David Hui

Approach to Internal Medicine

A Resource Book for Clinical Practice

Third Edition

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Third Edition

by

David Hui, MD, M.Sc., FRCPC

Edited by

Alexander Leung, BSc(Med), MD(STIR), DABIM, MRCP(UK), FRCPC

and

Raj Padwal, MD, M.Sc., FRCPC

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David Hui MD, M.Sc., FRCPC
The University of Texas M.D. Anderson
Cancer Center
Houston, TX 77030 USA
dhui@mdanderson.org

Author: David Hui
Associate editors: Alexander Leung, Raj Padwal

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Approach to Internal Medicine: A Resource Book for Clinical Practice

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To Ella and Rupert

David Hui

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.

Preface

Practice is science touched with emotion.
Confessio Medici, Stephen Paget, 1909

The third edition of *Approach to Internal Medicine* builds upon previous efforts to create a practical, evidence-based, and concise educational resource for everyday clinical use and examination preparation. *Approach to Internal Medicine* now has an expanded repertoire of over 250 internal medicine topics, classified under 17 subspecialties. With the input of a new editor and publisher, we were able to significantly expand and update the content and substantially improve the layout, while maintaining the same conciseness and practicality found in previous editions.

Under each topic, the sections on differential diagnoses, investigations, and treatments are designed for the rapid retrieval of high-yield clinical information and can be particularly useful when one is all alone assessing a patient at 3 o'clock in the morning. Other sections contain many clinical pearls that are intended to help one to excel in patient care. We also included many comparison tables aimed at highlighting the distinguishing features between various clinical entities and numerous mnemonics (marked by ★). In addition to everyday practice, *Approach to Internal Medicine* can be effectively used as an examination study guide and teaching script.

For this new edition, we are very fortunate to have recruited a new associate editor, Dr. Alexander Leung, who brings with him a wealth of knowledge and outstanding commitment to medical education. We are most grateful to our section editors and contributors for their meticulous review of each subspecialty, providing expert input on the most up-to-date information. We would also like to take this opportunity to thank Jean-Claude Quintal as a resident reviewer and the Canadian Federation of Medical Students for its support of the previous edition. Finally, we would like to thank all previous and current users of this manual for their support and feedback.

We are pleased that Springer has taken this title under its direction and has helped to improve its quality in preparation for international release. In addition to International System (SI) units, this edition also provides US customary units [in square brackets] for quick reference. We would particularly like to thank Laura Walsh, senior editor, and Stacy Lazar, editorial assistant, from Springer for their expert guidance and support throughout this mammoth project from design to production. We would also like to thank Walter Pagel, director of scientific publishing at M.D. Anderson Cancer Center, for believing in this work and making this collaboration possible.

While every effort has been made to ensure the accuracy of information in this manual, 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.

David Hui, MD, M.Sc., FRCPC(Med Onc)
Author, Approach to Internal Medicine
Assistant Professor (tenure track), The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Alexander Leung, BSc(Med), MD(STIR), DABIM, MRCP(UK), FRCPC
Associate Editor, Approach to Internal Medicine
Clinical Scholar, Division of General Internal Medicine University of Calgary, Calgary, AB, Canada
Research Fellow, Division of General Internal Medicine Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Raj Padwal, MD, M.Sc., FRCPC
Associate Editor, Approach to Internal Medicine
Associate Professor, Clinical Pharmacology, Clinical Epidemiology and General Internal Medicine, University of Alberta Edmonton, AB, Canada

Section Editors

PULMONARY MEDICINE
Mohit Bhutani, MD, FRCPC, FACP
Assistant Professor of Medicine
Division of Pulmonary Medicine
Department of Medicine
University of Alberta
Edmonton, AB, Canada

CARDIOLOGY
Mustafa Toma, MD, FRCPC
Fellow, Advanced Heart Failure
and Cardiac Transplantation
Cleveland Clinic Foundation
Cleveland, OH, USA

Jason Andrade, MD, FRCPC
Fellow, Cardiology
Division of Cardiology
University of British Columbia
Vancouver, BC, Canada

NEPHROLOGY
Alan McMahon, MD, FRCPC
Associate Professor of Medicine
Division of Nephrology and Transplant
Immunology, Department of Medicine
University of Alberta
Edmonton, AB, Canada

CRITICAL CARE
Wendy Sligl, MD, FRCPC
Assistant Professor of Medicine
Divisions of Infectious Diseases
and Critical Care Medicine, Department of
Medicine
University of Alberta
Edmonton, AB, Canada

GASTROENTEROLOGY
Winnie Wong, MD, FRCPC
Associate Professor of Medicine
Director, Gastroenterology Subspecialty
Training Program
President-Elect
Canadian Association for Study of Liver
Division of Gastroenterology
Department of Medicine
University of Alberta
Edmonton, AB, Canada

HEMATOLOGY
Michael H. Kroll, MD, FACP
Professor of Medicine and Chief
Benign Hematology
The University of Texas M.D. Anderson
Cancer Center
Houston, TX, USA

ONCOLOGY
Sharlene Gill, MD, FRCPC
Associate Professor of Medicine
Division of Medical Oncology,
British Columbia Cancer Agency
University of British Columbia
Vancouver, BC, Canada

INFECTIOUS DISEASES
A. Mark Joffe, MD, FRCPC
Professor of Medicine
Division of Infectious Diseases,
Department of Medicine
University of Alberta and Royal
Alexandra Hospital
Edmonton, AB, Canada

RHEUMATOLOGY
Elaine Yacyshyn, MD, FRCPC
Assistant Professor of Medicine
Director, Rheumatology Subspecialty
Training Program
Division of Rheumatology
Department of Medicine
University of Alberta
Edmonton, AB, Canada

NEUROLOGY
Brian Thiessen, MD, FRCPC
Assistant Professor of Medicine
Department Of Medical Oncology
British Columbia Cancer Agency
Division of Neurology
Vancouver General Hospital
Vancouver, BC, Canada

ENDOCRINOLOGY
Laurie E. Mereu, MD, FRCPC
Associate Professor of Medicine
Division of Endocrinology
Department of Medicine
University of Alberta
Edmonton, AB, Canada

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

GERIATRICS
Fiona Lawson, MD, FRCPC
Assistant Professor of Medicine
Division of Geriatrics
Department of Medicine
University of Alberta
Edmonton, AB, Canada

PALLIATIVE CARE
Eduardo Bruera, MD
Professor of Medicine and Chair
Department of Palliative Care
and Rehabilitation Medicine
Division of Cancer Medicine
The University of Texas
M.D. Anderson Cancer Center
Houston, TX, USA

Sriram Yennurajalingam, MD
Assistant Professor of Medicine
Department of Palliative Care
and Rehabilitation Medicine
Division of Cancer Medicine
The University of Texas
M.D. Anderson Cancer Center
Houston, TX, USA

NUTRITION
Raj Padwal, MD, M.Sc., FRCPC
Associate Professor of Medicine
Divisions of Clinical Epidemiology
Clinical Pharmacology and General Internal
Medicine, Department of Medicine
University of Alberta
Edmonton, AB, Canada

OBSTETRICAL MEDICINE
Winnie Sia, MD, FRCPC
Assistant Professor of Medicine
and Obstetrics and Gynecology
Divisions of General Internal Medicine
and Maternal-Fetal-Medicine
University of Alberta
Edmonton, AB, Canada

GENERAL INTERNAL MEDICINE
Peter Hamilton, MBBCh, FRCPC
Professor of Medicine
Division of General Internal Medicine
Department of Medicine
University of Alberta
Edmonton, AB, Canada

Contributors

GENERAL: **Jean-Claude Quintal**, MD
ONCOLOGY: **Francine Aubin**, MD; **Anna Tinker**, MD; **Emma Beardsley**, MD; **Robyn Macfarlane**, MD; **Sophie Sun**, MD
DERMATOLOGY: **Elizabeth Farley**, MD; **Catherine Riddel**, BA; **Glynda Caga-Anan**, BA
NUTRITION: **Leanne Mulesa**, RD; **Miranda Wong**, RD

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PULMONARY MEDICINE
Section Editor: Dr. Mohit Bhutani

Asthma Exacerbation

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, and laryngospasm
- **VOCAL CORDS**—vocal cord dysfunction, paralysis, hematoma, tumor, cricoarytenoid arthritis

INTRATHORACIC AIRWAY OBSTRUCTION

- **TRACHEAL OBSTRUCTION**—tracheal stenosis, tracheomalacia, tracheobronchitis (herpetic), malignancy, benign tumor, aspiration
- **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

EXACERBATORS OF ASTHMA

- **INFECTIONS**—viral, bacterial
- **OUTDOORS**—respirable particulates, ozone, sulfur dioxide, cold air, humidity, smoke
- **INDOORS**—smoke, dust mites, air conditioners, humidity, perfumes, scents, smoke
- **NON-ADHERENCE**

CLINICAL FEATURES

HISTORY—history of asthma and any life-threatening exacerbations, number of ER visits/hospital admissions in the last 6 months or ever, any ICU admissions, previous prednisone use, triggers for attacks, normal peak expiratory flow rate, change in peak flow rates, wheezing, cough, dyspnea, decreased function, exercise limitation, nocturnal symptoms, absenteeism from work/school, post-nasal drip, recurrent sinusitis, GERD, occupational and work environment, past medical history, medication history, psychosocial issues, home environment (pets, heating source, filter changes)

CLINICAL FEATURES (CONT'D)

PHYSICAL—HR ↑, RR ↑, pulsus paradoxus, O_2 requirement, moderate-severe dyspnea, barrel chest, cyanosis, 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**—CBCD, lytes, urea, Cr, troponin/CK
- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S
- **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-bronchodilators suggest asthma
- **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%

ACUTE MANAGEMENT

ABC—O_2 to keep sat >92%, IV

BRONCHODILATORS—*salbutamol* 2.5–5.0 mg NEB q6h + q1h PRN and ***ipratropium*** 0.5 mg NEB q6h (frequency stated is a guide, can increase or decrease on a case by case basis)

STEROID—*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, $MgSO_4$

MECHANICAL VENTILATION—BIPAP, intubation

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_1,

LONG-TERM MANAGEMENT

EDUCATION—**smoking cessation** (see p. 418). **Asthma action plan**. **Puffer technique** education and review

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

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

FIRST LINE—**short-acting β2-agonist** (*salbutamol* 2 puffs PRN). Proceed to second line if using more than 2×/week or 1×/day for exercise-induced symptoms, symptoms >2×/week, any nocturnal symptoms, activity limitation or PEF <80%

SECOND LINE—**inhaled corticosteroids** plus short-acting β2-agonist PRN

THIRD LINE—inhaled corticosteroid plus **long-acting β2-agonist** (note that long-acting β2-agonist should never be used alone in asthma), **leukotriene receptor antagonist** (most effective in asthma complicated with sinus disease and exercise-induced asthma)

FOURTH LINE—**anti-IgE therapy** (omalizumab) for refractory allergic asthma, administered subcutaneously q2–4weeks, dosed by IgE level and body weight, for add-on therapy or inadequately controlled moderate-to-severe allergic asthma despite use of high doses of inhaled corticosteroid therapy

NEJM 2009 360:10

TREATMENT ISSUES

COMMON INHALED MEDICATIONS

- **SHORT-ACTING β-AGONISTS**—*salbutamol* metered dose inhaler (MDI) 100 μg 1–2 puffs PRN or 2.5 mg NEB PRN, *fenoterol* MDI 100 μg 1–2 puffs PRN, *terbutaline* 500 μg INH PRN
- **SHORT-ACTING ANTICHOLINERGICS**—*ipratropium* MDI 20 μg 2 puffs QID or 500 μg NEB QID
- **LONG-ACTING β-AGONISTS**—*formoterol* 6–24 μg INH BID, *salmeterol* diskus 50 μg i puff BID
- **LONG-ACTING ANTICHOLINERGICS**—*tiotropium* 18 μg INH daily
- **INHALED CORTICOSTEROIDS**—*beclomethasone* 50–400 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)

Related Topics
Chronic Obstructive Pulmonary Disease (p. 3)
Pulmonary Function Tests (p. 21)

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

OXYGEN DELIVERY DEVICES

Device	Flow rates	Delivered O_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	6 L/min	60%
(non-rebreather mask)	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	40–50%

NOTE: delivered O_2 (FiO_2) is approximate. Oxygen delivery can approach 100% with intubation and mechanical ventilation

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, given 5–10 min before exercise. Consider leukotriene antagonists or inhaled glucocorticoids if frequent use of prophylaxis

TRIAD ASTHMA (Samter's syndrome)—triad of asthma, aspirin/NSAIDs sensitivity, and nasal polyps. Cyclooxygenase inhibition → ↓ prostaglandin E_2 → ↑ leukotriene synthesis → asthma symptoms. Management include ASA/NSAIDs avoidance and leukotriene antagonists (montelukast)

SPECIFIC ENTITIES (CONT'D)

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, recurrent episodes of fever, dyspnea, and productive cough (brownish sputum). Peripheral eosinophilia. CXR findings of patchy infiltrates and central bronchiectasis
- **DIAGNOSIS**—above clinical features plus *Aspergillus* extract skin test, serum IgE level, sputum for *Aspergillus* and/or serologic tests (IgE and IgG against *Aspergillus*)
- **TREATMENTS**—systemic glucocorticoids, itraconazole

COPD Exacerbation

NEJM 2004 250:26

DIFFERENTIAL DIAGNOSIS OF ACUTE DYSPNEA

RESPIRATORY

- **AIRWAY**—COPD exacerbation, asthma exacerbation, acute bronchitis, infectious exacerbation of bronchiectasis, foreign body obstruction
- **PARENCHYMA**—pneumonia, cryptogenic organizing pneumonia, 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

OTHERS—neuromuscular, psychogenic, anxiety

PATHOPHYSIOLOGY

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

CLINICAL FEATURES

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

	Sens	Spc	LR+	LR−
History				
Smoking >70 pack year	40%	95%	8	0.63
Smoking ever	92%	49%	1.8	0.16

CLINICAL FEATURES (CONT'D)

	Sens	Spc	LR+	LR−
Sputum >1/4 cup	20%	95%	4	0.84
Chronic bronchitis Sx	30%	90%	3	0.78
Wheezing	51%	84%	3.8	0.66
Any exertional dyspnea	27%	88%	2.2	0.83
Coughing	51%	71%	1.8	0.69
Any dyspnea	82%	33%	1.2	0.55
Physical				
Wheezing	15%	100%	36	0.85
Barrel chest	10%	99%	10	0.90
Decreased cardiac dullness	13%	99%	10	0.88
Match test	61%	91%	7.1	0.43
Rhonchi	8%	99%	5.9	0.95
Hyperresonance	32%	94%	4.8	0.73
FEV1 >9 s	–	–	4.8	–
FEV1 6–9 s	–	–	2.7	–
FEV1 <6 s	–	–	0.45	–
Subxyphoid cardiac apical impulse	8%	98%	4.6	0.94
Pulsus paradoxus (>15 mmHg)	45%	88%	3.7	0.62
Decreased breath sounds	37%	90%	3.7	0.70
Accessory muscle use	24%	100%	–	0.70

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 subxyphoid 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"

JAMA 1995 273:4

CLINICAL FEATURES (CONT'D)

STEREOTYPES (not useful clinically)

- **BLUE BLOATER** (more chronic bronchitis)—cough and sputum, hypoxemia, CO_2 retention, pulmonary hypertension, right-sided heart failure
- **PINK PUFFER** (more emphysema)—cachexia, relatively preserved blood gases, dyspnea even at rest

PREDICTION RULE FOR OBSTRUCTIVE AIRWAY DISEASE

- **AGE ≥45 YEARS**—LR+ 1.3
- **SMOKING >40 PACK YEAR**—LR+ 8.3
- **SELF-REPORTED HISTORY OF CHRONIC OBSTRUCTIVE AIRWAY DISEASE**—LR+ 7.3
- **MAXIMUM LARYNGEAL HEIGHT <4 CM [<1.6 IN.]**—distance between the top of thyroid cartilage and suprasternal notch at end of expiration. LR+ 2.8

JAMA 2000 283:14

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK, Ca, Mg, PO_4
- **MICROBIOLOGY**—sputum Gram stain/AFB/C&S/fungal
- **IMAGING**—CXR
- **ECG**—left atrial enlargement, atrial fibrillation, sinus tachycardia
- **SPIROMETRY/PFT**—FEV1/FVC <0.7, partially reversible. Severity based on FEV1
- **ABG**—if acute respiratory distress

SPECIAL

- **BNP**—if suspect HF
- **D**-dimer—if suspect PE
- **ECHOCARDIOGRAM**

PROGNOSTIC ISSUES

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

GOLD CLASSIFICATION 2007—all have FEV1/FVC <0.7

- **STAGE I (MILD)**—FEV1 ≥80% predicted
- **STAGE II (MODERATE)**—FEV1 50–79% predicted
- **STAGE III (SEVERE)**—FEV1 30–49% predicted
- **STAGE IV (VERY SEVERE)**—FEV1 <30% predicted, or <50% predicted + cor pulmonale

BODE INDEX

- **BMI**—0= >21, 1= ≤21
- **OBSTRUCTION** (post-bronchodilator FEV1)—0 ≥65% predicted, 1=50–64%, 2=36–49%, 3= ≤35%
- **DISTANCE WALKED IN 6 MIN**—0=≥350 m, 1=250–349 m, 2=150–249 m, 3= ≤149 m
- **EXERCISE MMRC DYSPNEA**—0=0–1, 1=2, 2=3, 3=4
- **SCORING**—hazard ratio for death from any cause per one-point increase in BODE score is 1.34

