myotomes, 349, 362
- Myxedema, 79, 110, 116, 322, 376,
 377, 473
- N**
- Narcolepsy, 22, 24, 336
- Narrow complex tachycardia, 49
- Nausea and vomiting
 adrenal insufficiency, 127
 chemotherapy-induced, 127
 palliative setting, 440–441
- Neck stiffness, 247, 249, 251, 253, 257,
 258, 325, 326
- Necrotizing enterocolitis, 252
- Necrotizing fasciitis, 116, 263, 264, 275
- Necrotizing pancreatitis, 157, 158
- Needle stick Injury, 290
- Negative predictive value (NPV), 477
- Negligence, 492, 495
- Nephritic syndrome, 87, 88, 91, 92, 305
- Nephrolithiasis, 103, 141, 259, 483
- Nephrotic syndrome, 14, 75, 85–87, 89,
 91, 98, 153, 155, 174, 305,
 387, 454
- Nerve roots, 303, 304, 347
- Neurocardiogenic syncope, 53, 425
- Neuroendocrine tumors, 139, 208, 221,
 235, 384
- Neurogenic claudication, 303, 304
- Neurogenic syncope, 425
- Neuroimaging, 277, 324, 326, 339,
 362–363, 421
- Neuroleptic malignant syndrome (NMS),
 257, 360, 481, 482, 490
- Neuropathy, 92, 108, 348, 365, 452, 483
- Neutropenia, 149, 165, 188, 190, 195,
 202, 230, 244, 245, 250–253,
 286, 288, 298, 304
 febrile, 165, 202, 245, 250–253, 288
- Neutropenic fever, 165
- New York Heart Association (NYHA)
 classification, 31
- Niacin deficiency, 222
- Nicotine addiction, 491
- Nikolsky's sign, 402, 403, 405
- Non-alcoholic steatohepatitis (NASH),
 52, 144, 146, 149
- Non-Hodgkin's lymphoma, 166, 184,
 187, 191, 192, 194–199, 238,
 243, 277, 278, 299, 321,
 449, 484
- Non-invasive positive pressure ventilation
 (NIPPV), 439
- Non-medical opioid use, 434, 436
- Non-nucleoside reverse transcriptase
 inhibitors (NNRTI), 269, 279
- Non-seminoma, 233–235
- Non-small cell lung cancer, 206, 208
- Non-ulcer dyspepsia, 130
- Normal pressure hydrocephalus (NPH),
 341, 419, 422, 426
- Normocytic anemia, 90, 161–163
- Nosocomial infections, 289–290
- Nosocomial pneumonia, 9, 11, 119
- NSAID-induced gastropathy, 131
- NSAID-induced renal failure, 86
- Number needed to treat (NNT), 478
- Numbness
 multiple sclerosis, 333
 stroke/TIA, 327
- Nutrition, 141, 142, 146, 158, 225, 252,
 417, 418, 424, 450, 454–458,
 472, 479
- O**
- Obesity, 1, 2, 12, 23, 24, 26, 27, 31, 41,
 49, 54, 71, 75, 77, 88, 131,
 133, 146, 150, 215, 219, 224,
 227, 245, 264, 284, 295, 308,
 315, 366, 372, 380, 386, 393,
 395, 396, 406, 450, 451, 455,
 462, 464, 470–472
- Obscure GI bleed, 137
- Obstetrical medicine, 466, 468
- Obstructive lung disease, 20, 164
- Obstructive sleep apnea, 22–24, 49, 70,
 113, 159, 322, 422, 449
- Obturator nerve, 352, 360, 365