NEJM 2004 350:10

ACUTE MANAGEMENT

ABC—O_2 to keep sat >90%, or 88–92% if CO_2 retainer, IV

BRONCHODILATORS—*salbutamol* 2.5–5 mg NEB q4h ATC + q1h PRN and ***ipratropium*** 0.25–0.5 mg NEB q4h. Puffers preferable for acute management if proper technique used

STEROIDS—*prednisone* 40–60 mg PO daily ×14 days (tapering dose not necessary in all cases) or ***methylprednisolone*** 60–125 mg IV daily (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 outcome (substantial comorbidities, severe COPD, frequent exacerbations >3/year, recent antibiotics within 3 months); choices depend on clinical circumstance (*levofloxawcin* 500 mg PO daily ×7 days, *doxycycline* 100 mg PO BID ×7–10 days, *amoxicillin* 500 mg PO BID ×7 days, *cefuroxime* 250–500 mg PO BID ×10 days, or *azithromycin* 500 mg PO ×1 day then 250 mg PO daily ×4 days)

MECHANICAL VENTILATION—BIPAP, intubation

OTHERS—DVT prophylaxis (*heparin* 5000 U SC BID), physiotherapy

NEJM 2002 346:13

LONG-TERM MANAGEMENT

EDUCATION—smoking cessation (see p. 418). Disease-specific self-management program. **Puffer technique** education and review

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

REHABILITATION—exercise training (increases quality of life and exercise tolerance)

FIRST LINE—short-acting β2-agonist or short-acting anticholinergic on an as-needed basis

SECOND LINE—long-acting β2-agonist or **long-acting anticholinergic** (*tiotropium* 1 puff [18 μg/puff] INH daily) plus short-acting β2-agonist PRN. Consider early initiation of long-acting agents if requiring regular PRN short-acting agents as long-acting agents are superior

THIRD LINE—long-acting β2-agonist plus **long-acting anticholinergic**, with short-acting β2-agonist PRN

FOURTH LINE—long-acting anticholinergic plus **long-acting β2-agonist/inhaled corticosteroid combination** (e.g. Advair, Symbicort). No role for inhaled corticosteroid alone in COPD

FIFTH LINE—fourth line plus ***theophylline*** 400 mg PO daily ×3 days, then 400–600 mg PO daily, therapeutic level 10–20 μg/mL

SIXTH LINE—fifth line plus **home O_2**

LONG-TERM MANAGEMENT (CONT'D)

SEVENTH LINE—lung volume reduction surgery (may be beneficial if upper lobe involvement and poor functional capacity) or **lung transplant**

Canadian Thoracic Society Guidelines 2003

TREATMENT ISSUES

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 O_2

INDICATIONS FOR SUPPLEMENTAL HOME O_2—ABG done in room air. PaO_2 <55 mmHg alone or PaO_2 <60 mmHg in the presence of bilateral ankle edema, cor pulmonale, or hematocrit >56%

SPECIFIC ENTITIES

α1-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**—α1-antitrypsin levels
- **TREATMENTS**—similar to COPD, α1-antitrypsin replacement

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
  - **SACCULAR 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-INFECTIONS**—bacterial (*Pseudomonas, Haemophilus*), mycobacterium, fungal, viral (adenovirus, measles, influenza, HIV)
    - **IMMUNODEFICIENCY**—cancer, chemotherapy, hypogammaglobulinemia, immunosuppression, sequelae of toxic inhalation or aspiration of foreign body
    - **INTERSTITIAL LUNG DISEASE**—traction bronchiectasis
    - **INFLAMMATORY**—RA, SLE, Sjogren's syndrome, relapsing polychondritis, IBD
    - **INHERITED**—α1-antitrypsin deficiency, cystic fibrosis, primary ciliary dyskinesia (Kartagener's syndrome, Young's syndrome), tracheobronchomegaly (Mounier–Kuhn syndrome), cartilage deficiency (Williams–Campbell syndrome), Marfan's syndrome
- **DIAGNOSIS**—high-resolution CT chest (signet ring sign), PFT (obstruction ± 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

NEJM 2002 346:18

Related Topics
Cryptogenic Organizing Pneumonia (p. 15)
Pulmonary Function Tests (p. 21)
Smoking (p. 418)

Pneumonia

NEJM 2002 345:25; NEJM 2001 344:9

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
- **FUNGAL**—blastomycosis, cryptococcus, histoplasmosis

ASPIRATION PNEUMONIA

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

PNEUMONIA IN THE IMMUNOCOMPROMISED

(see p. 259)

NOSOCOMIAL PNEUMONIA

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

VENTILATOR-ASSOCIATED PNEUMONIA

NURSING HOME-ACQUIRED PNEUMONIA

PATHOPHYSIOLOGY

COMPLICATIONS OF PNEUMONIA

- **PULMONARY**—ARDS, lung abscess ± cavitary formation, parapneumonic effusion/empyema, pleuritis ± hemorrhage
- **EXTRAPULMONARY**—purulent pericarditis, hyponatremia, 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	0.10	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	0.90
Egophony	2.0–8.6	0.76–0.96

PREDICTION RULE—Diehr (rhinorrhea −2, sore throat −1, night sweats +1, myalgias +1, sputum all day +1, RR >25 +2, temp ≥37.8°C [≥100°F] +2. If cut off = 1 (i.e. ≥1 suggests pneumonia), LR+ 5, LR− 0.47. If cut off = 3, LR+ 14, LR− 0.82), **Singal**, **Heckerling**

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"

JAMA 1997 278:17

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. 92)
Parapneumonic Effusion and Empyema (p. 10)
Ventilator-Associated Pneumonia (p. 96)

INVESTIGATIONS

BASIC

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

INVESTIGATIONS (CONT'D)

SPECIAL

- **BRONCHOSCOPY**
- **NASOPHARYNGEAL SWAB**—if suspect viral infection, check for influenza A/B, parainfluenza, human metapneumovirus, RSV, adenovirus
- **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°C [>104°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

NEJM 2002 347:25

MANAGEMENT

ACUTE—ABC, **O_2**, IV, consider ***salbutamol*** 2.5 mg NEB 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 ×10 days
  - **MACROLIDES**—*azithromycin* 500 mg PO first day, then 250 mg PO daily ×4 days; *clarithromycin* 250–500 mg PO BID ×10 days
  - **FLUOROQUINOLONES**—*levofloxacin* 500 mg PO daily ×10 days (or 750 mg ×5 days), *moxifloxacin* 400 mg PO daily ×10 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
  - **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)

MANAGEMENT (CONT'D)

  - **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**—10–14 days for most, 21 days for *Pseudomonas*, *Staphylococcus aureus*, and *Acinetobacter*
- **ASPIRATION PNEUMONIA**—*clindamycin* 600 mg IV BID, switch to 300 mg PO QID when stable. May add cefotaxime for Gram-positive and Gram-negative coverage
- **TUBERCULOSIS PNEUMONIA**—see p. 250
- **PNEUMOCYSTIS JIROVECI PNEUMONIA**—see p. 259

NON-PHARMACOLOGIC TREATMENTS

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

TREATMENT ISSUES

IMPORTANT NOTE—avoid using the same antibiotic class if given within 3 months

OUTPATIENT ANTIBIOTICS CHOICE

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

TREATMENT ISSUES (CONT'D)

DISCHARGE DECISION—clinical stabilization usually takes 2–3 days. When symptoms have significantly improved, vital signs are 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

IDSA Guidelines 2003

Note: consider vancomycin or linezolid if MRSA suspected; emergence of community-acquired MRSA associated with serious necrotizing infections

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)

SPECIFIC ENTITIES (CONT'D)

CAUSES OF RECURRENT PNEUMONIA

- **IMMUNOCOMPROMISED ★SADDIST★**—**S**uppressants (steroids, chemotherapy, transplant medications, alcohol), **A**IDS, **D**iabetics, **D**ecreased nutrition, **I**mmunoglobulin (hypogammaglobulinemia), **S**olid organ failure (renal, liver, splenectomy), **T**umors
- **PULMONARY**—bronchiectasis, COPD, cystic fibrosis, abnormal anatomy
- **GI**—aspiration

LUNG ABSCESS

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

Pulmonary Embolism — NEJM 2008 359:26

DIFFERENTIAL DIAGNOSIS OF ACUTE DYSPNEA

RESPIRATORY

- **AIRWAY**—COPD exacerbation, asthma exacerbation, acute bronchitis, infectious exacerbation of bronchiectasis, foreign body obstruction
- **PARENCHYMA**—pneumonia, cryptogenic organizing pneumonia, 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, endocarditis
- **PERICARDIAL**—pericardial effusion, tamponade

SYSTEMIC—sepsis, metabolic acidosis, anemia

OTHERS—neuromuscular, psychogenic, anxiety

PATHOPHYSIOLOGY

VIRCHOW'S TRIAD—risk factors for venous thromboembolism

- **INJURY**—fracture of pelvis, femur, or tibia
- **HYPERCOAGUABILITY**—obesity, pregnancy, estrogen, smoking, **cancer** (high suspicion of occult malignancy in patients who develop pulmonary embolism while on anticoagulation), **autoimmune disorders** (anticardiolipin 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, PISA-PED, Geneva rule

APPROACH—"use of clinical prediction rules recommended. Not enough evidence to suggest any of the rules as superior. Clinical gestalt of experienced physician similar to use of rules. D-dimer can be used to rule out pulmonary embolism for patients with low pre-test probability"

JAMA 2003 290:21

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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 U/S 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 $S_1Q_3T_3$ (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
- **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 antiphospholipid syndrome in cases of combined arterial–venous thrombosis

DIAGNOSTIC ISSUES

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

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

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

CT PE PROTOCOL (sens 57–100%, spc 78–100%)—can be very helpful as it provides clues to other potential diagnoses/pathologies as well. Not good for subsegmental pulmonary emboli

LEG VEIN DOPPLER (sens 50%, spc 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

WELL'S 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

DIAGNOSTIC ISSUES (CONT'D)

- **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

NEJM 2003 349:13

Related Topics
Anticoagulation Therapy (p. 160)
DVT (p. 158)
Hypercoagulable States (p. 156)
Pulmonary Embolism in Pregnancy (p. 410)

MANAGEMENT

ACUTE—ABC, O_2 to keep sat >94%, IV, consider thrombolysis (must be done in ICU) for massive PE (hemodynamic instability, right ventricular strain)

ANTICOAGULATION—if moderate to high risk of developing PE, consider initiating anticoagulation while waiting for investigations. **Heparin** (*unfractionated heparin* 5000 U IV bolus, then 1000 U/h and adjust to 1.5–2.5× normal PTT), **LMWH** (*enoxaparin* 1 mg/kg SC BID or 1.5 mg/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). Start ***warfarin*** 5 mg PO daily within 72 h and continue heparin/LMWH/fondaparinux until INR is between 2 and 3; ensure overlap of heparin and coumadin with therapeutic INR for at least 48 h

THROMBOLYTICS—controversial as increased risk of intracranial bleed and multiple contraindications (see below). Consider only if hemodynamically unstable or life-threatening pulmonary embolism. *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

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, brain tumors, major trauma in previous 2 months, intra-cranial surgery or head injury within 3 weeks

TREATMENT ISSUES (CONT'D)

- **RELATIVE CONTRAINDICATIONS**—TIA within 6 months, oral anticoagulation, pregnancy or within 1 week postpartum, non-compressible puncture sites, traumatic CPR, uncontrolled hypertension (SBP >185 mmHg, DBP >110 mmHg), 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**—treatment with SC LMWH better than oral warfarin. Treatment should be continued until eradication of cancer as long as there are no significant contraindications to anticoagulation
- **PE AND PREGNANCY**—SC LMWH is preferred for outpatient treatment. Total duration of therapy should be 6 months unless patient has risk factors for hypercoagulable state

SPECIFIC ENTITIES

FAT EMBOLISM

- **PATHOPHYSIOLOGY**—embolism of fat globules to lungs, brain, and other organs → 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 and maybe steroids

Pleural Effusion

NEJM 2002 346:25

DIFFERENTIAL DIAGNOSIS

EXUDATIVE—malignancy, infections, connective tissue disease, pulmonary embolism, hemothorax, pancreatitis, chylothorax

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

Note: pulmonary embolism, malignancy, and sarcoidosis can present as either exudative or transudative effusions. HF following diuresis may become "pseudo-exudative" (check albumin gradient)

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

PHYSICAL—vitals, cyanosis, clubbing, tracheal deviation away from side of effusion (if no collapse or trapped lung), peripheral lymphadenopathy, Horner's syndrome, respiratory examination (decreased breath sounds and tactile fremitus, stony dullness to percussion), cardiac examination, leg swelling (HF or DVT)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THE PATIENT HAVE PLEURAL EFFUSION?

AUSCULTATORY PERCUSSION—auscultate with the diaphragm of the stethoscope over the posterior chest wall while gently tapping over the manubrium with the distal phalanx of one finger. Diminished resonance suggests effusion

	Sens	Spc	LR+	LR−
Physical				
Asymmetric chest expansion	74%	91%	8.1	0.29
Auscultatory percussion	77%	92%	7.7	0.27
Crackles	56%	62%	1.5	0.71
Diminished breath sounds	42–88%	83–90%	4.3–5.2	0.15–0.64
Dullness to conventional percussion	73%	91%	8.7	0.31
Pleural friction rub	5.30%	99%	3.9	0.96

CLINICAL FEATURES (CONT'D)

	Sens	Spc	LR+	LR−
Reduced tactile fremitus	82%	86%	5.7	0.21
Reduced vocal resonance	76%	88%	6.5	0.27

APPROACH—"dullness to percussion and tactile fremitus are the most useful findings for pleural effusion. Dull chest percussion makes the probability of a pleural effusion much more likely but still requires a CXR to confirm the diagnosis. When the pretest probability of pleural effusion is low, the absence of reduced tactile fremitus makes pleural effusion less likely so that a CXR might not be necessary depending on the overall clinical situation"

JAMA 2009 301:3

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, LDH, total protein, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—CXR (PA, lateral, decubitus), 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, medical thoracoscopy, bronchoscopy, surgical biopsy (video-assisted thoracic surgery)

DIAGNOSTIC ISSUES

OVERALL APPROACH—generally, if the effusion is >1/4 of hemithorax, enough fluid is present for diagnostic thoracentesis; obtain decubitus film to assess for loculation. In the absence of loculation, and with >10 mm [0.4 in.] layering of fluid on decubitus film, bedside thoracentesis can be attempted; otherwise, request U/S-guided thoracentesis. If only a small amount of fluid is present (<10 mm [<0.4 in.]) and/or HF suspected, start with diuresis for 2–3 days. If no improvement, perform thoracentesis to distinguish between transudative and exudative causes

LIGHT'S 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

THORACENTESIS PROCEDURE—see **NEJM 2006 355:e16**

PLEURAL FLUID ANALYSIS

- **FLUID ACIDOSIS** (pH <7.2)—complicated parapneumonic, TB, paragonimiasis, malignancy, rheumatoid arthritis, SLE, hemothorax, esophageal rupture
- **FLUID GLUCOSE** (<3.3 mmol/L [<60 mg/dL])—parapneumonic, TB, paragonimiasis, malignancy, rheumatoid arthritis, Churg–Strauss, hemothorax

DIAGNOSTIC ISSUES (CONT'D)

- **FLUID EOSINOPHILIA** (>10%)—paragonimiasis, malignancy, Churg–Strauss, asbestos, drug reaction, pulmonary embolism, hemothorax, pneumothorax, idiopathic (20%)
- **CYTOLOGY FOR MALIGNANCY**—the 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

MANAGEMENT

SYMPTOM CONTROL—**O_2**, **diuresis** (furosemide), **drainage** (thoracentesis, pigtail catheter, PleurX 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
- **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
- **EMPYEMA**—presence of bacteria in Gram stain or pus in drainage (culture not necessary). pH often <7.2. For unloculated fluid, chest tube/small-bore catheter drainage usually adequate. For loculated effusions, thrombolytics such as streptokinase or TPA could be considered. Thoracoscopy represents an alternative to fibrinolytics. Open decortication is the last resort

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

SPECIFIC ENTITIES (CONT'D)

during thoracentesis. Treat by lung re-expansion, sometimes requiring thoracotomy with decortication

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

DIFFERENTIAL DIAGNOSIS

NON-PULMONARY—post-nasal drip, GERD, ACE inhibitors, occult congestive heart failure

PULMONARY

- **AIRWAY**—asthma, chronic 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

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

INVESTIGATIONS (CONT'D)

- **IMAGING**—CXR (order inspiratory and expiratory views if foreign body aspiration or endobronchial lesion suspected)
- **SPIROMETRY/PFT**

SPECIAL

- **SINUS IMAGING**
- **METHACHOLINE CHALLENGE**
- **ESOPHAGEAL PH MONITORING**

MANAGEMENT

SYMPTOM CONTROL—*codeine* 20 mg PO q4h PRN, *dextromethorphan* 20 mg PO q4h PRN

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

SPECIFIC ENTITIES

POST-NASAL DRIP

- **PATHOPHYSIOLOGY**—secretions in the upper airway stimulate cough receptors within the pharyngeal or laryngeal mucosa
- **CAUSES**—allergic, perennial non-allergic, vasomotor rhinitis, acute nasopharyngitis, sinusitis
- **DIAGNOSIS**—non-specific findings
- **TREATMENTS**—reduce irritant exposure, antihistamine-decongestant combinations (*diphenhydramine* 25–50 mg PO q4–6h PRN, pseudoephedrine, *ipratropium nasal spray* 0.03% 2 sprays/nostril BID–TID, nasal corticosteroids, nasal saline rinses BID), surgical correction for anatomical abnormalities