- Occult GI bleed, 137
 Octreotide, 136, 146, 152, 222, 223, 381, 385, 440, 441, 447
 Oculocephalic reflexes, 109
 Oculomotor nerve lesions, 330
 Odds ratio (OR), 478
 Opening snap, 55, 57, 61, 63
 Opiate overdose, 139
 Opioid use, 434, 435, 440, 441
 Optic atrophy, 313, 331, 344, 377, 453
 Optic neuritis, 206, 269, 331, 334, 483
 Oral airways, 114
 Oropharyngeal dysphagia, 128, 129, 442
 Orthostatic hypotension, 52, 53, 65, 134, 341, 357, 384, 428, 429
 Orthostatic proteinuria, 92
 Oseltamivir, 282, 283
 Osler nodes, 66
 Osmolar gap, 95, 120, 123, 424, 480
 Osteitis fibrosa, 90
 Osteoarthritis (OA), 293, 295, 296, 304, 308, 309, 380, 449
 Osteomyelitis, 14, 66, 164, 247, 264–266, 274, 276, 286, 293
 Osteoporosis, 143, 157, 158, 179, 203, 214, 232, 246, 338, 380, 385, 387–392, 395, 417, 426, 436, 490
 risk assessment, instrument, 390
 Ovarian ablation, 213
 Overdose
 acetaminophen, 121–122
 digoxin, 47
 opioids, 121
 Overflow incontinence, 426, 427
 Overlap syndrome, 7, 306, 360
 Oxaliplatin, 216, 218, 220, 225, 246
 Oxazolidinones, 273
 Oximetry, 71, 110, 117, 119, 123, 159
 Oxygen saturation gap, 123
- P**
 Pacemaker, 38, 49, 50, 78, 223, 244, 493, 494
 Paclitaxel, 37, 208, 210, 213, 214, 216, 218, 225, 409
 Paget's disease, 58, 304, 308, 392
 Pain control, 34, 103, 115, 133, 158, 164, 225, 302–304, 309, 340, 404, 424, 434–439, 441, 442, 466, 474–475
 Palindromic rheumatism, 293, 297, 299, 300
 Palliative
 care, 22, 212, 217, 218, 220, 222, 225, 229, 285, 431–433, 438, 439, 441, 445, 497
 dyspnea, 210
 medication route, 22, 128, 222, 285, 432, 434, 439, 441, 445
 nausea and vomiting, 440
 pain control, 432
 sedation, 429
 Palliative performance scale (PPS), 432, 445, 446
 Palliative prognostic index (PPI), 446
 Palliative prognostic score (PaP), 446
 Palmar xanthoma, 77
 Palpable purpura, 247, 305, 311–314, 413
 Palpitations
 atrial fibrillation, 48
 pheochromocytoma, 48
 P-ANCA, *see* Peripheral smear (TTP)
 Anti-MPO
 Pancoast tumor, 19, 205
 Pancolitis, 140, 142
 Pancreatic cancer, 144, 156–158, 224, 237, 238
 Pancreatitis, 14, 29, 31, 75, 76, 123, 130, 132, 134, 144, 153, 224, 237, 238, 278, 279, 303, 365, 371, 388, 456
 Pancytopenia, 164, 170, 171, 187, 189, 199, 202, 210, 287, 453
 multiple myeloma, 199
 Panhypopituitarism, 374, 383
 Papilledema, 70, 319, 331, 339, 341
 Pappenheimer bodies, 183
 Papulosquamous lesions, 398
 Paranasal sinus lymphoma, 197
 Parapneumonic effusion, 9, 10, 15
 Parasomnia, 23
 Parkinson's disease, 53, 123, 341, 345–347, 357, 362, 400, 419, 428, 441, 482
 Paroxysmal hemicrania, 340

- Paroxysmal nocturnal hemoglobinuria (PNH), 12, 163, 170, 171, 176
- Parvovirus B19, 164, 306, 311, 313, 402
- Pelvic inflammatory disease, 132, 238, 260, 262, 293
- Pemphigus vulgaris, 403, 405
- Penciclovir, 282
- Penicillin allergy, 130, 274
- Penicillins, 84, 85, 138, 162, 166, 247, 248, 270, 403, 405, 412, 413, 422, 470, 490
- Peptic ulcer disease (PUD), 29, 31, 130, 132, 134–136, 237, 388, 451
- Percutaneous coronary intervention (PCI), 37
- Performance status, 196, 198, 207, 209, 210, 214, 216, 218, 225, 228, 252, 320, 432, 433, 442, 445
- Pericardial effusion, 5, 39, 40, 163, 206, 209, 298, 305, 375, 439
- Pericardial tamponade, 29, 41, 52
- Pericarditis, 9, 29–31, 33, 37–41, 49, 63, 66, 79, 80, 84, 202, 287, 305, 307, 485
- Peri-operative assessment, 216
- Perioral dermatitis, 402
- Peripartum cardiomyopathy, 466, 467
- Peripheral blood smear, 159, 183–184, 189
- Peripheral nerves, 358–361
- Peripheral neuropathy, 67, 90, 149, 162, 163, 199, 245, 246, 250, 269, 299, 305, 311, 312, 314, 344, 348, 355–361, 405, 426, 453, 470, 479, 484
- Peripheral smear (TTP) anti-MPO (p-ANCA), 17, 85, 88, 89, 311, 312, 314, 443
- Peripheral vascular disease (PVD), 67–69, 73, 264, 365, 406
- Peritoneal carcinomatosis, 236, 443
- Peritoneal dialysis, 14, 84–86, 91, 104–105, 455
- Peritonitis, 104, 132, 133, 155, 238, 253, 262, 275, 455
- Peroneal nerve, 347, 352, 357, 360
- Pheochromocytoma, 41, 48, 49, 70, 71, 159, 221, 229, 242, 247, 365, 366, 382, 383, 492
- Photophobia, 52, 302, 340, 342
- Photosensitivity, 52, 293, 305, 316, 411
- Pica, 160, 330
- Pigmented lesions, 407
- Pitting edema, 43, 68, 177, 302
- Pituitary tumors, 380–381, 384, 393, 395, 396
- Pityriasis rosea, 397–399
- Plasma cell dyscrasias, 199, 483
- Platelet activation pathway, 171
- Platinating agents, 409–410
- Pleural based disease, 15
- Pleural effusion, 5, 10, 13–16, 24, 29, 30, 41, 49, 79, 105, 119, 151, 206, 207, 209, 215, 256, 267, 298, 299, 307, 375, 439, 484, 485
- Pleuritis, 9, 29, 30, 299, 305
- Plummer–Vinson syndrome, 161, 215
- Pneumocystis jirovecii* pneumonia (PJP), 277, 278
- Pneumonia, 66, 251, 252, 257, 258, 275, 277, 278, 281–283, 285–288
recurrent, 490
- Pneumonia severity of illness score (PSI), 10
- Podagra, 295
- POEMS syndrome, 199, 201
- Polyarteritis nodosa (PAN), 147, 149, 247, 248, 299, 310–313, 316, 405
- Polyarthritis
fever, 297
rheumatoid arthritis, 297
seronegative spondyloarthropathies, 302
systemic lupus erythematosus, 306
- Polycystic kidney disease, 70, 71, 89, 92, 93, 159, 227, 259
- Polycystic ovarian syndrome (PCOS), 393, 394
- Polycythemia vera, 70, 159, 160, 167, 174, 185, 186
- Polydipsia, 98, 100, 366, 367, 381, 382, 393
- Polymyalgia rheumatica (PMR), 247, 293, 296, 297, 300, 309, 312
- Polymyositis, 108, 128, 224, 293, 297, 299, 300, 306, 307, 309, 315, 316, 360, 361, 442, 481