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

DIFFERENTIAL DIAGNOSIS (CONT'D)

  - **INFECTIONS**—necrotizing pneumonia (*Staphylococcus, Pseudomonas*), abscess, septic emboli, TB, fungal
  - **ALVEOLAR HEMORRHAGE**—Wegener's granulomatosis, Churg–Strauss, Goodpasture disease, pulmonary capillaritis, connective tissue disease
- **VASCULAR**—pulmonary embolism, pulmonary hypertension, AVM, iatrogenic

PATHOPHYSIOLOGY

MASSIVE HEMOPTYSIS—100–600 mL blood in 24 h. 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's syndrome, respiratory and cardiac examination, leg swelling (HF or DVT), joint examination, skin examination

INVESTIGATIONS

BASIC

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

INVESTIGATIONS (CONT'D)

SPECIAL

- **ETIOLOGY WORKUP**—ANA, p-anca (myeloperoxidase MPO antibodies), c-anca (antiproteinase-3 PR3 antibodies), anti-GBM antibody, rheumatologic screen
- **ABG**—if respiratory distress

MANAGEMENT

ACUTE—ABC, **O_2**, **IV**, **intubation** to protect airway if significant hemoptysis

SYMPTOM CONTROL—cough suppressants, sedatives, stool softeners. **Transfusions**. Urgent interventional **bronchoscopy** (topical epinephrine, cold saline, cautery). **Angiographic arterial embolization**. **Lung resection**

TREAT UNDERLYING CAUSE—**correct coagulopathy** (*vitamin K* 10 mg SC $\times$1 dose or FFP); **antibiotics**; **radiation** for tumors; **diuresis** for HF; **immunosuppression** for vasculitis

SPECIFIC ENTITIES

GOODPASTURE DISEASE

- **PATHOPHYSIOLOGY**—antibasement membrane antibodies $\rightarrow$ attack pulmonary and renal basement membrane
- **CLINICAL FEATURES**—hemoptysis and hematuria, with respiratory and renal failure if severe
- **DIAGNOSIS**—lung/kidney biopsy
- **TREATMENTS**—steroids, cyclophosphamide, plasmapheresis

Solitary Pulmonary Nodule

NEJM 2003 348:25

DIFFERENTIAL DIAGNOSIS

MALIGNANT—bronchogenic, carcinoid, metastatic cancer

BENIGN—healed infectious granuloma, benign tumors (hamartoma), AVM, rheumatoid nodule, Wegener's granulomatosis, hydatid cyst, round atelectasis, intra-pulmonary lymph nodes, pseudotumor

CLINICAL FEATURES

HISTORY—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's syndrome, SVC syndrome, lymphadenopathy, respiratory examination, abdominal examination (hepatomegaly), bony tenderness

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, LDH, AST, ALT, ALP, bilirubin, INR, PTT
- **IMAGING**—old films (2 years ago), 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★

- **A**ge >50
- **B**order—irregular, nodular cavity with thick wall, or spiculation
- **C**alcification—eccentric or uncalcified

DIAGNOSTIC ISSUES (CONT'D)

- **D**iameter >3 cm [>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/uncalcified calcification
- **TUBERCULOSIS OR HISTOPLASMOSIS**—central/complete calcification
- **BENIGN HAMARTOMA**—popcorn calcification

MANAGEMENT

TREAT UNDERLYING CAUSE—if **low probability**, observation with serial CT scans. If **medium probability**, bronchoscopy with biopsy/brush or transthoracic (CT/US-guided) biopsy. If **high probability**, thoracotomy with resection or video-assisted thoracoscopy (for patients who cannot tolerate thoracotomy medically and physiologically)

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's syndrome** (upper lid ptosis, lower lid inverse ptosis, miosis, anhydrosis, enophthalmos, absence of ciliary-spinal reflex and heterochromia), 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

SPECIFIC ENTITIES (CONT'D)

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's, 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's maneuver** (Valsalva maneuver with the neck fully extended, affected arm elevated, 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's maneuver** (light percussion of brachial plexus in supraclavicular fossa reproduces symptoms)
- **DIAGNOSIS**—cervical spine films, CXR, MRI
- **TREATMENTS**—conservative (keep arms down at night, avoiding hyperabduction), surgery

Related Topics
Lung Cancer (p. 185)
SVC Syndrome (p. 228)

Pulmonary Hypertension

NEJM 2004 351:15; NEJM 2004 351:16

WHO CLASSIFICATION OF PULMONARY HYPERTENSION

GROUP I. PULMONARY ARTERIAL HYPERTENSION

- **IDIOPATHIC**—primary
- **FAMILIAL AND RELATED DISORDERS**—collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV, drugs and toxins, thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy
- **ASSOCIATED WITH SIGNIFICANT VENOUS OR CAPILLARY INVOLVEMENT**—pulmonary veno-occlusive disease, pulmonary–capillary hemangiomatosis
- **PERSISTENT PULMONARY HYPERTENSION OF NEWBORN**

GROUP II. PULMONARY VENOUS HYPERTENSION—left-sided atrial or ventricular heart disease, left-sided valvular heart disease

WHO CLASSIFICATION OF PULMONARY HYPERTENSION (CONT'D)

GROUP III. PULMONARY HYPERTENSION ASSOCIATED WITH HYPOXEMIA—COPD, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, developmental abnormalities

GROUP IV. PULMONARY HYPERTENSION DUE TO CHRONIC THROMBOTIC DISEASE, EMBOLIC DISEASE, OR BOTH—thromboembolic obstruction of proximal pulmonary arteries, thromboembolic obstruction of distal pulmonary arteries, pulmonary embolism (tumor, parasites, foreign material)

GROUP V. MISCELLANEOUS—sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangiomatosis, compression of pulmonary vessels (adenopathy, 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, palpable P2, narrowly split or paradoxically split S2, right-sided S4, tricuspid regurgitation murmur, Graham Steell murmur (high-pitched, decrescendo diastolic rumble over LUSB), crackles, congestive liver, ascites, ankle edema

CLINICAL FEATURES (CONT'D)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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
- **ECG**
- **OVERNIGHT POLYSOMNOGRAPHY**—if suspect OSA
- **ABG**
- **PFT**

SPECIAL

- **RIGHT HEART CATHETERIZATION**

MANAGEMENT

SYMPTOM CONTROL—**O_2, calcium channel blockers** if positive vasoreactivity test (high doses), **vasodilators** (prostacyclin, sildenafil, bosentan, NO), **anticoagulation**

TREAT UNDERLYING CAUSE

ATRIAL SEPTOSTOMY

LUNG TRANSPLANT

SPECIFIC ENTITIES

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

THYROTOXIC-ASSOCIATED PULMONARY HYPERTENSION—pulmonary artery hypertension and isolated right-sided heart failure are associated with hyperthyroidism. Restoration to a euthyroid state may reverse pulmonary hypertension

Interstitial Lung Disease

DIFFERENTIAL DIAGNOSIS

PRIMARY (idiopathic)—usual interstitial pneumonia (UIP), respiratory bronchiolitis-associated interstitial lung disease (RBILD), desquamative 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, sulfonylurea, gold, penicillamine, phenytoin, amiodarone, nitrofurantoin

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **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

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **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 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. 3)
Restrictive Lung Disease (p. 21)
Rheumatoid Arthritis (p. 277)
Sarcoidosis (p. 420)
Tuberculosis (p. 250)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, ANA, RF, anti-CCP antibody, anti-SCL antibody, anticentromere antibody, anti-Jo antibody
- **IMAGING**—CXR, CT chest (high resolution), echocardiogram (if suspect pulmonary hypertension)
- **ABG**
- **PFT**

SPECIAL

- **BIOPSY**—bronchoscopy (transbronchial biopsy), open 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

DIAGNOSTIC ISSUES (CONT'D)

- **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—steroids in most cases. **Idiopathic pulmonary fibrosis** (steroids plus either azathioprine or cyclophosphamide). **Sarcoidosis** (if ≥stage II or symptomatic, give steroids for at least 6 months, even with improvement of symptoms. See p. 420 for details)
LUNG TRANSPLANT

SPECIFIC ENTITIES

IDIOPATHIC PULMONARY FIBROSIS (IPF), ALSO KNOWN AS USUAL INTERSTITIAL PNEUMONIA (UIP)

- **PATHOPHYSIOLOGY**—unknown. Fibrotic rather than inflammatory process
- **DIAGNOSIS**—CT chest (honeycombing, interlobular septal thickening, traction bronchiectasis, peripheral, sub-pleural, lack of ground glass pattern), bronchoscopy (to rule out other causes, mostly infectious); consider open lung biopsy if CT is not consistent with above
- **TREATMENTS**—steroid monotherapy usually ineffective. For patients <50 with early disease and minimal fibrosis, consider steroids plus either azathioprine or cyclophosphamide. Lung transplant referral should be done early

CMAJ 2004 171:2

HYPERSENSITIVITY PNEUMONITIS

- **PATHOPHYSIOLOGY**—inhaled organic antigens → immune response → acute, subacute, or chronic granulomatous pneumonia
- **DIAGNOSIS**—**major criteria** (compatible symptoms, antigen exposure, imaging findings, lavage lymphocytosis, histologic findings (poorly formed granulomas), reexposure triggers symptoms); **minor criteria** (bilateral crackles, ↓ DLCO, hypoxemia). Combination of major and minor criteria will help raise suspicion of hypersensitivity pneumonitis. Serology may be helpful
- **TREATMENTS**—cessation of exposure, steroids

CRYPTOGENIC ORGANIZING PNEUMONIA (COP)—previously known as bronchiolitis obliterans organizing pneumonia (BOOP)

- **CAUSES**—**idiopathic** (80%), **post-infectious** (CMV, influenza, adenovirus, Chlamydia), **drugs**

SPECIFIC ENTITIES (CONT'D)

(amiodarone, bleomycin, gold, sulfasalazine, cephalosporin, cocaine), **connective tissue disease** (RA, SLE, scleroderma, Sjogren's, 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

Obstructive Sleep Apnea

NEJM 2007 356:17

DIFFERENTIAL DIAGNOSIS OF SLEEP DISORDERS

HYPERSOMNOLENCE

- **SLEEP DISRUPTION**—obstructive sleep apnea (OSA), periodic limb movement disorder
- **INADEQUATE SLEEP TIME**—medicine residents, shift workers
- **INCREASED SLEEP DRIVE**—narcolepsy, primary CNS hypersomnolence, head injury, severe depression, medications

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. 94)
Hypertension (p. 57)
Pulmonary Hypertension (p. 14)

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 may be used as a screening questionnaire

PHYSICAL—vitals (hypertension, hypoxia). Obtain weight and height (BMI often >30 kg/m^2). Asterixis and plethora secondary to hypercapnia. Check for low-hanging soft palate, large uvula, 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)

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, consider weight loss through exercise and dieting, 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,

MANAGEMENT (CONT'D)

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—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 $PaCO_2$ >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/m^2. Treatment options include respiratory stimulants, ventilatory support, oxygen therapy, and weight loss

SPECIFIC ENTITIES (CONT'D)

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

NEJM 2003 348:21

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

PHYSIOLOGIC COMPENSATION—secondary to metabolic alkalosis

PATHOPHYSIOLOGY

DEFINITION OF RESPIRATORY ACIDOSIS—$PaCO_2$ >40 mmHg (or upper limit of normal), which is synonymous with hypoventilation

INVESTIGATIONS

BASIC

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

MANAGEMENT

ACUTE—ABC, O_2, IV, BIPAP, intubation

TREAT UNDERLYING CAUSE

Related Topics
Approach to ABG (p. 77)
Metabolic Acidosis (p. 77)
Metabolic Alkalosis (p. 78)

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—$PaCO_2$ <40 mmHg (or lower limit of normal), which is synonymous with hyperventilation

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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. 92)

Ventilation Issues

See VENTILATION ISSUES (p. 94)

Approach to Chest Imaging

APPROACH TO CHEST X-RAY INTEPRETATION

1. **ID**—note patient's name, date/time, technique (PA + lateral, or AP); if not stated, assume PA + lateral by default
2. **QUALITY OF CXR**
   - **ROTATION**—equi-distance between clavicular heads and spinous process
   - **PENETRATION**—intervertebral space seen behind cardiac silhouette
   - **INSPIRATION**—at least 6–8 ribs anteriorly, or 9–11 ribs posteriorly
   - **FIELD**—ensure the entire thorax is captured on film
3. **DEVICES**—previous sternotomy, mechanical valves, pacemaker, central lines (tip at level of carina), PICC line, Swan Ganz, endotracheal tube (two vertebral spaces above carina or aortic notch), NG tube, ECG leads, pacer wires, O_2 tubing, nipple markers (used to differentiate nipple shadows from pulmonary nodules)
4. **MSK**
   - **SOFT TISSUES**—fat, muscle, breast shadow
   - **BONES**—rib or clavicle #, osteoporosis
5. **MEDIASTINUM WIDENING**—right paratracheal stripe >4 mm, azygous region >4 mm, hilar involvement, AP window, tracheal deviation, carina angle widening
6. **HEART**
   - **CARDIOTHORACIC RATIO**—heart to thorax ratio of >30% on PA film or >50% on AP suggests cardiomegaly
   - **CHAMBER ENLARGEMENT**—see table below

CHAMBER ENLARGEMENT

	PA film	Lateral film
Left ventricular hypertrophy	Enlargement of left heart border inferiorly and laterally	Enlargement of inferior and posterior aspects of heart (start where left diaphragm intersects IVC, go up 2 cm [0.8 in.] and then posteriorly 1.8 cm [0.7 in.], LVH is likely if still in heart shadow)
Left atrial enlargement	Prominence of left atrial appendage	Enlargement of posterior border of heart
Right atrial enlargement	Bulging right heart border	Enlargement of anterior and superior aspects of heart
Right ventricular hypertrophy	Enlargement of left heart border laterally	Enlargement of anterior and superior aspects of heart

APPROACH TO CHEST X-RAY INTEPRETATION (CONT'D)

7. **LUNGS**
   - **DIAPHRAGM**—right diaphragm is usually higher on lateral, left diaphragm touches heart border
   - **COSTOPHRENIC ANGLE**—blunting suggests effusion
   - **PLEURA**—convex lesion, thickening, calcifications, pneumothorax (veil-like pleural margin over lung edge with no lung markings extending beyond darker zone)
   - **PARENCHYMA CONSOLIDATION SIGNS**—fluffy density, air bronchograms, silhouette signs (right heart border = RML, left heart border = lingular, right diaphragm = RLL, left diaphragm = LLL)
   - **PARENCHYMA RETICULAR NODULAR PATTERN**
8. **BLIND SPOTS**—behind heart, below diaphragm, spine, paraspinal lines, lung apices, peripheral bones

LUNG CAVITIES

INFECTIONS—**bacterial** (*Staphylococcus*, β-hemolytic *Streptococcus*, *Klebsiella*, Enterobacteriaceae, Nocardia [multiple cavities], anaerobes), **mycobacteria** (TB, non-TB), **fungal** (histoplasmosis, coccidioidomycosis), **parasites** (echinococcus or hydatid infection), **seeding from another site** (septic emboli from right-sided endocarditis, multiple cavities)

NEOPLASMS—**bronchogenic cancer** (squamous cell), **metastatic seeding** (usually multiple cavities; squamous cell carcinomas such as nasopharynx, esophagus, or cervix; adenocarcinomas such as lung, breast, and GI tract tumors; melanoma)

VASCULAR—**Wegener's granulomatosis** (multiple cavities with airspace disease), **necrotic rheumatoid nodules** (multiple cavities), **pulmonary embolus** (infarction)

FOCAL INFILTRATE

LOBAR PNEUMONIA

LUNG INFARCTION OR HEMORRHAGE

FOCAL INFILTRATE (CONT'D)

NEOPLASM (less likely)—bronchoalveolar carcinoma is commonly mistaken as pneumonia initially, with radiographic appearance of focal consolidation in 30%, lymphoma

DIFFUSE AIRSPACE DISEASE

PULMONARY EDEMA (fluid)—**cardiogenic** (left ventricular failure, valvular disease), **non-cardiogenic** (toxic inhalation, drug reaction, aspiration, fat embolism, ARDS)

INFECTIONS (pus)—bacterial, viral, atypical (TB), fungal

HEMORRHAGE (blood)—**bleeding diathesis**, **DIC**, **anticoagulation**, **vasculitis** (Wegener's granulomatosis, Goodpasture's, SLE)

INFLAMMATORY—cryptogenic organizing pneumonia, eosinophilic pneumonia, pulmonary alveolar proteinosis

MALIGNANCY—bronchoalveolar carcinoma, lymphoma

RETICULAR PATTERN

PULMONARY EDEMA

INFECTIONS—bacterial, viral, PJP

INTERSTITIAL LUNG DISEASE—idiopathic pulmonary fibrosis, drug-induced fibrosis, pneumoconiosis, hypersensitivity pneumonitis, connective tissue disease-related fibrosis, asbestosis, ankylosing spondylitis, sarcoidosis, ABPA, opportunistic infections

TUMOR—lymphangitic carcinomatosis (subacute)

NODULAR OR RETICULONODULAR PATTERN

INFECTIONS—TB (miliary), viral, fungal

INFLAMMATORY GRANULOMAS—sarcoidosis, silicosis, histiocytosis X, hypersensitivity pneumonitis

METASTASES—melanoma, lung cancer, breast cancer, renal cell carcinoma, germ cell tumors (in young men), thyroid

PLEURAL-BASED DISEASE

THICKENING (obtuse angle, linear)—tumor, edema/post-radiation thickening, fibrosis, consolidation
CALCIFICATIONS—asbestos, TB, empyema, hemothorax