- Polyneuropathy, 52, 108, 201, 313, 314, 355, 361, 365
 Polypharmacy, 417, 428, 438
 Polyuria
 diabetes insipidus, 382
 diabetes mellitus, 386
 hypercalcemia, 381
 Porphyria, 127, 132, 335, 394, 411, 482, 484–485
 Porphyria cutanea tarda, 149, 403, 412, 485
 Portal hypertension, 16, 20, 74, 134, 150–152, 154, 155, 184, 226, 298
 Portal vein thrombosis, 153, 227
 Portopulmonary hypertension, 152
 Positive predictive value (PPV), 15, 477
 Posterior infarction, 36
 Post-nasal drip, 1, 2, 16, 17
 Postpartum thyroiditis, 471, 473
 Post-test probability, 477, 478
 Post-transfusion purpura (PTP), 182
 Post transplant lymphoproliferative disorders (PTLD), 195, 198
 Postural proteinuria, 92
 Power of attorney, 418, 433
 Precordial examination, 54
 Preeclampsia, 169, 461–464, 467, 468, 470–475
 Pregnancy, 12–14, 25, 29, 37, 42, 48, 53–55, 63, 70, 72, 74, 76, 86, 120, 127, 132, 144, 148, 156, 168, 174, 176, 178, 209, 213, 238, 269, 284, 292, 305, 338, 339, 356, 365, 372, 374, 377, 378, 380, 381, 386, 392, 393, 404, 405, 459–470, 472–475
 Preoperative workup, 216
 Pre-test probability, 78, 477, 478
 Priapism, 164
 Primary biliary cirrhosis (PBC), 75, 144, 149, 166, 389
 Primary CNS lymphoma, 195, 197, 278
 Primary sclerosing cholangitis (PSC), 141, 144, 149, 157, 166, 301
 Primitive reflexes, 329, 419, 420
 Prinzmetal's angina, 80
 Proctitis, 140–142, 246
 Prognostication, 231, 445–447
 Progressive multi-focal leukoencephalopathy (PML), 188, 277, 333
 Prolactinoma, 380, 381
 Prolonged QT interval, 387
 Prolymphocytic leukemia, 190, 191
 Prophylaxis
 asplenic patients, 164, 165
 hepatitis B, 146–148, 280, 467
 HIV, 176, 197, 277, 279
 neisseria meningitidis, 257, 269
 traveler, 138, 253, 254
 Proprioception changes, 262, 331, 334, 341, 344, 355, 425, 453
 Prostate cancer, 230–232, 237, 240, 243, 246, 426, 445
 Prostate specific antigen (PSA), 230–232, 235, 237–240, 246, 388, 443
 Prostatitis, 86, 132, 166, 231, 237, 260, 289, 302
 Prosthetic joint infections, 266
 Protease inhibitor (PI), 8, 75, 102, 269, 279, 365
 Proteinuria, 70, 72, 73, 87–93, 152, 200, 209, 228, 256, 305, 306, 365, 385, 462, 464, 484
 Pruritus, 90, 149, 156, 157, 159, 186, 192, 195, 224, 256, 397, 400, 447, 467, 468
 Pseudo-exacerbation, 334
 multiple sclerosis, 334
 Pseudogout, 293–297, 300
 Pseudomembranous colitis, 138, 139
 Pseudomonas, 8, 9, 11, 17, 248, 250, 257, 261, 270, 275, 293
 Pseudo-renal failure, 85
 Pseudotumor cerebri, 258, 340, 449
 Psoriasis vulgaris, 398–400
 Psoriatic arthritis (PA), 39, 293, 295–297, 300, 302, 399, 400
 Ptosis, 19, 205, 210, 329, 330, 332, 353–355
 Pulmonary embolism (PE), 1, 5, 6, 12–15, 17, 25, 29, 30, 33, 41, 46, 49, 50, 52, 54, 66, 80, 110, 111, 116, 159, 177, 178, 181, 322, 439, 465, 487, 490
 Pulmonary eosinophilia, 166, 167