HILAR ENLARGEMENT

LARGE PULMONARY ARTERIES—see PULMONARY HYPERTENSION (p. 57)
BILATERAL HILAR ADENOPATHY—**neoplasm** (lymphoma, metastases), **infections** (viral, TB, fungal), **nonspecific inflammation** (sarcoidosis, silicosis, Berylliosis, connective tissue disease)
LUNG MASS ABUTTING THE HILUM

MEDIASTINAL MASSES

SUPERIOR MEDIASTINUM (above horizontal line drawn between sternomanubrial joint and T4 vertebra)—thyroid goiters, cystic hygromas, adenopathy, aneurysm
ANTERIOR MEDIASTINUM (in front of heart border)
★5T's★

- **T**hymoma
- **T**hyroid retrosternal
- **T**eratoma
- **T**errible lymphoma
- **T**umor—bronchogenic carcinoma

MIDDLE MEDIASTINUM (between anterior heart border and vertebral bodies)—**infections** (TB, fungal), **neoplastic** (bronchogenic, lymphoma, metastases, neurogenic, mesothelioma), **sarcoidosis**, **aneurysm**, **cysts** (bronchogenic, pericardial, esophageal), **Castleman's disease** (giant LN hyperplasia)
POSTERIOR MEDIASTINUM—**neural tumors** (sheath tumors [schwannomas, neurofibromas], ganglion cell tumors [neuroblastoma, ganglioneuroma]), **non-neural tumors** (mesenchymal, vertebral, lymphoma), **Bochdalek's hernia**

SIGNS FOR DISEASE PROCESSES

HEART FAILURE—vascular redistribution/bat wings, cardiomegaly, peribronchial cuffing, Kerley B lines, pulmonary edema, pleural effusion
COPD—hyperinflation, hemidiaphragm height <1 cm on lateral film, large retrosternal airspace, peripheral vessels end bluntly
CYSTIC FIBROSIS—**hyperinflation** (flattened diaphragms, large retrosternal airspace), prominent **interstitial markings** (upper lobes progressing to the lower lobes), **bronchiectasis** (peribronchial cuffing, "tram tracks," ring shadows), **cysts**, **scarring** (retraction of hilar regions), **pulmonary arterial hypertension** (pulmonary arteries dilatation), **pneumothorax**

CT CHEST PROTOCOLS

HIGH RESOLUTION—1 mm cut every 1 cm (10% of chest only). Non-contrast. Best for pulmonary fibrosis
LUNG CANCER PROTOCOL—7–10 mm cut of entire chest. Also scans adrenals and liver. Contrast enhanced. Best for nodules and mediastinal and pleural structures
PULMONARY EMBOLISM PROTOCOL—contrast bolus timed for optimal imaging of pulmonary arteries. Best for vascular structures, reasonable for nodules and mediastinal and pleural structures

Related Topics
Interstitial Lung Disease (p. 15)
Solitary Pulmonary Nodule (p. 13)

Approach to Pulmonary Function Tests

OVERALL APPROACH TO PFT INTERPRETATION

1. **ID AND DEMOGRAPHICS**—name, date/time, age, height, weight, BMI, smoking history
2. **ANALYZE FLOW VOLUME LOOP AND SPIROMETRY**—identify obstructive or restrictive pattern
3. **ANALYZE SPIROMETRY**—identify obstructive defect, reversibility, and severity. Note that restrictive defect cannot be diagnosed without knowledge of lung volumes
4. **ANALYZE LUNG VOLUMES**—identify restrictive defect, severity
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

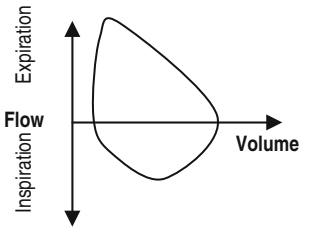
DLCO—carbon monoxide diffusion capacity
FEF25–75%—forced expiratory flow during the middle of a FVC maneuver, represents flow of small airways

TERMINOLOGIES (CONT'D)

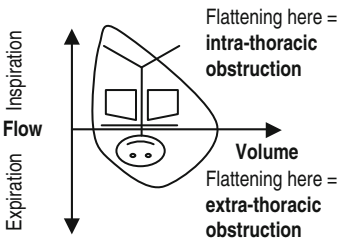
FEV1—forced expiratory volume during the first second of a FVC maneuver
FVC—forced vital capacity, maximum volume exhaled after maximum inhalation
MEP—maximum expiratory pressure
MIP—maximum inspiratory pressure
TLC—total lung capacity at maximal inhalation

FLOW–VOLUME LOOP PATTERNS

NORMAL

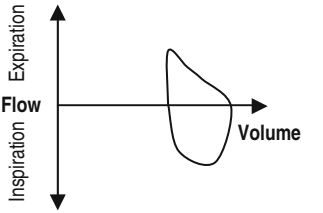


OBSTRUCTIVE DISEASE—scooped appearance of expiratory curve seen in COPD. Variable extrathoracic obstruction (e.g. paralyzed vocal cords) appears as flattening of inspiratory curve. Variable intrathoracic obstruction (e.g. tracheal tumor) appears as flattening of expiratory curve. As illustrated by the man below, scooping of the inspiratory curve (i.e. negative portion of the flow–volume loop) represents extrathoracic obstruction, compared to intrathoracic obstruction, affecting the expiratory curve (i.e. positive portion of the flow–volume loop)



FLOW–VOLUME LOOP PATTERNS (CONT'D)

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 <70%. 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 (in+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%

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

ANALYZING DLCO (CONT'D)

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

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

Notes

2
CARDIOLOGY

Section Editors: Dr. Mustafa Toma and Dr. Jason Andrade

Aortic Dissection

DIFFERENTIAL DIAGNOSIS

CARDIAC

- **MYOCARDIAL**—myocardial infarction, angina
- **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's, cholecystitis, pancreatitis

OTHERS—musculoskeletal, shingles, anxiety

PATHOPHYSIOLOGY

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

AORTIC TEAR AND EXTENSION—aortic tear may produce a tearing, ripping sudden chest pain radiating to the back. Aortic regurgitation can produce diastolic murmur. Pericardial tamponade may occur, leading to hypotension or syncope. Initial aortic tear and subsequent 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
- **CAROTID**—syncope/hemiplegia/death
- **ANTERIOR SPINAL**—paraplegia/quadriplegia, anterior cord syndrome

CLASSIFICATION SYSTEMS

- **STANFORD**—**A** = any ascending aorta involvement, **B** = all others

PATHOPHYSIOLOGY (CONT'D)

- **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, syphilitic aortitis
- **COLLAGEN DISORDERS**—Marfan syndrome, Ehlers–Danlos syndrome, cystic medial necrosis
- **VALVULAR**—bicuspid aortic valve, aortic coarctation, Turner syndrome, aortic valve replacement
- **OTHERS**—cocaine, trauma

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
CXR/ECG		
Enlarged aorta or wide mediastinum	2.0	0.3
LVH 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"

JAMA 2002 287:17

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_2,

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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 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%

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **TYPE B**—with aggressive hypertensive treatment, 1-month survival >90%, 10-year survival 56%

MANAGEMENT

ABC—**O_2** to keep sat >95%, IV, **antihypertensive** (keep HR <60 and SBP <120 mmHg. *Labetalol* 2 mg/min IV loading drip, then 2–8 mg/min (target heart rate 55–60) or 20–80 mg IV q10min, maximum 300 mg, then 200–400 mg PO BID. If SBP still >100 mmHg, *sodium nitroprusside* 0.25–0.5 μg/kg/min IV initially, then 0.25–10 μg/kg/min)

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

Related Topics
Acute Coronary Syndrome (p. 26)
Stroke (p. 299)

Acute Coronary Syndrome

ACC/AHA 2004 STEMI Guidelines
ACC/AHA 2007 STEMI Focused Update
ACC/AHA 2007 UA/NSTEMI Guidelines

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN

CARDIAC

- **MYOCARDIAL**—myocardial infarction, angina (atherosclerosis, vasospasm)
- **VALVULAR**—aortic stenosis
- **PERICARDIAL**—pericarditis
- **VASCULAR**—aortic dissection

RESPIRATORY

- **PARENCHYMAL**—pneumonia, cancer

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN (CONT'D)

- **PLEURAL**—pneumothorax, pneumomediastinum, pleural effusion, pleuritis
- **VASCULAR**—pulmonary embolism

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

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
NSTEMI	Partial occlusion	Non-ST elevation MI
STEMI	Complete occlusion	ST elevation MI

PATHOPHYSIOLOGY (CONT'D)

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 due to supply–demand mismatch

PATHOPHYSIOLOGY (CONT'D)

- **TYPE 3**—MI associated with sudden unexpected cardiac death
- **TYPE 4**—MI associated with PCI (4A) or stent thrombosis (4B)
- **TYPE 5**—MI associated with CABG

PATHOPHYSIOLOGY (CONT'D)

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 (↑ CRP), chronic infections, renal failure

POST–MI COMPLICATIONS—arrhythmia (VT/VF, bradycardia), sudden death, papillary muscle rupture/dysfunction, myocardial rupture (ventricular wall, interventricular septum), ventricular aneurysm, valvular disease (especially acute mitral regurgitation), heart failure/cardiogenic shock, pericarditis (Dressler's 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

- **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

- **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** = unstable angina
  - **IVA** = unstable angina resolves with medical treatment
  - **IVB** = unstable angina on oral treatment, symptoms improved but angina with minimal provocation
  - **IVC** = unstable angina persists, not manageable on oral treatment or hemodynamically unstable

KILLIP CLASS CLASSIFICATION

- **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	
Radiation to right shoulder	2.9
Radiation to left arm	2.3

CLINICAL FEATURES (CONT'D)

	LR+
Radiation to both arms	7.1
Nausea or vomiting	1.9
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

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 ↑, new Q waves, or new conduction Δ make acute MI very likely. Normal ECG is very powerful to rule out MI"

JAMA 1998 280:14

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, troponin/CK ×3 q8h, AST, ALT, ALP, bilirubin, INR/PTT, Mg, Ca, PO_4, albumin, lipase, fasting lipid profile, HbA1C
- **IMAGING**—CXR, echocardiogram (first 72 h), MIBI/thallium (>5 days later)
- **ECG**—q8h ×3 or with chest pain
- **STRESS TESTS**—ECG, echocardiogram, 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

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

arrhythmia, acute pericarditis, aortic dissection, PE, severe symptomatic aortic stenosis
- **GOAL**—keep on treadmill until subject reaches 85–90% of age-predicted heart rate (220–age)
- **ISCHEMIA CRITERIA**—≥1 mm horizontal or downsloping ST ↓ over multiple leads, or ST ↑ → myocardial ischemia (sens 68%, spc 77%) → proceed to angiogram
- **INCONCLUSIVE**—premature termination due to chest pain/poor exercise tolerance → proceed to pharmacological stress test
- **DUKE TREADMILL SCORE**—(exercise time in minutes) – 5×(maximum ST ↓ in mm) – 4×(treadmill angina index [0=none, 1=non-limiting, 2=exercise limiting]). **Low risk** ≥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 → stress test → cardiac CT, MIBI or stress echo → angiography

DIFFERENTIAL DIAGNOSIS OF TROPONIN ELEVATION
- **CARDIAC**—myocardial infarction, myocarditis, congestive heart failure, pericarditis, vasospasm, tachycardia with hemodynamic compromise, cocaine ingestion
- **PULMONARY**—pulmonary embolism
- **HEPATIC**—liver failure
- **RENAL**—chronic kidney disease
- **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)

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **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, should do markers (e.g. troponin) at least twice separated by 6–8 h and serial ECG. Despite all appropriate investigations, MI missed rate is 2–5%

ECG CHANGES IN ACUTE MI—see APPROACH TO ECG p. 62

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 7 days, ≥2 angina episodes within 24 h, ↑ cardiac marker, ST deviation ≥0.5 mm
- **RISK GROUPS**—**low** = 0–2, **intermediate** = 3–4, **high** = 5–7. Consider GPIIb/IIIa and early angiography with revascularization in intermediate or high-risk groups
- **RISK OF DEATH, MI OR REVASCULARIZATION IN 14 DAYS**—0/1=5%, 2=8%, 3=13%, 4=20%, 5=26%, 6/7=41%

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 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—O_2 to keep sat >95%, IVs, inotropes, consider balloon pump if hemodynamic instability

PAIN CONTROL—**nitroglycerin** (*nitro drip* 25 mg in 250 mL D5W, start at 5 μg/min IV, then ↑ by 5–10 μg/min every 3–5 min to 20 μg/min, then ↑ by 10 μg/min every 3–5 min up to 200 μg/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 ×3.

ACUTE MANAGEMENT (CONT'D)

Beware if suspect right ventricular infarction or if patients on sildenafil). ***Morphine*** 2–4 mg IV every 5–15 min PRN

CLOT CONTROL

- **ANTIPLATELET**—***ASA*** 162–325 mg PO chew ×1 dose, then 75–162 mg PO daily (for medically treated unstable angina/NSTEMI), or 162–325 mg PO daily (post-PCI minimum ×1 month for bare-metal stent, ×3 months for sirolimus-eluting stent, or ×6 months for paclitaxel-eluting stent), then 75–162 mg PO daily indefinitely. If NSTEMI or STEMI, ***clopidogrel*** 300–600 mg ×1 dose then 75 mg PO daily. Combination ASA plus clopidogrel for minimum of 1 month (ideally 1 year)-post PCI with bare-metal stent, or minimum 12 months (possibly indefinitely) for drug-eluting stents. If post-PCI, pain unresponsive to nitroglycerin or intermediate/high-risk NSTEMI, consider **GPIIb/IIIa inhibitor** (*tirofiban* 0.4 μg/kg/min ×30 min IV, then continue 0.1 μg/kg/min ×18–24 h after angioplasty/atherectomy. *Eptifibatide* 180 μg/kg IV bolus, then 2 μg/kg/min ×72–96 h)
- **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 4000U] IV bolus, then 18 U/kg/hr [up to 1000U/h] and adjust to 1.5–2.5× normal PTT for 72 h). **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/hr initially, followed by second 0.5 mg/kg bolus before PCI and 1.75 mg/kg/hr during PCI, then continue infusion for up to 4 h post-PCI, if needed)
- **REPERFUSION THERAPY**—see **PCI** for details. **Fibrinolytics** (*TPA* 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]. *Streptokinase* 1.5 million units IV over 30–60 min. *Tenectepalse* IV bolus over 10–15 s, weight-based: 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—IV metoprolol is mostly contraindicated. Start with *metoprolol* 25 mg PO BID and titrate slowly. Alternatively, *atenolol* 25 mg PO daily and titrate to 100 mg PO daily. The goal heart rate is 50–55 with normal activity. If β-blocker contraindicated, consider non-dihydropyridine calcium channel blockers *diltiazem* 30–120 mg PO QID or *verapamil* 80–120 mg PO TID (contraindicated if LV dysfunction)

LIPID CONTROL—*simvastatin* 40 mg PO daily or *atorvastatin* 80 mg PO daily

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

OVERALL APPROACH

	Stable angina	Unstable angina or NSTEMI	STEMI
ASA	✓	✓	✓
Nitrates	✓	✓	✓
Morphine	±	✓	✓
β-blockers	✓	✓	✓
ACE inhibitors	✓	✓	✓
HMG-CoA inhibitors	✓	✓	✓
Heparin or antithrombin	NO	✓	✓
Clopidogrel	NO	✓	✓
GPIIb/IIIa inhibitors	NO	✓ (if TIMI ≥3)	NO
Fibrinolytics or PCI[a]	NO	NO	✓
Cardiology consult	Outpatient[b]	CCU[c]	CCU[c]

[a]for fibrinolytics, the ideal door-to-needle time is <30 min; for PCI, the ideal door-to-balloon time is <90 min; urgent CABG is also an option post-catheterization
[b]Outpatient cardiology for stress test
[c]CCU 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 non-dihydropyridine calcium channel blockers if clinical 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 q5min ×3; *isosorbide mononitrate* 30 mg PO daily, maximum 240 mg), **β-blocker** (*metoprolol* 25–100 mg PO BID, *atenolol* 50–100 mg PO daily, *bisoprolol* 5–10 mg PO daily), **calcium channel blocker** (*amlodipine* 5–10 mg PO daily)

ACE INHIBITOR—*ramipril* 2.5–10 mg PO daily

ANTIPLATELET—***ECASA*** 81 mg PO daily and/or ***clopidogrel*** 75 mg PO daily

ANTICOAGULATION—controversial especially in combination with ASA and/or clopidogrel. May be considered for patients post-STEMI or NSTEMI with one of the following criteria: (1) atrial fibrillation, (2) left ventricular thrombus, (3) significant left ventricular dysfunction with extensive regional wall motion abnormalities. Start *warfarin* 5 mg daily within 72 hours and continue heparin/LMWH until INR is between 2 and 3 (unless planning angioplasty)

RISK REDUCTION ★ABCDEFG★

- **ASA/ACE INHIBITOR**
- **BLOOD PRESSURE CONTROL** (see HYPERTENSION p. 57)
- **CHOLESTEROL CONTROL** (see DYSLIPIDEMIA p. 61)
- **DIABETIC CONTROL** (see DIABETES p. 337)
- **EXERCISE** (30 min of moderate-intensity exercise 3–4×/week)
- **FAT REDUCTION** (see OBESITY ISSUES p. 403)
- **GET GOING TO QUIT SMOKING!** (see SMOKING ISSUES p. 418)

DRIVING POST-MYOCARDIAL INFARCTION—see p. 426 for details

TREATMENT ISSUES

RIGHT VENTRICULAR INFARCTION—evidence of inferior MI should automatically trigger one to check right- sided leads (V4R) to assess for the possibility of RV infarction, which occurs in about 50% of patients with inferior MI. May see increased JVP and clear lungs clinically. ST elevation in V4R is diagnostic and prognostic. Hypotension should be treated with fluid bolus to ensure good preload

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

POST-MI RISK STRATIFICATION

- **EXTENT OF INFARCT/RESIDUAL FUNCTION**—assessment is based on clinical factors (↑ HR, ↓ BP, Killip class, diabetes, renal failure, ↑ WBC), ECG, biomarkers (CK, troponin), imaging (echocardiogram, MIBI), and angiography. Early measurement of LV function, although of prognostic importance, is misleading as myocardium function may improve in first 2 weeks. Medical management
- **EXTENT OF MYOCARDIUM AT RISK**—assessment is based on exercise stress test, stress echocardiogram, stress sestamibi (ischemic tissue), thallium scan (viable tissue), PET scan, 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

TREATMENT ISSUES (CONT'D)

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. Indicated if cardiogenic shock with hemodynamic instability. May be used in conjunction with inotropes. Contraindicated in aortic regurgitation, AAA, aortic dissection, uncontrolled sepsis bleeding disorder, and severe PVD

FIBRINOLYTICS USE (TPA, SK, RPA, TNK)

- **INDICATIONS**—≥30 min of chest pain, patient presents within 12 h (ideal door to needle time <30 min), ECG criteria (>1 mm ST ↑ in ≥2 contiguous leads, or new LBBB with suggestive history, age <75)
- **ABSOLUTE CONTRAINDICATIONS**—any intracranial hemorrhage, ischemic stroke within 3 months, cerebral vascular malformation or brain tumor, closed-head or facial trauma within 3 months, suspected aortic dissection, bleeding diathesis, or active bleeding
- **RELATIVE CONTRAINDICATIONS**—severe hypertension (>180/110 mmHg, may be an absolute contraindication for patients at low risk), ischemic stroke >3 months, other intracranial diseases not already specified above, dementia, internal bleeding within 2–4 weeks, active peptic ulcer, major surgery within 3 weeks, non-compressible vascular punctures, current warfarin therapy, pregnancy, traumatic CPR >10 min, prior exposure to streptokinase or anistreplase (if planning to use these fibrinolytics)
- **RISK OF BLEEDING**—average risk of severe bleed is 1.8%. Increased risk with women, BP >165/95 mmHg, age >65, weight <70 kg [<154lbs], 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 require urgent rescue catheterization. Other causes of ST elevation include pericarditis, ventricular aneurysm, hyperkalemia, LBBB, and early repolarization abnormality

Related Topics
Aortic Dissection (p. 25)
Asystole (p. 431)
Diabetes Mellitus (p. 337)
ECG (p. 62)
Hyperlipidemia (p. 61)
Hypertension (p. 57)
Pericarditis (p. 32)
Shock (p. 97)
Smoking Cessation (p. 418)

TREATMENT ISSUES (CONT'D)

PERCUTANEOUS CORONARY INTERVENTION (PCI, PTCA)

- **INDICATIONS FOR ACUTE STEMI**—patient presents within 12 h of chest pain (ideal time from initial medical contact to treatment or "door-to-balloon time" <90 min), ECG criteria (>1 mm ST ↑ in ≥2 contiguous leads, new or presumed new left bundle branch block), or in patients in cardiogenic shock within 18 h of infarct
- **INDICATIONS FOR CHRONIC STABLE CAD**—single/double vessel disease refractory to medical therapy
- **ADVERSE EVENTS**—access site (bleeding, hematomas, arteriovenous fistulae, pseudoaneurysms), contrast nephropathy, arrhythmia (VT, VF), stroke, dissection, myocardial infarction
- **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 or paclitaxel) are designed to inhibit cell proliferation and decrease the risk of in-stent restenosis. There has been some controversy regarding higher observed mortality rate in patients with drug-eluting stents. The most recent outcomes research analysis suggests that drug-eluting stents are associated with decreased rate of repeat revascularization (19% vs. 23%, HR 0.82) at 2 years and no significant difference in mortality (8.4% vs. 8.4%)
- **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 were able to seek medical attention within 1 h of chest pain onset, allergic to contrast dye, or do not have access to PCI in a timely fashion should consider fibrinolytics

TREATMENT ISSUES (CONT'D)

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%

NEJM 2007 356:1; NEJM 2007 356:10; NEJM 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)
  - **DOMINANT ARTERY**—defined as the artery that supplies PDA and at least one posterolateral (PL) artery
- **INDICATIONS**—CABG provides mortality benefit for specific subgroups, including patients with (1) left main disease >50% occlusion, (2) 2 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
- **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
- **MEDICATIONS**—hold clopidogrel 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
INFARCTION—MI (early, late)
INFECTIOUS—HIV, Coxsackie, echovirus, adenovirus, TB
INFLAMMATORY—psoriatic arthritis, enteric arthritis, rheumatoid arthritis, SLE, mixed connective tissue disease

DIFFERENTIAL DIAGNOSIS (CONT'D)

IDIOPATHIC
NEOPLASTIC—primary (mesothelioma), metastasis (breast, lung, melanoma), leukemia, lymphoma
TRAUMA—stab, gunshot wound, blunt, CPR, postpericardiotomy

CLINICAL FEATURES

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

	Sens	Spc
History		
Dyspnea	87–89%	
Fever	25%	
Chest pain	20%	
Cough	7–10%	
Physical		
Tachycardia	77%	
Pulsus paradoxus >10 mmHg[a]	82%	70%
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%	

[a]Pulsus 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"

JAMA 2007 297:16

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's 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**—CBCD, 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—***ASA*** (650 mg PO TID ×3–4 weeks), **NSAIDs** (*indomethacin* 25–50 mg PO TID × 2–4 weeks). Add ***colchicine*** 0.6 mg PO BID ×3 months for adjuvant treatment and long-term prophylaxis. ***Prednisone*** 0.25–0.5 mg/kg PO daily may be used 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×4–8 weeks). Add ***colchicine*** (0.6 mg PO BID×2 months) for adjuvant treatment and long-term prophylaxis. 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

MANAGEMENT (CONT'D)

TAMPONADE—ABC, $\mathbf{O_2}$, IV's, 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—complete 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's syndrome, and post-pericardiotomy syndrome

TAMPONADE—a *clinical* diagnosis based on dyspnea, tachycardia, hypotension, pulsus paradoxus, and elevated JVP. Tamponade causes 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, leading to left and/or right heart failure. May follow pericarditis or radiation. May be difficult to distinguish from restrictive cardiomyopathy clinically

Heart Failure

NEJM 2003 348:20
Canadian Heart Failure Guidelines 2006

DIFFERENTIAL DIAGNOSIS OF HF EXACERBATION/ DYSPNEA

CARDIAC

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

RESPIRATORY

- **AIRWAY**—COPD exacerbation, asthma exacerbation, acute bronchitis, bronchiectasis, foreign body obstruction
- **PARENCHYMA**—pneumonia, cryptogenic organizing pneumonia, ARDS, interstitial lung disease exacerbation

DIFFERENTIAL DIAGNOSIS OF HF EXACERBATION/ DYSPNEA (CONT'D)

- **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

PATHOPHYSIOLOGY (CONT'D)

- **HYPERTROPHIC** (disorder with disproportionate hypertrophy of the left ventricle and occasionally right ventricle)—**idiopathic** (autosomal dominant inheritance with incomplete penetrance), **storage disease** (Fabry's disease, Pompe disease, Hurler's syndrome, Noonan's syndrome), athlete's heart, obesity, amyloid
- **RESTRICTIVE** (non-dilated ventricles with impaired ventricular filling)—idiopathic familial, **infiltrative** (amyloidosis, hemochromatosis, sarcoidosis), drugs, radiation, endomyocardial fibrosis
- **ARRHYTHMOGENIC RIGHT VENTRICULAR** (replacement of right ventricular free wall with fatty tissue)—arrhythmogenic RV dysplasia
- **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** (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's disease, Gaucher's disease, Niemann–Pick disease), **nutritional deficiencies** (Beriberi, Kwashiorkor, pellagra), **deposition** (amyloidosis, hemochromatosis, sarcoidosis)

PATHOPHYSIOLOGY (CONT'D)

- **MUSCULAR DYSTROPHIES** (mostly dilated)—Duchenne, Becker's, myotonic dystrophy
- **NEUROMUSCULAR**—Friedreich's ataxia (hypertrophic), Noonan's syndrome, lentiginosis
- **GENERAL SYSTEMIC DISEASE** (mostly dilated)—**connective tissue diseases** (rheumatoid heart disease, ankylosing spondylitis, SLE, scleroderma, dermatomyositis), granulomatous (sarcoidosis, Wegener's granulomatosis, 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. 411

FUNCTIONAL CLASSIFICATION OF HEART FAILURE

- **SYSTOLIC DYSFUNCTION** (↓ LVEF <45%)—S3 (dilated ventricle with volume overload). Mechanisms include decreased contractility and increased afterload. Causes include MI, cardiomyopathy (dilated, infiltrative), valvular (aortic regurgitation, mitral regurgitation, burn out aortic stenosis), burn out hypertension and myocarditis
- **DIASTOLIC DYSFUNCTION** (normal LVEF)—S4 (stiff ventricle), LVH, ↓ ventricular relaxation, normal LVEF, ↑ 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★

- **F**orget to take medications (non-adherence)
- **A**rrhythmia, anemia
- **I**nfection, ischemia, infarction
- **L**ifestyle change
- **U**pregulators (thyroid, pregnancy)
- **R**heumatic heart disease, acute valvular disease
- **E**mbolism

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

CLINICAL FEATURES (CONT'D)

	COPD	Heart Failure
Resp. exam	Hyperresonance Prolonged expiratory time	Bilateral crackles
Investigations	CXR shows hypeinflation 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

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

CLINICAL FEATURES (CONT'D)

NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

- **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

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				
S3	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
S4	5%	97%	1.6	0.98
SBP ≥150 mmHg	28%	73%	1.0	0.99
Wheezing	22%	58%	0.52	1.3
Ascites	1%	97%	0.33	1.0
CXR				
Pulmonary venous congestion	54%	96%	12	0.48

CLINICAL FEATURES (CONT'D)

	Sens	Spc	LR+	LR−
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 Twave 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 $\geq$100 pg/mL			4.1	0.09

For patients with an estimated GFR of 15–60 mL/min/1.73 m^2, 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 of 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"

JAMA 2005 294:15

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 abdominojugular reflux (AJR). To perform the AJR, the blood pressure cuff is pumped 6$\times$ 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+ 6.4)

APPROACH—"once the JVP is identified, measure the vertical height. A distance $\geq$4 cm above the sternal angle is considered abnormal (i.e. CVP $\geq$9cmH_2O). An assessment of low JVP has an LR+ for low CVP of 3.4, while an assessment of high JVP has an LR+ for high CVP of 4.1"

JAMA 1996 275:8

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: CAN THE CLINICAL EXAMINATION DIAGNOSE LEFT-SIDED HEART FAILURE IN ADULTS?

INCREASED FILLING PRESSURE—very helpful findings are **radiographic redistribution** and **jugular venous distension**. Somewhat helpful findings are dyspnea, orthopnea, tachycardia, decreased systolic or pulse pressure, S3, rales, and abdominojugular reflux. Edema is helpful only when present

SYSTOLIC DYSFUNCTION—very helpful findings are **radiograph** (cardiomegaly, redistribution), **anterior Q waves**, **LBBB**, and **abnormal apical impulse** (especially if sustained). Somewhat helpful findings are tachycardia, decreased blood pressure or pulse pressure, S3, rales, dyspnea, previous infarction other than anterior, and high peak CK (post-infarct). Edema and increased jugular venous pressure are helpful if present

DIASTOLIC DYSFUNCTION—very helpful finding is **elevated blood pressure** during the episode of increased filling pressure. Somewhat helpful findings are obesity, lack of tachycardia, older age, and

CLINICAL FEATURES (CONT'D)

absence of smoking or CAD. Normal radiographic heart size is helpful if present

APPROACH—"in patients without known systolic dysfunction, ≤1 finding of increased filling pressure can exclude diagnosis, ≥3 findings suggests increased filling pressure. In patients with known systolic dysfunction, absence of finding of increased filling pressure can exclude diagnosis, ≥1 finding suggests increased filling pressure. For systolic dysfunction, can exclude diagnosis if no abnormal findings, including no sign of increased filling pressure are present (LR– 0.1). ≥3 findings are needed to confirm the diagnosis (LR+ 14)"

JAMA 1997 277:21

INVESTIGATIONS

BASIC

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

SPECIAL

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

DIAGNOSTIC AND PROGNOSTIC ISSUES

B-TYPE NATRIURETIC PEPTIDE

- **DIAGNOSIS**—in addition to heart failure, BNP is also elevated with PE, pulmonary hypertension, LVH, ACS, AF, renal failure, overload, and sepsis

BNP	Heart Failure diagnosis
<100 pg/mL	Unlikely
100–250 pg/mL	Compensated LV dysfunction
250–500 pg/mL	HF with both diastolic and systolic dysfunction
500–1000 pg/mL	Decompensated HF
>1000 pg/mL	High risk of substantial 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—O_2 to keep sat >95%, IV's

SYMPTOM CONTROL—★**LMNOP**★ ***L****asix/furosemide* 20–100 mg IV PRN, ***M****orphine* 2–5 mg IV PRN, ***N****itroglycerin* 0.4 mg SL PRN, **O_2**, **P**osition (upright)

LONG-TERM MANAGEMENT

★**DDDD**★

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

DIURETICS—***furosemide*** 20–100 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* 2.5–20 mg PO BID, *ramipril* 2.5–10 mg PO daily, *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 mg PO QID and *nitropatch* 0.4 mg PO daily. **β-blockers** (*metoprolol* 50–100 mg PO BID, *carvedilol* 3.125–25 mg PO BID, *bisoprolol* 2.5–10 mg PO daily)

DIGITALIS—***digoxin*** 0.125–0.25 mg PO daily

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

DEVICES—if ejection fraction <30–35%, consider **cardiac resynchronization therapy** (CRT/biventricular pacing) ± **implantable cardioerter defibrillators** (ICD). **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 (Jong, J Am Coll Cardiol 2002, 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, African Americans, or those who developed renal insufficiency while on ACE inhibitor, or as add-on therapy

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 euvolemic

SPIRONOLACTONE (RALES 1999, EPHESUS 2003)—hazard ratios for total mortality 0.7 and mortality/hospitalization 0.65. For patients with NYHA III–IV,

TREATMENT ISSUES (CONT'D)

LVEF <35%, and on maximum treatment already. 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 treatment

OVERALL APPROACH—treat underlying cause if possible. Non-pharmacological treatments (diet, exercise, smoking cessation) → add ACE inhibitor for all (or hydralazine/nitrates if renal failure, ARB if cough secondary to ACE inhibitor) → add β-blocker when euvolemic → add spironolactone/eplerenone if NYHA III/IV → add digoxin ± ARB if still symptomatic. If ejection fraction is <30–35% despite optimal medical therapy, consider revascularization, implantable cardioverter defibrillator, cardiac resynchronization (if QRS is wide), and ventricular-assist device/heart transplant

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, thyroid disease)

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), microvascular obstruction, and high-risk genetic defect
- **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) ± 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)

Digoxin Intoxication

Circulation 2004 109:24

DIFFERENTIAL DIAGNOSIS

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

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

PHARMACOKINETICS

- **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 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

PATHOPHYSIOLOGY (CONT'D)

leads to intracellular loss of K and gain of Na. Increase in intracellular Ca leads to ↑ 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, unifocal or multifocal PVCs, bidirectional ventricular tachycardia, accelerated junctional tachycardia
- **GI**—anorexia, N&V, diarrhea, abdominal pain
- **METABOLIC**—hyperkalemia

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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

DIAGNOSTIC ISSUES (CONT'D)

- **TOXIC LEVELS**—first degree heart block, paroxysmal atrial tachycardia, regularized atrial fibrillation, unifocal or multifocal PVCs, ventricular bigeminy, bidirectional VT

MANAGEMENT

ACUTE—ABC, O_2, IV, **treat arrhythmia**

TREAT UNDERLYING CAUSE—**observe, cardiac monitoring, activated charcoal** (if ingestion within 4 h). **Correct** electrolyte disturbances and reverse acidosis. **Atropine** for bradycardia. **Digibind/purified antidigoxin FAB fragments** (if ingested 10 mg of more in adults, or digoxin level >13 nmol/L [10 ng/mL], K >5 mM and life-threatening arrhythmia, hemodynamic instability or severe bradycardia. 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 $t_{½}$ 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

NEJM 2001 344:14; NEJM 2004 351:23

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

DIFFERENTIAL DIAGNOSIS OF NARROW COMPLEX TACHYCARDIA

REGULAR NARROW COMPLEX TACHYCARDIA—sinus tachycardia, atrial flutter with fixed block (rate 300, 150, 100, 75, 60), supraventricular tachycardia (atrial tachycardia, AV nodal reentry, 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 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, SSS), **pericardial** (pericarditis), cardiac surgery
- **PULMONARY**—COPD, pulmonary embolism, pleural effusion

PATHOPHYSIOLOGY (CONT'D)

- **METABOLIC**—thyrotoxicosis, obesity
- **DRUGS**—theophylline, adenosine, digitalis, β-agonists, alcohol
- **IDIOPATHIC** (10%)

CLASSIFICATION OF ATRIAL FIBRILLATION

- **PAROXYSMAL ATRIAL FIBRILLATION**—episodes of AF last <7 days (usually <24 h). Self-terminating
- **PERSISTENT ATRIAL FIBRILLATION**—lasts longer than 7 days and fails to self-terminate (i.e. requires cardioversion)
- **PERMANENT ATRIAL FIBRILLATION**—arrhythmia lasts longer than 1 year; unable to cardiovert
- **LONE ATRIAL FIBRILLATION**—atrial fibrillation 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, blood pressure), cardiac and pulmonary examination for heart failure

CAROTID SINUS MASSAGE, VALSALVA, OR ADENOSINE—SVT may spontaneously terminate, while AF or atrial flutter may slow down. Avoid adenosine if suspect WPW

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH PALPITATIONS HAVE A CARDIAC ARRHYTHMIA?