- Pulmonary function test, 9, 25–27, 207, 489
- Pulmonary hypertension, 5, 12, 16, 17, 20–21, 23, 27, 29, 30, 33, 41, 43, 45, 49, 52, 54, 55, 61–64, 110, 152, 164, 177, 299, 305, 307, 439, 449, 466, 483, 486, 489
- Pulmonary regurgitation, 56, 61, 222
- Pulse, 29, 110, 135
irregularly irregular, 53
- Pulseless disease, 312
- Pulse pressure, 54, 57, 59, 61, 460
wide, 54, 61, 460
- Pulsus alternans, 54
- Pulsus paradoxus, 2, 5, 39, 40, 54
- Pure red cell aplasia, 191, 210
- Purpura, 168, 172, 182, 248, 284, 311–314, 484, 485
- Pyelonephritis, 84, 85, 127, 132, 199, 227, 259–261, 289, 303, 469
- Pyoderma gangrenosum, 141, 300, 301, 406, 407
- Pyridoxine deficiency, 452
- Q**
- Q fever, 65, 247, 249, 250, 253, 254, 469
- QT prolongation, 51, 326, 436
- R**
- Radial nerve, 350, 359
- Radiculopathy, 199, 303, 347–353, 357
- Radioactive iodine, 377
- Rai staging, 191
- Ramsay Hunt syndrome, 332, 333
- Ranson's criteria, 157
- Rapidly progressive glomerular nephritis (RPGN), 84, 87, 89, 92, 314, 484
- Raynaud's phenomenon, 19, 73, 74, 201, 293, 299, 306, 307, 316, 475, 484
- Reactivation tuberculosis, 250, 267, 268
- Reactive hypoglycemia, 374
- Rectal cancer, 219–221, 246
- Reed-Sternberg cell, 192
- Refeeding syndrome, 102, 457, 458
- Reflex syncope, 53
- Rehabilitation criteria, 7, 22, 129, 326, 361, 493, 497
- Relapsing polychondritis, 9, 310
- Relative risk (RR), 6, 254, 334, 478
- Relative risk reduction (RRR), 46, 241, 327, 478
- Renal artery stenosis (RAS), 46, 69, 71, 72, 74, 83, 97, 100, 219
- Renal cell carcinoma, 178, 227–229, 242, 243, 383
- Renal colic, 132
- Renal crisis, 307
- Renal cysts, 94
- Renal failure
glomerulopathies, 87–89, 92
hypercalcemia, 81, 123, 192, 199, 201, 388–389
- Renal osteodystrophy, 90
- Renal replacement, 84–86, 91, 119, 123, 146, 150, 152
dialysis, 84–86, 91
- Renal tubular acidosis, 96, 299
- Renal ultrasound, 94
- Renin, 71, 97, 100, 101, 152, 227, 228, 382, 383, 460
- Research ethics, 496
- Resource allocation, 495, 496
- Respiratory acidosis, 24–25, 95
- Respiratory alkalosis, 25, 95, 102, 122
- Respiratory failure
hypercarbic, 111
hypoxemic, 111, 182, 439
- Restless leg syndrome, 23, 24, 90, 345
- Restrictive cardiomyopathy, 41, 54
- Restrictive lung disease, 20–23, 164, 300, 301
- Resuscitation
CPR, 109
intubation, 109, 117, 290
shock, 117–119, 136
- Retinopathy, 71, 164, 201, 206, 365, 366, 370, 452, 470, 471
- Revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar), 480
- Rhabdomyolysis, 85, 100–102, 107, 124, 281, 336, 337, 360, 361, 386, 425, 481–482
- Rheumatic fever, 41, 56, 58, 62, 63, 248, 296, 297, 300, 403

- Rheumatoid arthritis (RA), 8, 15, 18, 21, 22, 24, 29, 39, 58, 88, 96, 184, 247, 293, 296–300, 308–310, 315, 348, 353, 356, 360, 391, 406, 482
- Rheumatoid factor (RF), 66, 85, 297, 300, 302, 315
- Rhythm, 12, 23, 45, 46, 48–50, 61, 63, 78–80, 425, 438
irregularly irregular, 49
- Richter's syndrome, 191
- Rickettsial infections
North America, 249, 256
outside of North America, 255
- Riedel's lobe, 375
- Right heart catheterization, 20, 21, 152
- Right ventricular infarction, 34–36
- Rigidity, 123, 124, 132, 197, 247, 249, 251, 254, 323, 345, 346, 419, 482
- Rimantadine, 282, 283
- Rinne test, 329, 343
- Risk reduction
cardiac, 322, 370, 422
ECG exercise stress test, 32
glycemic control, 119, 450, 470, 471
hyperlipidemia, 327, 450
hypertension, 20, 36, 51, 69, 70, 74, 103, 327, 421, 450
post-MI, 31, 32, 36, 40, 46, 72, 73, 322, 327
- Rocky Mountain spotted fever, 248, 249, 253, 402
- Rooting reflex, 323, 329
- Rosacea, 401, 411
- Roth spots, 66
- Rouleaux, 184
- S**
- Sacroiliitis, 256, 300–302
- Salicylate overdose, 122
- Salmonella*, 137–139, 157, 164, 248, 253, 264, 269, 275, 277, 278, 296, 302
- Samter's syndrome, 4
- Sarcoidosis, 14, 20–22, 26, 41, 42, 49, 84, 99, 128, 144, 184, 185, 194, 244, 248, 287, 293, 295–297, 299, 300, 315, 332, 333, 355, 375, 380, 381, 383, 384, 388, 389, 397, 398, 414, 482, 483
- SARS-CoV-2, 9, 10, 283, 284, 469
- Saturday night palsy, 359
- Scabies, 397, 398
- Scarlet fever, 41, 63, 166, 248, 402, 403
- Schilling test, 452, 453
- Schistosomiasis, 20, 144, 149, 153, 229, 253, 254, 256, 482
- Sciatica, 300, 303
- Sciatic nerve, 313, 352, 353, 360
- Scleroderma, 21, 22, 39, 42, 70, 84, 127–131, 139, 143, 156, 203, 209, 232, 293, 297, 299, 300, 306, 307, 315, 316, 360, 441, 482
- Seborrheic dermatitis, 397, 398, 400
- Seborrheic keratosis, 217, 410
- Secretion of inappropriate anti-diuretic hormone (SIADH), 9, 98, 205, 455
- Seizures
alcohol withdrawal, 337, 479, 493
first time, 338
in pregnancy, 339, 474
- Selective estrogen receptor modulators (SERMs), 213, 391, 396
- Seminoma, 233, 234, 236
- Sensitivity, 2, 4, 42, 74, 83, 115, 118, 142, 176, 177, 186, 214, 230, 239, 241, 251, 255, 258, 260, 265, 268–274, 281, 371, 372, 374, 420, 421, 433, 454, 469, 477, 478
- Sensorineural hearing loss, 342, 343
- Sensory ataxia, 341, 344, 347
- Sensory cortex, 323
- Sentinel lymph node biopsy, 213, 408, 409
- Sepsis, 5, 9, 25, 33, 36, 41, 45, 46, 54, 83–85, 109, 112, 116–119, 123, 124, 133, 142, 144–146, 153, 155–158, 164, 165, 169, 170, 174, 182, 184, 199, 203, 219, 249, 252, 260, 264, 275, 293–295, 297, 300, 309, 311, 355, 361, 362, 374, 375, 377, 383, 384, 403, 422, 439, 451, 455, 457, 461, 467, 469, 487, 490

- Septic arthritis, 66, 266, 276, 293–294
 Septic transfusion, 182
 Sequestration crisis, 164
 Serology
 hepatitis B, 147
 rheumatology, 249, 254, 262, 278, 297–300, 306, 311
 Seronegative spondyloarthropathies, 89, 300–302
 Serotonin, 143, 168, 171, 221, 222, 438, 443
 Serotonin syndrome, 257, 481, 482, 492
 Serum-ascites albumin gradient (SAAG), 154, 155
 Sheehan's, 380
Shigella, 137–139, 253, 269, 275, 278, 296, 302
 Shock
 acute coronary syndrome, 30–38, 47, 48, 86, 180
 sepsis, 118, 133, 169
 tamponade, 117, 209
 Shoulder examination, 19, 23, 32, 56, 80, 317
 Shoulder instability, 317
 Sicca, 149, 156, 157, 203, 293, 299, 316, 451
 Sick euthyroid syndrome, 376
 Sick sinus syndrome, 78
 Sickle cell anemia, 138, 161, 482
 Sickle cell crisis, 264, 284, 389
 Siderocytes, 183
 Simple kidney cysts, 295, 304, 307, 312, 314
 Sister Mary Joseph nodule, 217
 Situational syncope, 53
 Sixth nerve palsy, 341
 Sjogren's syndrome, 9, 22, 84, 96, 128, 195, 297–299, 306, 315, 316, 397, 398
 Sleep disorders, 22–23, 310, 336, 420
 Sliding scale, 488
 Small bowel obstruction, 132, 133
 Small cell lung cancer, 206–208, 353, 355, 384
 Small lymphocytic lymphoma (SLL), 187, 191, 194
 Smoke inhalation, 125, 245
 Smoking cessation, 2, 7, 8, 16, 37, 46, 91, 131, 160, 209, 391, 488, 490–492
 Smoldering multiple myeloma (SMM), 200, 201
 Snout reflex, 329
 Soft tissue infections, 263–264
 Solitary plasmacytoma of bone, 201
 Solitary pulmonary nodule, 18–20, 52
 lung cancer, 18–20, 52
 Solitary thyroid nodule, 19, 329
 Sorafenib, 226
 Spastic gait, 341, 347
 Spasticity, 328, 334, 335, 362, 422, 453
 Specificity, 433, 454, 477, 478
 Spherocytes, 184
 Spinal cord compression, 143, 193, 196, 243, 244, 298, 303, 347, 435, 441
 malignant, 243, 244
 Spinal stenosis, 67, 304, 426
 Spirituality, 433
 Splenomegaly, 66, 150, 159, 161–163, 167, 168, 184–186, 189, 191, 192, 254, 255, 297, 298, 377, 479, 484
 Spondylolisthesis, 302, 303
 Spontaneous bacterial peritonitis (SBP), 153–155
 Spur cells, 184
 Squamous cell carcinoma (SCC), 19, 161, 166, 208, 209, 215, 216, 229, 230, 235, 236, 241, 279, 398, 405, 410
 Staghorn calculi, 102
 Staphylococcal scalded skin syndrome (SSSS), 248, 402, 403
 Stasis dermatitis, 397, 398
 Status epilepticus, 336, 337, 423
 ST depression, 31–33, 36, 44, 79, 80, 100, 326
 ST elevation, 31–34, 36, 37, 39, 40, 44, 78–80, 121
 Stem cell transplant (SCT), 171, 176, 183, 186, 188, 189, 194, 195, 197, 198, 202–203, 252, 253, 286, 307
 Steroids
 complications, 71