	Any arrhythmia		Significant arrhythmia	
	LR+	LR−	LR+	LR−
History				
Cardiac disease	2.03	0.71	0.42	1.07
Male sex	1.63	0.76	1.20	0.90
Age >60	1.70	0.83	1.89	0.77
Smoking >11/day	0.78	1.03	0.77	1.03
Anxiety disorder	0.98	1.01	0.92	1.04
FH of palpitations	0.86	1.04	1.07	0.98
EtOH >10 days/week	0.76	1.05	1.02	1.00
Panic disorder	0.26	1.30	–	–
Any psychiatric disorders	–	–	0.67	1.12
Palpitations				
Regular	1.66	–	1.38	0.55
Irregular	1.65	0.62	–	1.23
Duration >5 min	1.52	0.38	0.79	0.95
Duration >60 s	1.15	0.69	1.17	0.63

CLINICAL FEATURES (CONT'D)

	Any arrhythmia		Significant arrhythmia	
	LR+	LR−	LR+	LR−
Continuous symp	1.06	–	0.93	1.20
HR >100/min	0.91	–	1.08	0.86
Precipitating factors				
Affected by sleep	2.29	0.70	2.44	0.63
Occurring at work	2.17	0.76	1.54	0.86
Caffeine	1.84	0.91	2.06	0.89
Occurs holiday	1.56	0.92	0.79	1.04
Occurs weekend	1.43	0.90	0.72	1.08
Alcohol	1.36	0.96	1.94	0.90
Lying in bed	1.30	0.61	1.02	0.97
Exercise	0.74	1.09	0.78	1.07
Breathing	0.52	1.23	0.52	1.20
While resting	–	–	1.02	0.97
Associated symptoms				
Regular rapid pounding sensation in neck	–	–	177	0.07
Neck fullness	–	–	0.85	1.04
Visible neck pulsations	–	–	2.68	0.87
Dizzy spells	0.93	1.08	1.34	0.67
Chest pain	0.81	1.07	0.92	1.02
Dyspnea	0.31	–	0.27	1.12
Vasovagal symp	–	–	1.72	0.63
Presyncope	–	–	1.04	0.95
Physical examination				
HR <60 or >100	–	–	3.00	0.78
Obesity	–	–	1.55	0.93
Hypertension	–	–	1.01	1.00

APPROACH—"while the presence of a regular rapid-pounding sensation in the neck or visible neck pulsations associated with palpitations makes the diagnosis of atrioventricular nodal reentry tachycardia likely, the reviewed studies suggest that the clinical examination is not sufficiently accurate to exclude clinically significant arrhythmias in most patients. Thus, prolonged electrocardiographic monitoring with demonstration of symptom-rhythm correlation is required to make the diagnosis of a cardiac arrhythmia for most patients with recurrent palpitations"

JAMA 2009 302:19

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, TSH, INR, PTT
- **IMAGING**—CXR, echocardiogram (enlarged left atrium)
- **ECG**
- **24-HOUR HOLTER**
- **EXERCISE STRESS TEST**

SPECIAL

- **ELECTROPHYSIOLOGY STUDIES**

ACUTE MANAGEMENT

ABC—O_2 to keep sat >95%, IV

SYNCHRONIZED CARDIOVERSION—premedicate if possible with *midazolam* 1–2 mg IV q2–3min, *fentanyl* 50–150 μg IV ×1, shock 50, 100, 200, 300, 360 J, prepare to intubate and give IV anti-arrhythmics PRN

ACUTE MANAGEMENT (CONT'D)

AV NODAL BLOCKING AGENTS ★ABCD★

- **AMIODARONE**—*amiodarone* 150 mg IV bolus over 10 min, q10–15 min. Alternatively, infusion 60 mg/h over 6 hours, then 30 mg/h over 18 h. Maximum 2.2 g/day
- **β-BLOCKERS**—*esmolol* 500 μg/kg IV over 1 min, maintenance dose 50–200 μg/kg/min IV, *metoprolol* 5 mg IV over 1 min q5min ×3 PRN
- **CALCIUM CHANNEL BLOCKERS**—*diltiazem* 15–20 mg IV over 2 min, repeat in 15min at 20–25 mg PRN, maintenance dose 5–20 mg/h IV; *verapamil* 2.5–5.0 mg IV over 1–2 minutes, followed by 5–10 mg in 15–30 minutes 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

ACUTE MANAGEMENT (CONT'D)

OVERALL APPROACH

- **UNSTABLE ATRIAL FIBRILLATION**—perform cardioversion immediately
- **STABLE ATRIAL FIBRILLATION <48 HOUR—rate control** (β-blockers, calcium channel blockers, digoxin) and consider **rhythm control** (DC cardioversion, amiodarone, propafenone, flecainide). Need to be anticoagulated for 4 weeks post-cardioversion
- **STABLE ATRIAL FIBRILLATION >48 HOUR OR UNKNOWN DURATION—rate control** (β-blockers, calcium channel blockers, digoxin) and consider **rhythm control** (IV heparin → TEE to exclude atrial thrombus → cardioversion within 24 h → anticoagulate ×4 weeks; ALTERNATIVELY anticoagulate ×3 weeks → cardioversion → anticoagulate ×4 weeks)
- **TREAT UNDERLYING CAUSE/PRECIPITANT**—infection, myocardial infarction, ischemia, drugs, pulmonary embolism, thyrotoxicosis

LONG-TERM MANAGEMENT

RATE CONTROL—aim for a resting heart rate <80 and exercise heart rate <110. **β-blocker** (*propranolol* 10–30 mg PO TID–QID, *metoprolol* 50–100 mg PO BID). **Calcium channel blockers** (*diltiazem CD* 120–480 mg PO daily). **Digitalis** (*digoxin* 0.5 mg PO ×1 dose, then 0.25 mg ×2 doses q6–12h, then 0.125–0.25 mg daily)

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* 80–160 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)

CLOT CONTROL—***ASA*** 81 mg daily if no other risk factors (see CHADS2). Otherwise, ***warfarin*** 5 mg PO daily within 72 hours and continue heparin until INR is between 2 and 3. Heparin is not required if no thrombosis

PROCEDURES—**radiofrequency ablation** of the pulmonary veins (PVI). Radiofrequency ablation of AV node with insertion of a permanent pacemaker and long-term anticoagulation as last resort. **Surgical** (corridor and maze procedures)

TREATMENT ISSUES

STROKE RISK FACTORS IN PATIENTS WITH ATRIAL FIBRILLATION ★CHADS2★

- **CHF** (any history, 1 point)
- **HYPERTENSION** (any history, 1 point)
- **AGE** >75 (1 point)

TREATMENT ISSUES (CONT'D)

- **DIABETES** (1 point)
- **STROKE OR TIA** (2 points)

- **RISK OF STROKE**—0 points=0.49%/year (lone AF), 1=1.5%, 2=2.5%, 3=5.3%, 4=6.0%, 5–6=6.9%
- **OTHER RISK FACTORS**—CAD, echocardiography abnormalities (atrial size >5 cm, LV dysfunction), rheumatic valve disease (RR 17). *All* mitral stenosis and HOCM patients with AF should have chronic anticoagulation
- **RISK REDUCTION**—anticoagulation decreases risk of stroke by ~60% (consider warfarin if CHADS2 score ≥1). ASA decreases risk by ~30%
- **RISK OF BLEEDING ON ANTICOAGULATION**—1.9% per year of major bleed. Thus, only recommend anticoagulation if risk of stroke ≥1.5% (i.e. at least one risk factor)

FACTORS INCREASING RISK OF BLEED WITH WARFARIN USE—advanced age (3–4% risk of significant bleeding per year if age >80), recent hemorrhage, uncontrolled hypertension, alcohol binge drinking or liver disease, cancer, renal insufficiency, low platelets, ASA/clopidogrel/NSAIDs (including COX-2 inhibitors). Note that risk of fall by itself is not a contraindication to warfarin use. Warfarin is teratogenic and should be avoided in pregnancy

IMPORTANT TOXICITIES OF AMIODARONE

- **CARDIAC** (5%)—sinus bradycardia and AV nodal block. QT prolongation leading to torsade de pointes may rarely occur
- **THYROID**—causes of hyperthyroidism (3%) include amiodarone-induced thyroiditis and Jod-Basedow phenomenon (excess iodine with amiodarone allows increased synthesis of T4 in patients with pre-existing toxic nodules). Patients on amiodarone may not develop classic symptoms of hyperthyroidism; however, recurrence of AF should prompt investigations. Hypothyroidism is more common (20%)
- **PULMONARY** (<3%)—chronic interstitial pneumonitis (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, grayish 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

NEJM 2007 356:9

Related Topics
ACLS (p. 431)
Digoxin (p. 38)
ECG (p. 62)
Wolff–Parkinson–White Syndrome (p. 65)

Syncope

See SYNCOPE (p. 312)

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)
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 ≥40% of arm circumference or length of bladder ≥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)
PSEUDOHYPERTENSION—false elevation of systolic blood pressure secondary to rigid arteries. The Osler's maneuver may be useful for determining the presence of pseudohypertension

BLOOD PRESSURE (CONT'D)

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's anomaly
- **CANNON A WAVE**—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

JUGULAR VENOUS PRESSURE (CONT'D)

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

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

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 6x, 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'S 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 impuse after S2)—constrictive pericarditis (up to 90%), tricuspid regurgitation

PRECORDIAL EXAMINATION (CONT'D)

- **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 is usually split

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

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

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

HEART SOUNDS (CONT'D)

High pitch sounds are best heard with the diaphragm, while low pitch sounds are best heard with the bell

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 heart 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

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 heart 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, aortopulmonary shunts
- **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 of RHD
- **PRE-SYSTOLIC**—mitral stenosis, tricuspid stenosis, atrial myxoma
- **CONTINUOUS MURMURS**—patent ductus arteriosus, arteriovenous fistula, aortopulmonary connection, venous hum, mammary souffle

MURMURS (CONT'D)

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
- **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

MURMURS (CONT'D)

DISTINGUISHING FEATURES AMONG COMMON SYSTOLIC AND DIASTOLIC MURMURS

	Systolic murmurs						Diastolic murmurs			
Findings[a]	**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's coliosis	Dyspnea	Normal	Dyspnea Sustained apex	Dyspnea Double apex	Normal	Dyspnea	**Mitral facies** Cyanosis Dyspnea	Argyll Robertson Marfan's Ank. spond
Radial pulse	Irregular (AF)	Normal	Irregular (AF)	Normal	**Brachioradial delay**	Brisk	Irregular (AF)	Normal	**Irregular** (AF)	**Waterhammer**
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 (pul. HTN), 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 (pul. HTN)	Absent a wave (AF) Prominent a wave (pul. HTN), cv wave (TR)	Normal
Palpation	Palpable P2 (pul. HTN), 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 (pul. HTN), thrill RV heave	RV heave Palpable P2 (pul. HTN)	Sustained, displaced apex, thrill LV heave
S1[b]	Soft	Normal	Soft	Normal	Normal	Normal	Wide splitting S1	Normal	**Loud S1**	Split (chronic) Absent (acute)
S2[b]	Loud (pul. HTN)	Normal	Normal	Normal	**Paradoxical split, soft**	Paradoxical split	Normal	Loud (pul. HTN)	**Palpable P2 (pul. HTN)**	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 **Low pitch** 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** (pul. HTN) 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 pul. HTN	**Pulmonary and tricuspid regurg. murmurs** (pul. HTN)	**Austin Flint murmur** (mid-diastolic over apex) Mid-systolic **flow** m. Other signs[f]

[a] Not all findings listed for each condition may be present on examination
[b] Loud heart sounds are usually due to mild-moderate stenotic lesions, while light heart sounds are usually due to regurgitant or severe stenotic lesions
[c] Regurgitant murmurs usually start early, while stenotic murmurs tend to start mid-way
[d] For mitral valve prolapse, maneuvers that increase murmur intensity also move both the click and murmur closer to S1
[e] For mitral stenosis, the murmur is classically described as mid-diastolic with presystolic accentuation
[f] All the following special signs for aortic regurgitation are related to increased pulse pressure. These include Quincke's pulses (pulsatile fingertips and lips), Becker's sign (pulsatile retinal artery), deMusset's sign (head bob), Mueller's sign (pulsatile uvula), Mayne's sign (DBP ↓ 15 mmHg), Ger-hard's sign (pulsatile spleen), Rosenbach's sign (pulsatile liver), Traube's sign (pistol shot pulse in femoral arteries), Duroziez's sign (femoral artery bruit with compression), Hill's 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 absence of any systolic murmur or murmur radiation to the right carotid artery reduces the likelihood of aortic stenosis"

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

MURMURS (CONT'D)

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"

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**"

MURMURS (CONT'D)

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"

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. Diastolic murmurs are always abnormal

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AORTIC REGURGITATION?

AORTIC REGURGITATION—"when a cardiologist hears the typical murmur of aortic regurgitation, the likelihood of mild or greater aortic regurgitation is increased significantly. The absence of a typical **diastolic murmur** significantly reduces the likelihood of aortic regurgitation"

MITRAL STENOSIS—"presence of a **mid-diastolic murmur** significantly increases the likelihood of mitral stenosis, while absence of a mid-diastolic murmur significantly reduces the likelihood of mitral stenosis"

PULMONARY REGURGITATION—"when a cardiologist hears a typical pulmonary regurgitation murmur, the likelihood of pulmonary regurgitation increases significantly. Absence of a typical murmur does not alter the likelihood of pulmonary regurgitation"

JAMA 1999 281:23

INVESTIGATIONS

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

Aortic Stenosis

ACC/AHA 2008 Guidelines
Lancet 2009 373:9667; NEJM 2002 346:9

DIFFERENTIAL DIAGNOSIS

VALVULAR

- **CONGENITAL MALFORMATIONS**—unicuspid, bicuspid, tricuspid
- **CALCIFICATION**—degenerative or senile, atherosclerosis, Paget's disease, chronic renal failure
- **INFECTIONS**—rheumatic fever, *Chlamydia pneumoniae*
- **RHEUMATOID ARTHRITIS**

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★

- **B**leeding (angiodysplasia + aortic stenosis + acquired vWD type IIa = Hedye's syndrome)
- **E**ndocarditis
- **E**mbolic 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

CLINICAL FEATURES (CONT'D)

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**—transthoracic
- **ECG**—left ventricular hypertrophy
- **EXERCISE TESTING**

SPECIAL

- **CARDIAC CATHETERIZATION**

DIAGNOSTIC AND PROGNOSTIC ISSUES

AORTIC VALVE AREA AND SEVERITY

- **NORMAL** = 3–4 cm^2
- **MILD** = 1.5–2 cm^2 or mean gradient <25 mmHg
- **MODERATE** = 1–1.5 cm^2 or mean gradient 25–40 mmHg
- **SEVERE** = <1 cm^2 or mean gradient >40 mmHg
- **SYMPTOMS**—usually do not appear until valve <1 cm^2. The significance of valve area depends on patient size (larger patient = more severe for same valve area)
- **PROGRESSION**—valve area decreases by ~0.1 cm^2/year and the mean gradient increases by 7 mmHg/year (particularly if cardiac risk factors)

PROGNOSIS OF AORTIC STENOSIS ★ASH★ (**A**ngina, **S**yncope, **H**eart 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). Statins may slow progression with early aortic stenosis

SEVERE OR SYMPTOMATIC AORTIC STENOSIS—**aortic valve replacement** (see criteria below), balloon valvuloplasty (offers no survival benefit and is only a temporizing measure)

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)

- **ABSOLUTE INDICATIONS**—severe aortic stenosis with any classic symptoms (angina, syncope, dyspnea) or with LV dysfunction, severe aortic stenosis and require CABG/surgery of aorta/other heart valves
- **POSSIBLE INDICATIONS**—moderate aortic stenosis and require CABG/surgery of aorta/other heart valves, asymptomatic severe aortic stenosis and one of hemodynamic instability during exercise, or ventricular tachycardia
- **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)

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 bioprosthesis 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 ACC/AHA 2008 Guidelines

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's, 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 systolic blood pressure 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's syndrome, ankylosing spondylitis, Argyll Robertson pupils, **Quincke's pulses** (capillary pulsations in the fingertips or lips), digital throb, **Becker's sign** (visible pulsations of the retinal arteries and pupils), **deMusset's sign** (head bob occurring with each heart beat), **Mueller's sign** (systolic pulsations of the uvula)
- **VITALS**—wide pulse pressure, **water hammer** (tapping impulse in forearm, especially when arm is raised vertically), **Corrigan's pulse, Mayne's sign** (>15 mmHg decrease in diastolic blood pressure with arm elevation)
- **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**—**Gerhard's sign** (systolic pulsations of the spleen), **Rosenbach's sign** (systolic pulsations of the liver), **Traube's sign** (pistol shot pulse with systolic and diastolic sounds heard over the femoral arteries), **Duroziez's sign** (systolic and diastolic bruit heard when the femoral artery is partially compressed), **Hill's 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**
Gender	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
- **ECHOCARDIOGRAM**
- **ECG**—LVH
- **EXERCISE TESTING**

SPECIAL

- **CARDIAC CATHETERIZATION**

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

LIFESTYLE CHANGES—salt restriction/diuretics

MEDICATIONS—afterload reduction with vasodilators (hydralazine, nifedipine, ACE inhibitors) 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.

FOLLOW-UP—asymptomatic mild AR with normal LV function and little/no LV dilatation can be followed annually with 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 2–3 years

PROCEDURES—**aortic valve replacement** if symptomatic; asymptomatic with end-systolic dimension >55 mm, end-diastolic dimension >75 mm, ejection fraction <50%; or asymptomatic severe aortic regurgitation at time of concomitant cardiac surgery. Intra-aortic balloon pumps should not be used

ANTIBIOTIC PROPHYLAXIS—not typically indicated unless aortic valve replacement or previous endocarditis

Mitral Stenosis ACC/AHA 2008 Guidelines; Circulation 2009 119:11

DIFFERENTIAL DIAGNOSIS

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

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

VALVE AREA—normal 4–5 cm^2, mild symptoms 1.5–2 cm^2 (mean gradient <5 mmHg), moderate symptoms 1–1.5 cm^2 (mean gradient 5–10 mmHg), severe symptoms <1 cm^2 (mean gradient >10 mmHg)

CLINICAL FEATURES

HISTORY—symptoms related to pulmonary hypertension (dyspnea, hemoptysis, chest pain), symptoms related to right heart failure (hepatomegaly, ascites, edema), hoarseness (Ortner's syndrome, due to enlarged left atrium compressing on recurrent laryngeal nerve), complications (endocarditis, thromboembolism), past medical history (rheumatic fever), medications

CLINICAL FEATURES (CONT'D)

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), 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) ± pre-systolic accentuation, tricuspid regurgitation
- **ABDOMINAL**—hepatomegaly, ascites, edema

INVESTIGATIONS

BASIC

- **CXR**—left atrial enlargement, splaying of carina
- **ECHOCARDIOGRAM**—TEE to exclude left atrial thrombus before treatment
- **ECG**—P mitrale, RVH

SPECIAL

- **CARDIAC CATHETERIZATION**

DIAGNOSTIC AND PROGNOSTIC ISSUES

MITRAL VALVE AREA AND SEVERITY

- **NORMAL** = 4–5 cm^2
- **MILD** = 1.5–2.5 cm^2 or mean gradient <5 mmHg
- **MODERATE** = 1–1.5 cm^2 or mean gradient 5–10 mmHg
- **SEVERE** = <1 cm^2 or mean gradient >10 mmHg
- **SYMPTOMS**—usually do not appear until valve <2.0 cm^2. Symptoms at rest appear when valve <1.5 cm^2. Onset of symptoms usually precipitated by exercise, emotional stress, infection, pregnancy, or rapid atrial fibrillation

PROGRESSION—~0.1–0.3 cm^2/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 to prolong diastolic filling (β-blockers, non-dihydropyridine calcium channel blockers). Anticoagulation for patients with concomitant atrial fibrillation, 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, mild mitral regurgitation, and no other cardiac interventions) is equivalent to **surgical valvuloplasty** in terms of success. Average increase in valve area is 1.0 cm^2

SPECIFIC ENTITIES

ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

- **PATHOPHYSIOLOGY**—group A *Streptococcus* infection → 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 ★J♥NES★**
    - **JOINT-MIGRATORY POLYARTHRITIS**
    - **♥CARDITIS** (pericarditis, myocarditis, valvulitis)
    - **NODULES** (subcutaneous)
    - **ERYTHEMA MARGINATUM**
    - **SYDENHAM CHOREA**
  - **MINOR CRITERIA**—clinical (fever, polyarthralgias), laboratory (↑ 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 prophylaxis for rheumatic fever (*penicillin G* 1.2 M U IM q4weeks, *penicillin V* 250 mg PO BID, or *erythromycin* 250 mg PO BID if allergic to penicillin). For patients with valve involvement, therapy should continue for at least 10 years after the last episode of rheumatic fever and to at least age 40. 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 — ACC/AHA 2008 Guidelines

DIFFERENTIAL DIAGNOSIS

VALVE ABNORMALITY—rheumatic heart disease, infective endocarditis, mitral valve prolapse, myxomatous degeneration, mitral annular calcification, ruptured chordae tendineae, drugs (fenfluramine)

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 apex

INVESTIGATIONS

BASIC

- **CXR**—cardiomegaly, LAE
- **ECHOCARDIOGRAM**
- **ECG**—P mitrale, LVH

SPECIAL

- **CARDIAC CATHETERIZATION**

MANAGEMENT

MEDICATIONS—no specific therapy for MR. 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

PROCEDURES—**mitral valve repair** (generally better outcome if technically possible) or **replacement** if symptomatic, atrial fibrillation, pulmonary hypertension, end-systolic dimension >40 mm, or ejection fraction 30–60%

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's anomaly). Rarely is it due to isolated tricuspid valve abnormality
- **CLINICAL FEATURES**—cachexia, jaundice, JVP cv wave, RV heave, S3 (with dilated RV), S4 (with stiff RV), holosystolic murmur (over left lower sternal border), hepatomegaly, edema
- **INVESTIGATIONS**—ECG (P pulmonale, RVH), CXR (cardiomegaly), echocardiogram, cardiac catheterization, rule out intracardiac shunts
- **TREATMENTS**—valve repair or replacement if severe symptoms

MITRAL VALVE PROLAPSE

- **PATHOPHYSIOLOGY**—autosomal dominant inherited 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**—*ASA* 75–325 mg PO daily for history of transient ischemic attacks, atrial fibrillation (age <65 years, no MR, no HTN, no HF). Anticoagulation with warfarin for atrial fibrillation (if age >65, MR, HTN, or HF), history of stroke/TIA, or left atrial thrombus

TWO SUBTYPES OF MITRAL VALUE 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 NEJM 2001 345:18

DIFFERENTIAL DIAGNOSIS

INFECTIVE ENDOCARDITIS

- **COMMON**—*Streptococcus viridans* (*S. sanguis*, *S. mutans*, *S. mitis*), *Streptococcus pneumoniae*, *Streptococcus bovis*, *Enterococcus* (*E. faecalis*, *E. faecium*), *Staphylococcus aureus*, Gram-negative bacilli
- **LONG INCUBATION TIME (7–21) DAYS ★HACEK★**
  - ***H****aemophilus*
  - ***A****ctinobacillus*
  - ***C****ardiobacterium*
  - ***E****ikenella*
  - ***K****ingella*
- **SPECIAL MEDIA**—*Mycoplasma*, *Chlamydia*, *Legionella*, *Brucella*, *Bartonella*, *Coxiella burnetii* (Q fever), *Histoplasma*, *Tropheryma whippelii*

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

PATHOPHYSIOLOGY

SUBTYPES—important to classify infective endocarditis 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. 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

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), 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

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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 positive blood culture ×1 for *C. burnetii*), 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 infarct, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions), **immunologic phenomena** (glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor), **positive blood culture** not meeting major criteria
- **DIAGNOSIS**—likely endocarditis if 2 major, 1 major plus 2 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 *Staphylococcus 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. 49)
Mitral Regurgitation (p. 51)
Tricuspid Regurgitation (p. 51)

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)—**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). ***S. aureus*** (*cloxacillin* 2 g IV q6h or *nafcillin* or *oxacillin* 3 g IV q6h or *cefazolin* 2 g IV q8h ×2–6 weeks (depending on right- or left-sided valve) ± *gentamicin* 1 mg/kg IV q8h ×3–5days: for native 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 is the most important indication. Other indications include perivalvular extension of infection, abscess, microbiologic failure, infection with fungi or untreatable pathogens, Staphylococci on a prosthetic valve, two major emboli events and one major embolus event with residual large mobile vegetation

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

- **HIGH-RISK CARDIAC CONDITIONS**—prosthetic cardiac valve, prosthetic material used for cardiac valve repair, unrepaired cyanotic congenital heart disease, completely repaired cyanotic congenital heart disease with residual defects at the site or adjacent to the site of the prosthetic device, cardiac transplant recipients with valvulopathy, previous endocarditis
- **PROCEDURES**
  - **ORAL CAVITY**—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
- **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, *cephalexin* 2 g PO, *clindamycin* 600 mg PO/IM/IV, *azithromycin* 500 mg PO, *clarithromycin* 500 mg PO

Peripheral Vascular Disease

NEJM 2007 356:12

DIFFERENTIAL DIAGNOSIS OF CLAUDICATION

ARTERIAL

- **ATHEROSCLEROSIS**
- **INTRALUMINAL OCCLUSION**—embolism, thrombosis, dissection, adventitial cystic disease, arterial fibrodysplasia, arterial tumor, occluded limb aneurysm
- **VASCULITIS**—Takayasu's arteritis, temporal arteritis, thromboangiitis obliterans
- **VASOSPASM**
- **DRUGS**—ergot

DIFFERENTIAL DIAGNOSIS OF CLAUDICATION (CONT'D)

- **FIBROSIS**—iliac endofibrosis, radiation fibrosis, retroperitoneal fibrosis
- **TRAUMA**

VENOUS—DVT, thrombophlebitis, venous congestion

NEUROPATHIC—spinal stenosis, peripheral neuropathy

OTHERS—arthritis (hips, knees), compartment syndrome

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), maximum walking distance, trauma, DVT risk factors, past medical history (CAD, HF, AF, stroke, TIA, renal disease, hypertension, cholesterol), medications

PHYSICAL

- **ANKLE BRACHIAL INDEX** (ABI)—>1.3 non-compressible calcified vessel, 0.90–1.3 normal, <0.90 indicates significant narrowing of one or more blood vessels in the legs, <0.8 intermittent claudication, <0.4 resting claudication, <0.25 severe limb-threatening peripheral vascular disease is probably present. An ABI that ↓ by 20% following exercise is diagnostic of peripheral vascular disease, while a normal ABI following exercise eliminates the diagnosis
- **BUERGER'S TEST**—abnormal pallor with elevation of leg 90° for 2 min and deep rubor when lowered for 2 min

CLINICAL FEATURES (CONT'D)

- **DEWEESE'S TEST**—disappearance of previously palpable distal pulses after walking exercise

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

JAMA 2006 295:5

CLINICAL FEAURES (CONT'D)

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, fasting lipids, HbA1C
- **ANKLE BRACHIAL INDEX**—with or without exercise
- **DUPLEX ULTRASOUND**
- **ECG**

SPECIAL

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

DIAGNOSTIC ISSUES

DIAGNOSTIC APPROACH—ABI <0.9 is sufficient for the diagnosis of peripheral arterial disease as it suggests >50% stenosis of peripheral vasculature (sens 90%, spc 98%). Patients with large vessel disease (distal aorta or iliac arteries) may only have abnormal ABI after exercise. Patients with non-compressible vessels should have toe-brachial index done. Perform duplex U/S or CT/MR angiogram if the diagnosis is uncertain or if revascularization is being considered. Digital-subtraction angiograph remains the gold standard

MANAGEMENT

RISK REDUCTION ★ABCDEFG★

- **ASA**
- **BLOOD PRESSURE CONTROL** (see HYPERTENSION p. 57)
- **CHOLESTEROL CONTROL** (see DYSLIPIDEMIA p. 61)
- **DIABETIC CONTROL** (see DIABETES p. 337)
- **EXERCISE** (30 min of moderate-intensity exercise 3–4×/week)
- **FAT REDUCTION** (see OBESITY ISSUES p. 403)
- **GET GOING TO QUIT SMOKING!** (see SMOKING ISSUES p. 418)

MEDICAL—**antiplatelet** (*ASA* 81–325 mg PO daily, dipyridamole, *clopidogrel* 75 mg PO daily, *cilostazol* 100 mg PO BID), **blood viscosity reducing agent** (*pentoxifylline* 400 mg TID) is of dubious benefit

SURGICAL—**revascularization** (surgery or percutaneous transluminal angioplasty)

TREATMENT ISSUES

REVASCULARIZATION—indicated for patients with significant functional limitations (lifestyle or jobs) despite maximal lifestyle and medical treatment. Not optimal for patients >40, 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 abd U/S for men 65–75 who have ever smoked. 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 >5 cm [>2 in.]

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ABDOMINAL AORTIC ANEURYSM?

PALPATION—to detect abnormal widening of the aortic pulsation (sens 50% for AAA 4–4.9 cm [1.6–1.9 in.], sens 76% for AAA ≥5 cm [≥2 in.], LR+ 12 and LR– 0.72 for AAA ≥3 cm [≥1.2 in.], LR+ 15.6 and LR– 0.51 for AAA ≥4 cm [≥1.6 in.])

APPROACH—"abdominal palpation will detect most AAAs large enough to warrant surgery, but it cannot be relied on to exclude the diagnosis. The sensitivity of palpation appears to be reduced by abdominal obesity. When a ruptured AAA is suspected, imaging studies such as ultrasound or computed tomography should be performed regardless of physical findings"

JAMA 1999 281:1

Hypertension

NEJM 2003 348:7; NEJM 2006 355:4; NEJM 2007 357:8

DIFFERENTIAL DIAGNOSIS

★0–1-2–3-4★

0 ESSENTIAL HYPERTENSION

1 ANATOMIC—aorta (coarctation, aortic dissection)

2 RENAL—renal parenchymal disease (chronic renal failure, polycystic kidney disease), renal artery stenosis

3 ADRENAL—pheochromocytoma, Conn's syndrome, Cushing's syndrome

4 SCENTS

- **SUPER GROWTH**—acromegaly
- **CALCIUM**—hypercalcemia
- **ESTROGEN OR OTHER DRUGS**—NSAIDs, steroids, oral contraceptives, cocaine, amphetamines, MAO inhibitors, erythropoietin, cyclosporin, tacrolimus, midodrine, alcohol excess
- **NEUROLOGIC**—Cushing's triad (hypertension, bradycardia and respiratory depression associated with increased intracranial pressure)
- **THYROID**—hyperthyroidism, hypothyroidism
- **SLEEP APNEA**

PATHOPHYSIOLOGY

CLASSIFICATION OF HYPERTENSION

- **MALIGNANT HYPERTENSION**—chronic marked hypertension with retinal hemorrhages, exudates, or papilledema
- **HYPERTENSIVE URGENCY**—>220/120 mmHg without findings of hypertensive emergency
- **HYPERTENSIVE EMERGENCY**—acute severe hypertension with end organ damage such as pulmonary edema, aortic dissection, myocardial infarction, cerebrovascular hemorrhage, papilledema, fundoscopic hemorrhages or exudates, and hypertensive encephalopathy

ISOLATED SYSTOLIC HYPERTENSION—younger people tend to have isolated diastolic hypertension (50–60% of patients under 40). With age, large arteries tend to stiffen with decreased elasticity secondary to a combination of atherosclerosis, calcification, and elastin degradation. Thus, isolated systolic hypertension predominates (over 90% of patients over 70)

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)
- **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

NEJM 2004 351:22

CLINICAL FEATURES

HISTORY—blood pressure levels, ambulatory/home monitoring, complications (ischemic heart disease, peripheral arterial disease, left ventricular hypertrophy, stroke, TIA, microalbuminuria or proteinuria, and chronic kidney disease), 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's), 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

MEASURING BLOOD PRESSURE—NEJM 2009 360:e6

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, creatinine, glucose, fasting lipid profile, CRP, urinalysis, urine microalbumin
- **24-HOUR AMBULATORY BLOOD PRESSURE MONITOR**
- **ECG**

INVESTIGATIONS (CONT'D)

SECONDARY CAUSES WORKUP

- **ENDOCRINE WORKUP**—Ca, albumin, TSH, serum renin/aldosterone, cortisol, 24-h urine metanephrine and creatinine, serum osmolality, urine osmolality, urine lytes, selective adrenal vein sampling
- **RENAL ARTERY STENOSIS WORKUP**—renal dopplers, captopril renogram, CT/MR angiogram, renal angiogram
- **SLEEP OXIMETRY TEST**—if suspect sleep apnea

DIAGNOSTIC ISSUES

CLINICAL DIAGNOSIS OF HYPERTENSION

1. **Hypertensive urgency or emergency during first visit?**
   - Yes=hypertension diagnosed
   - No=proceed to step 2
2. **What is blood pressure during second visit?**
   - BP ≥180/110 mmHg=hypertension diagnosed
   - BP 140–179/90–109 mmHg=proceed to step 3
   - BP <140/90 mmHg=continued follow-up
3. **Target organ damage, diabetes, or chronic kidney disease?**
   - Yes=hypertension diagnosed
   - No=proceed to step 4 for clinic patient, step 6 for ambulatory BP monitoring, or step 7 for home BP monitoring
4. **BP ≥160/100 mmHg during third visit?**
   - Yes=hypertension diagnosed
   - No=consider ambulatory BP monitoring (step 6) or proceed to step 5
5. **BP ≥140/90 mmHg during fourth or fifth visit?**
   - Yes=hypertension diagnosed
   - No=continue follow-up
6. **Ambulatory BP monitoring: mean awake BP ≥135/85 mmHg OR mean 24-h BP ≥130/80 mmHg?**
   - Yes=hypertension diagnosed
   - No=continue followup
7. **Home BP monitoring: average BP ≥135/85 mmHg?**
   - Yes=hypertension diagnosed
   - No=continue follow-up or proceed to ambulatory BP monitoring (step 6)

CHEP Guidelines 2009
http://www.hypertension.ca

ACUTE MANAGEMENT

ACUTE—ABC, O_2, 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/hr IV initially, titrate to a maximum of 15 mg/hr. *Fenoldopam* 0.1 μg/kg/min IV initially, titrate dose q15min. Consider ICU admission. Workup and treatment of underlying causes once stabilized