- myopathy, 308
 - physiologic dose, 384
 - replacement, 384, 489
 - stress dose, 464, 489
 - Stevens-Johnson syndrome (SJS), 279, 403–405, 412
 - Stigmata of chronic liver disease, 147, 149, 150
 - Still's disease, 184, 194, 247, 296, 297, 300
 - Stomach cancer, 236
 - Stomatocytes, 184
 - Storage pool disease, 171, 173
 - Streptogramins, 273
 - Stress dose, 385, 464, 489
 - Stress incontinence, 427
 - Stress test, 33, 35, 36, 45, 49, 52, 60, 370, 427, 449, 467, 486, 489
 - Stress tests, 32
 - Stroke, 13, 24, 30, 33, 34, 36–38, 47, 49–52, 61, 64, 66, 67, 70–73, 75, 76, 79, 107, 110, 116, 123, 124, 128, 129, 143, 152, 159, 164, 175, 176, 178, 186, 233, 257, 299, 305, 311, 312, 321–330, 332, 333, 335, 336, 339, 341, 342, 344, 349, 361–363, 365, 370, 419, 420, 423, 425, 426, 441, 449, 459, 462, 464, 486, 487, 490, 494
 - risk factors, 51
 - Struvite stones, 102, 103
 - Subacute combined degeneration, 162, 163, 344, 453
 - Subacute cutaneous lupus, 411
 - Subarachnoid hemorrhage, 98, 99, 258, 326, 335, 363, 422
 - Subclinical hypothyroidism, 376, 472
 - Subdural hemorrhage, 98, 322, 363, 419
 - Submersion injury, 124
 - Subscapular nerve, 359
 - Suckling reflex, 323
 - Sudden death, 31, 47, 48, 52, 62, 65, 79, 483
 - hypertrophic obstructive cardiomyopathy (HOCM), 47, 55
 - Sulfa antibiotic, 21, 273, 278
 - Sunitinib, 222, 223, 228
 - Superior vena cava syndrome, 19, 205, 244
 - Supratherapeutic INR, 181
 - Sural nerve, 352
 - Surface lung markings, 10
 - Sympathetic response, 127, 331, 357, 382, 415, 426, 442
 - Sympathomimetic overdose syndromes, 121, 123
 - Syncope
 - aortic stenosis, 52
 - hypertrophic obstructive cardiomyopathy, 47
 - Syndrome of inappropriate antidiuretic hormone (SIADH), 9, 98, 205, 455
 - Syndrome X, 77
 - Syphilis, 61, 88, 128, 194, 247, 248, 250, 253, 261, 262, 270, 276, 293, 308, 343, 398, 405, 406, 411, 469
 - Systemic anaplastic large cell lymphoma, 198
 - Systemic inflammatory response syndrome (SIRS), 118, 260
 - Systemic lupus erythematosus (SLE), 248, 304, 411
 - Systolic dysfunction, 42, 50, 73, 80
 - Systolic murmur, 56–59, 65
- T**
- Tabes dorsalis, 262, 344, 347
 - Tachycardia, 6, 12, 20, 33, 39–41, 48, 49, 54, 73, 78, 80, 81, 100, 107, 117, 118, 121, 122, 124, 125, 134, 135, 140, 142, 247, 249, 251, 254, 357, 377, 383, 434, 467, 479, 482, 485
 - Takayasu's aortitis, 310–312
 - Tamoxifen, 75, 146, 212–214, 242, 245
 - Tamponade, 5, 29, 38–41, 52, 54, 116, 117, 136, 439
 - Target cells, 161, 184
 - Tarsal tunnel syndrome, 360
 - T-cell lymphoma, 195, 198
 - Tear drop cells, 184
 - Telangiectasia, 187, 201, 224, 307, 401, 409, 411

- Temporal arteritis, 67, 310–313, 315, 339, 340, 405
- Tender points, 66, 202, 310, 313, 415
- Tendon xanthoma, 75, 77
- Tensilon test, 355
- Tension headache, 340
- Testicular cancer, 233–235, 279
- Testicular lymphoma, 198
- Tetracyclines, 10, 47, 128, 130, 138, 144, 157, 270, 273, 343, 401, 402, 405, 411–413, 454, 470
- Thalassemia index, 161
- Thiamine deficiency syndromes, 344, 419, 452, 480
- Thin basement disease, 93
- Third nerve palsy, 324, 353, 354
- Thoracentesis, 15, 16, 119, 151, 207, 209, 237, 244, 267, 439, 459, 487
- Thoracic outlet obstruction, 19
- Thromboangiitis obliterans, 67, 311
- Thrombocytopenia
post-operative, 490
in pregnancy, 474
- Thrombocytosis, 100, 167–168, 185, 209, 228, 306, 411, 454
- Thrombolytics
ACS, 326
stroke, 322, 326
- Thrombophilia, 12, 134, 174, 177, 178, 465, 487
- Thrombotic stroke, 322, 326
- Thrombotic thrombocytopenic purpura (TTP), 168, 169
- Thymoma, 98, 210, 244, 353–355
- Thyroid cancer, 178, 376, 378, 379, 383
- Thyroiditis, 51, 88, 151, 375–378, 473
- Thyroid storm, 257, 377, 378, 473, 490
- Tilt table testing, 52, 53
- TIMI score, 33, 34
- Tinea infections, 400
- Tinea versicolor, 400
- Todd's paralysis, 322, 337
- Tonic-clonic seizures, 337, 462, 479
- Tonsillar herniation, 321
- Topoisomerase inhibitors, 187, 245
- TORCHES infections, 469
- Torsade de pointes, 101
- Total parenteral nutrition (TPN), 456–458
- Toxic epidermal necrolysis (TEN), 403–405
- Toxic megacolon
C. difficile, 138, 139, 142
inflammatory bowel disease, 141, 175, 253
- Toxic shock syndrome, 248, 249, 402, 403
- Toxoplasma, 157, 250, 276, 277, 279, 469
- Tracheostomy tubes, 113, 114
- Transaminitis, 75, 76, 146, 151, 305
- Transesophageal echocardiogram, 66
- Transfusion infection risks, 153, 183
- Transfusion reactions, 112, 182–183
- Transfusion related acute lung injury (TRALI), 182, 183
- Transient arterial occlusion, 56, 58
- Transient ischemic attack (TIA), 13, 323, 370, 464, 486, 487, 494
- Transitional cell carcinoma, 166
- Transtentorial herniation, 321
- Trastuzumab, 211–214, 216, 218, 220, 245
- Traveler's fever, 253, 254
- Treatment response criteria
lymphoma, 166, 234, 247
solid tumors, 166, 244
- Tremor, 334, 344–346, 377, 382, 434, 479
- Tremors, 480
- Trendelenburg gait, 341, 347
- Treponema pallidum*, 248, 262, 311, 443
- Triad asthma, 4
- Tricuspid regurgitation, 20, 54–56, 58, 62–64, 66, 151, 153, 155, 184, 222
- Tricuspid stenosis, 52, 54, 56, 65, 222
- Trigeminal nerve lesions, 330
- Troponin, 2, 6, 10, 12, 30–33, 36, 40, 45, 49, 52, 110, 112, 116, 119, 120, 124, 153, 284, 326, 337, 369, 424, 481, 484, 486, 487
- Trousseau's sign, 387
- Trusteeship, 418
- Truth telling, 444, 495
- Tuberculin skin test, 267, 268, 470

Tuberculosis
 HIV co-infection, 468
 in pregnancy, 267
 Tuberos xanthoma, 75, 77
 Tumor lysis syndrome, 188, 190, 197,
 203, 244
 Tumor marker, 211, 231, 233–235,
 237–240, 362, 384
 Turner's syndrome, 29, 392, 393
 Tylenol overdose, 122, 146
 Typhlitis, 252
 Typhoid fever, 41, 194, 253–255
 Typhus, 248, 249, 253, 255, 256, 402
 Tyrosine kinase inhibitors, 186, 223

U

Ulcerative colitis, 8, 137, 139, 140, 142,
 151, 219, 240, 301, 311,
 406, 415
 Ulcers, 68, 124, 132, 136, 140, 141, 164,
 166, 247, 249, 251, 254, 264,
 265, 287, 293, 301, 302, 305,
 307, 312, 314, 366, 385, 398,
 405–407, 411, 483
 Ulnar nerve, 351, 353, 355, 359
 Uncal herniation, 321
 Unconscious patients, 114
 Undifferentiated connective tissue
 disease, 306
 Undulant fever, 256
 Unstable angina, 31–33, 35, 486,
 492, 493
 Upper GI bleed, 17, 134–136, 151,
 215, 217
 Upper motor neuron, 303, 328, 330, 332,
 334, 347, 362
 Uremia, 38, 84, 95, 123, 127, 132, 143,
 184, 305, 335, 355, 397, 419,
 436, 440, 441
 Ureteral calculus, 102–103
 Urethritis, 259, 300–302, 403, 426
 Urge incontinence, 230, 422, 427
 Uric acid stones, 102, 103, 199
 Urinalysis
 hematuria, 83–86, 90, 92, 93, 95, 97,
 99–101, 103, 228
 proteinuria, 228

Urinary incontinence, 232, 260, 321,
 336, 426–427
 Urinary tract infection, 92, 259–261
 recurrent, 89, 93
 Urine chloride, 97
 Urine electrolytes, 84, 103, 121
 Urine net charge (UNC), 96
 Urticaria, 182, 183, 192, 274, 284, 397,
 400, 411–413
 Usual interstitial pneumonia
 (UIP), 21, 22
 Uveitis, 141, 149, 256, 261, 293,
 300–302, 314, 483, 485

V

Vaccination, 2, 7, 11, 22, 147, 148, 165,
 254, 268, 279, 281, 290, 405
 Vaginal bleeding, 262
 Vaginal discharge, 261
 Vaginitis, 261, 286, 426
 Valacyclovir, 282, 333, 405
 Valganciclovir, 282
 Valsalva maneuver, 19, 43, 56, 71, 108,
 339, 348, 447
 Valvular cardiomyopathy, 41
 Valvular diseases
 aortic regurgitation, 42
 aortic sclerosis, 59
 aortic stenosis, 58
 mitral regurgitation, 31, 42, 64
 mitral stenosis, 50, 51
 mitral valve prolapse, 58
 in pregnancy, 467
 rheumatic fever, 63
 tricuspid regurgitation, 64, 222
 Vancomycin, 11, 66, 104, 116, 119, 139,
 142, 168, 182, 249, 251, 252,
 259, 261, 263, 264, 266, 270,
 273–276, 294, 343, 403,
 412, 470
 dosing, 142, 274
 Vancomycin-resistant enterococci
 (VRE), 270
 Varicella zoster virus (VZV), 144, 145,
 163, 203, 250, 257, 258, 282,
 403, 405
 Varices, 134, 136, 151, 153

- Vascular dementia, 419, 421
 Vasculitis, 17, 29, 30, 33, 67, 70, 84, 87, 89, 149, 156, 166, 247–249, 257, 283, 296, 297, 299, 300, 310–315, 355, 357, 411, 482, 484
 Vasoocclusive pain crisis, 164
 Vasopressors, 37, 116–119, 124, 249, 413, 465
 Vasovagal syncope, 52, 53, 336
 Venous filling time, 68
 Venous insufficiency, 68, 263
 Venous thromboembolism, 107, 174, 175, 464–465, 487
 in pregnancy, 464
 Venous ulcers, 406
 Ventilation, 285, 357
 indications, 113
 modes, 113
 settings, 114–115
 weaning, 114, 115
 Verruca vulgaris, 410
 Vertebral osteomyelitis, 266
 Vertigo, 122, 341–344
 Vesicles, 229, 249, 302, 400, 405
 Vestibular ataxia, 344
 Vestibular neuronitis, 343
 Vincristine, 98, 190, 194, 197, 412
 Vinorelbine, 208, 210, 213
 Viral load, 276, 277, 280, 470
 Virchow's node, 215
 Virchow's triad, 12
 Virilization, 382, 394
 Visual field defects, 330, 393
 Vitamin B12 deficiency, 163, 218, 361, 452–454
 Vitamin D deficiency, 96, 101, 102, 452
 Vitamin deficiency, 355, 387, 438
 Von Hippel-Lindau syndrome, 227
 Von Willebrand's disease, 171, 172, 490
 Voriconazole, 286, 288
 V/Q mismatch, 110–112
 VZV, *see* Varicella zoster virus
- W**
 Waldenstrom's macroglobulinemia, 484
 Wallenberg syndrome, 331
 Warfarin, 13, 14, 17, 36, 50, 51, 60, 175, 176, 179, 181, 429, 466, 490
- Warts, 410
 Weakness
 Guillain-Barré syndrome, 333, 357
 ICU, 145, 285
 inflammatory myopathies, 307
 Lambert-Eaton syndrome, 353
 multiple sclerosis, 127, 341
 myasthenia gravis, 353–355
 stroke/TIA, 365
 Weber test, 343
 Weight gain, 23, 103, 211, 214, 232, 338, 370, 443, 471, 472, 491
 Weight loss, 14, 17, 18, 22, 24, 66, 131, 146, 156, 163, 166, 191, 193, 196, 205, 207, 209–211, 215–217, 219, 223–225, 228–230, 233, 245, 247, 249, 251, 253, 267, 303, 313, 382, 442, 450, 452, 453, 458, 472, 483, 484
 Well's criteria, 13
 for DVT, 177–181, 464
 pulmonary embolism, 12, 13, 177
 Wernicke's aphasia, 328
 Wernicke's encephalopathy, 108
 West Nile virus encephalitis, 259
 Wheezing
 asthma exacerbation, 5, 439
 COPD exacerbation, 5, 41
 Whipple's disease, 247, 293, 296, 297, 300, 482, 485–486
 Whipple's procedure, 225
 Whipple's triad, 375
 Wilson's disease, 146
 Wolff-Parkinson-White syndrome, 81
 Wrist examination, 309, 354, 355, 391
- X**
 Xanthelasma, 75, 156
- Y**
Yersinia, 137, 138, 253, 269, 278, 482
- Z**
 Zanamivir, 282, 283