HYPERTENSIVE URGENCY—*furosemide* 20–40 mg PO/IV ×1 dose. *Nifedipine* 0.25–0.5 mg/kg PO q4–6h. *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. Workup and treatment of underlying cause once stabilized

ACUTE MANAGEMENT (CONT'D)

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×/week). **Reduction in alcohol** (<2 drinks/day in men and <1 drink/day in women). **Weight loss** (in those with BMI >25 kg/m^2, lose >5 kg). **Smoke free environment**

ANTIHYPERTENSIVES ★ABCD★

- **ACE INHIBITOR**—*ramipril* 2.5–10 mg PO daily-BID, *captopril* 12.5–50 mg PO TID, *perindopril* 2–8 mg PO daily, *lisinopril* 2.5–10 mg PO daily
- **ARB**—*candesartan* 8–32 mg PO daily, *losartan* 50–100 mg PO daily
- **β-BLOCKERS**—no longer first line agent for age >60. *Metoprolol* 50–100 mg BID, *atenolol* 50–100 mg PO daily, *labetalol* 100–400 mg PO TID, *bisoprolol* 5–10 mg PO daily
- **CALCIUM CHANNEL BLOCKERS**—*amlodipine* 2.5–10 mg PO daily, *diltiazem CD* 180–360 mg PO daily
- **DIURETICS**—*hydrochlorothiazide* 12.5–25 mg PO daily, *chlorthalidone* 25 mg PO daily, *spironolactone* 12.5–50 mg PO daily
- **α1 AGONISTS**—*clonidine* 0.1–0.5 mg PO BID, *terazosin* 1–20 mg PO daily
- **OTHERS**—minoxidil, phentolamine, hydralazine

TREAT UNDERLYING CAUSE—**renal artery stenosis** (angioplasty with stenting, nephrectomy of atrophic kidney ± endarterectomy)

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 (less with ARB), angioedema, hyperkalemia

TREATMENT ISSUES (CONT'D)

β-BLOCKERS

- **INDICATIONS**—resting tachycardia, HF, migraine, glaucoma, CAD/post-MI
- **CONTRAINDICATIONS**—asthma, severe PVD, Raynaud's 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, nicardipine, amlodipine, felodipine
- **NON-DIHYDROPYRIDINE** (heart rate control)—verapamil (cardiac depressant activity), diltiazem (some cardiac depressant, some vasodilator)
- **INDICATIONS**—angina pectoris, recurrent SVT (verapamil), Raynaud's 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)

TREATMENT ISSUES (CONT'D)

DIURETICS

- **INDICATIONS**—most patients, particularly those of African descent, edema, HF, elderly
- **CONTRAINDICATIONS**—allergy
- **ADVERSE EFFECTS**—↓ K, hyperuricemia, ↑ cholesterol, ↑ glucose, ↑ insulin resistance, impotence

BLOOD PRESSURE TREATMENT TRIGGERS AND TARGETS

	Blood pressure (mmHg)
When to start therapy?	
No macrovascular target organ damage	160/100
Macrovascular target organ damage or cardiovascular risk factors	140/90
What should the targets be?	
Diabetes, chronic kidney disease	<130/80
All others	<140/90

CHEP Guidelines 2009
http://www.hypertension.ca

OVERALL APPROACH TO CHOICE OF 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 blacks
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
BPH	α-blockers
Perioperative	B (if moderate to high risk)
Migraine	B
Thyrotoxicosis	B
Essential tremor	B
Postural hypotension	Avoid vasodilators and diuretics
Raynaud's	C (dihydropyridine)
Gout	D
Osteoporosis	D

TREATMENT ISSUES (CONT'D)

Condition	Drug of Choice
Hyperkalemia	A/B/C/D. Avoid aldosterone antagonists
Hyponatremia	A/B/C. Avoid D
Pregnancy	B/methyldopa/vasodilators. Avoid ACE inhibitors and ARB

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**—MR angiogram (preferred as non-invasive and high sensitivity/specificity), CT angiogram, duplex U/S (anatomic and functional information), captopril-enhanced radioisotope renogram (functional scan but out-of-fashion), contrast angiogram (gold standard)
- **TREATMENTS**—**medical** (risk factor reduction with emphasis on blood pressure control. ACE inhibitors/ARBs are particularly useful in renal artery stenosis, but should be used with caution in *severe bilateral* renal artery stenosis. Diuretics should be added if hypertension persists), **angioplasty** (consider if severe or refractory hypertension, recurrent flash pulmonary edema, acute significant decline in renal failure due to renal artery stenosis. Unlikely to reverse renal failure if small kidneys or high creatinine >300 μmol/L [3.4 mg/dL]), **surgery**

NEJM 2001 344:6

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, arterioportal 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?

	Sens	Spc	LR+	LR−
Systolic and diastolic abdominal bruit	39%	99%	39	0.6
Any epigastric or flank bruit, including isolated systolic bruit	63%	90%	6.4	0.4
Systolic bruit	78%	64%	2.1	3.5

APPROACH—"given the high prevalence (7–31%) of innocent abdominal bruits in the 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"

JAMA 1995 274:16

Related Topics
Aortic Dissection (p. 25)
Hyperaldosteronism (p. 349)
Pheochromocytoma (p. 349)

Hyperlipidemia

Canadian Cardiovascular Society Dyslipidemia Guidelines 2006

DIFFERENTIAL DIAGNOSIS OF HYPERCHOLESTEROLEMIA

PRIMARY—polygenic, familial (suspect when total cholesterol >6 mmol/L [>232 mg/dL], LDL >5 mmol/L [>193 mg/dL])

SECONDARY—obesity, diabetes, hypothyroidism, nephrotic syndrome, medications (estrogen, tamoxifen, β-blockers, glucocorticoids)

DIFFERENTIAL DIAGNOSIS OF HYPERTRIGLYCERIDEMIA

PRIMARY—dietary, familial (suspect when TGL >5 mmol/L [>440 mg/dL])

SECONDARY—obesity, diabetes, nephrotic syndrome, hypothyroidism, alcoholism, drugs (tamoxifen, cyclosporine, glucocorticoids)

DIFFERENTIAL DIAGNOSIS OF LOW HDL

PRIMARY

SECONDARY—obesity, smoking, inactivity

CLINICAL FEATURES

TELLTALE SIGNS

Lesions	I	IIa	IIb	III	IV	V
Tendon xanthoma (LDL)		✓				
Palmer xanthoma				✓		
Eruptive xanthoma	✓				✓	✓
Xanthelasma	✓	✓	✓	✓	✓	✓
Tuberous xanthoma (LDL)		✓	✓	✓		

INVESTIGATIONS

BASIC

- **LABS**—Cr, fasting glucose, TSH, total chol, TGL, LDL, HDL, apoB, Lp(a), CRP, CK, AST, ALT, ALP, bilirubin, LDH

MANAGEMENT

LIFESTYLE CHANGES—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). **Exercise**

RISK REDUCTION MEDICATIONS

- **RESINS** (↓ LDL, ↑ cholesterol synthesis)—*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)
- **HMG-COA REDUCTASE INHIBITORS** (↓ LDL)—*atorvastatin* 10–80 mg daily, *pravastatin* 10–40 mg daily, *rosuvastatin* 2.5–40 mg daily, *simvastatin* 10–80 mg daily. Main side effects include hepatotoxicity, myalgia and myopathy
- **FIBRATES** (↑ HDL, ↓ TGL)—*gemfibrozil* 600–1200 mg daily, *fenofibrate* 67–200 mg daily. Main side effects include GI upset, gallstones, and myalgia
- **NIACIN** (↓ LDL, ↑↑ HDL, ↓ TGL)—*nicotinic acid* 1–3 g. Main side effects include ↑ blood sugar; flushing, hepatotoxicity, and gastric irritation
- **ASPIRIN**—*ASA* 81 mg PO daily

TREAT SECONDARY CAUSES/METABOLIC SYNDROME IF PRESENT

TREATMENT ISSUES

TREATMENT TARGETS BASED ON RISK CATEGORY (CCS 2009 Guideline)

	High risk	Moderate risk	Low risk
LDL	<2 mmol/L [<77 mg/dL] or ≥50% ↓ LDL	<2 mmol/L [<77 mg/dL] or ≥50% ↓ LDL	≥50% ↓ LDL
ApoB	<0.80 g/L [<80 mg/dL]	<0.80 g/L [<80 mg/dL]	

TREATMENT ISSUES (CONT'D)

RISK CATEGORIES

- **HIGH**—≥20% 10-year Framingham risk or established CAD, diabetes, CVD, or PVD. All high risk patients require treatment
- **MODERATE**—10–19% 10-year CAD risk. Consider initiating treatment if LDL >3.5 mmol/L [135 mg/dL], TChol/HDL >5.0, high sensitivity CRP >2 mg/L, men age >50, women age >60, or significant family history
- **LOW**—<10% 10-year CAD risk. Consider initiating treatment if LDL ≥5.0 mmol/L [≥193 mg/dL]
- **UTILITY**—10-year risk calculation is based on Framingham study (gender, age, total chol, HDL, SBP, smoking)

SPECIFIC ENTITIES

METABOLIC SYNDROME (syndrome X or insulin resistance syndrome)—National Cholesterol Education Program's Adult Treatment Panel (ATC) III report criteria ≥3 of the following five features:

- ↑ **TGL**—≥1.7 mmol/L [≥150 mg/dL]
- ↓ **HDL**—♀ <1.3 mmol/L [<50 mg/dL], ♂ <1.0 mmol/L [<40 mg/dL]

SPECIFIC ENTITIES (CONT'D)

- **INSULIN RESISTANCE**—fasting glucose ≥5.6 mmol/L [≥110 mg/dL]
- **WAIST CIRCUMFERENCE**—♀ >88 cm [>35 in.], ♂ >102 cm [>40 in.]
- **HYPERTENSION**—≥130/85 mmHg or on treatment

Other features include hyperuricemia and prothrombotic state

FAMILIAL DYSLIPIDEMIA

Type	Mechanism	Lipid profile	Cardiac risk	Treatment(s)
Type I. Hyperchylomicronemia	lipoprotein lipase deficiency	↑ chylo, ↑↑ TAG	-	Low fat diet
Type IIa. Hypercholesterolemia	↓ LDL receptor. Tendon xanthoma is essential for diagnosis	↑ LDL, ↑ CE	↑↑	Resin, statin, niacin
Type IIb. Familial combined hyperlipidemia	↑ liver VLDL production	↑ VLDL, ↑ LDL, ↑ TAG, ↑ CE	↑	Resin, statin, niacin
Type III. Dysbetalipoproteinemia	apoE Δ. Classically associated with palmer xanthoma	↑ chylo-r, ↑ IDL, ↑ TAG, ↑ CE	↑	Niacin, statin
Type IV. Hypertriglyceridemia	↑ hepatic VLDL production	↑ VLDL, ↑ TAG	↑	Low fat diet, weight loss, fibrate, statin, niacin
Type V. Mixed hypertriglyceridemia	↑ production and ↓ clearance VLDL/chylo	↑ VLDL, ↑ chylo, ↑↑ TAG, ↑ CE	-	Low fat diet, niacin, statin

Smoking Issues

See SMOKING ISSUES (p. 418)

Approach to ECG

AHA/ACCF/HRS 2009 Recommendations
Circulation 2007 115:10
Circulation 2009 119:10

TEN STEPS TO ECG

1. **ID**—name and age, date, technique (12 lead, calibration, paper speed)
2. **RATE**—normal 60–100 beats/min. 300/150/100/75/60/50 rule
3. **RHYTHM**—regular/irregular, wide/narrow complex, sinus, atrial, atrioventricular, ventricular
4. **AXIS**—deviation, rotation
5. **PR INTERVAL**—normal 120–200 ms; first, second, third degree AV block
6. **QRS INTERVAL**—normal 80–110 ms, intraventricular conduction delay 110–120 ms, RBBB, LBBB, LAHB, LPHB
7. **QT INTERVAL**—QT <50% of RR interval; normal QTc 390–460 ms (women), 390–450 ms (men)

TEN STEPS TO ECG (CONT'D)

8. **HYPERTROPHY/ENLARGEMENT**—RAE, LAE, RVH, LVH
9. **ISCHEMIA**—ST elevation/depression, T wave inversion
10. **INFARCTION**—Q waves
11. **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 II+III, 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 (rate 300, 150, 100, 75, 60), supraventricular tachycardia (atrial tachycardia, AV nodal reentry, AV reentrant/WPW orthodromic conduction), 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, accelerated idioventricular rhythm, regular narrow complex tachycardia with aberrant conduction, pacemaker-mediated tachyarrhythmia, WPW with antidromic conduction
IRREGULAR WIDE COMPLEX TACHYCARDIA—coarse ventricular fibrillation, polymorphic ventricular tachycardia, atrial fibrillation with WPW (anterograde conduction), irregular narrow complex tachycardia with aberrant conduction
DISTINGUISHING FEATURES SUGGESTIVE OF VT RATHER THAN SVT WITH ABERRANT CONDUCTION—older age, history of coronary artery disease, AV dissociation (dissociated P waves, fusion beats, capture beats), concordance of precordial leads, QRS width >160 ms in LBBB or >140 ms in RBBB, atypical BBB, extreme LAD (–90° to –180°)

BRADYCARDIA AND PROLONGED PR

SINUS—sinus bradycardia, sick sinus syndrome with sinus pause, bradycardia–tachycardia syndrome (SSS+AF usually)
AV BLOCK—prolonged PR interval

- **FIRST DEGREE**—PR >200 ms constantly
- **SECOND DEGREE**
  - **MOBITZ TYPE I** (Wenckebach)—PR progressively longer and then dropped QRS
  - **MOBITZ TYPE II**—PR constant and then sudden dropped QRS. When any but not all ventricular beats are dropped, second degree block exists
- **THIRD DEGREE**—complete blockage with independent atrial and ventricular rhythms

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 monomorphic R in I 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 HEMIBLOCK—QRS 100–120 ms, left axis deviation –30° to –90°, qR in I, rS in III, II, and aVF. May be benign, LAD involvement/anterior infarction. Shortcut to diagnosis—I up, II down, aVF down
LEFT POSTERIOR HEMIBLOCK—right axis deviation 90–180°, normal or slightly widened QRS, rS in I, and qR in III. RCA involvement/anterior infarction
BIFASCICULAR BLOCK—RBBB+LAHB, RBBB+LPHB
TRIFASCICULAR BLOCK—first degree AV block + bifascicular block

PROLONGED QT

NORMAL—QTc=square root (QT in seconds/RR interval in seconds); QT <50% of RR interval; normal QTc 390–460 ms (women), 390–450 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 evolve into torsade de pointes, VT, and sudden death (amiodarone less likely)
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
LAE—wide notched P in II (>2.5 mm long); biphasic P in V1 with broad negative phase; P wave duration >120 ms
LVH—tall R in aVL (>11 mm); R in V5 or V6 (whichever is taller) plus S in V1 >35 mm; R in V5 or R in V6 >27 mm; poor R wave progression in precordial leads;

HYPERTROPHY CRITERIA (CONT'D)

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 behavior between aVL + III

PRINZMETAL'S 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

LV ANEURYSM—persistent ST elevation after MI

PULMONARY EMBOLISM—changes simulating MI seen often in both inferior and anteroseptal leads

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), disconcordant ST-segment changes (ST elevation ≥5 mm in leads with negative QRS complex)

LVH—concave, other features of LVH

HYPERKALEMIA—see below

HYPOTHERMIA—Osborne waves may be seen

NEJM 2003 349: 22

INFARCTION ZONES

Territory	Leads	Artery	Comment
Inferior	II, III, aVF[a]	RCA, LAD[b]	RV, SA, AV nodes
Lateral	I, aVL, V5, V6	LCX, RCA	
Posterior	V1i, V2i, V8, V9[c]	RCA	
Anterior	V1–V4[d]	LAD	Massive LV
RV	R leads (V1), V4R	RCA	Preload

[a]evidence of inferior MI should trigger one to automatically check V4R to assess 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

[b]inferior 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)

[c]i=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

[d]V1-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, bidirectional VT

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), widen QRS, wide and flat P wave

HYPOKALEMIA—flattened T wave/inversion, U wave

SPECIAL CONDITIONS (CONT'D)

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 (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

Notes

3
NEPHROLOGY
Section Editor: Dr. Alan McMahon

Acute Renal Failure: Pre-renal
NEJM 2007 357:8

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**

RENAL HEMODYNAMICS
- **AFFERENT**—renal artery stenosis (RAS), renal vein thrombosis, fibromuscular dysplasia, ASA, NSAIDs, cyclosporin, tacrolimus, cocaine, hypercalcemia (vasospasm)
- **EFFERENT**—ACE inhibitors, ARB

PATHOPHYSIOLOGY

RISK FACTORS—patients with advanced age, hypertension, chronic kidney disease and renal artery stenosis, or on medications (NSAIDs, ACE inhibitors, ARBs) are particularly susceptible to ischemic insults due to impaired autoregulation

Related Topic
Renal Artery Stenosis (p. 57)

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, Ca, urinalysis, urine lytes, urine Cr
- **MICROBIOLOGY**—blood C&S, urine C&S

SPECIAL
- **RENAL ARTERY STENOSIS WORKUP**—renal dopplers, captopril renogram, CT/MR renal angiogram (use with caution in renal failure)

DIAGNOSTIC ISSUES

COCKCROFT–GAULT FORMULA
- **CREATININE CLEARANCE (SI UNITS)**—CrCl=(140−age) ×(weight in kg)/(Cr in μmol/L), multiply by 1.2 if male
- **CREATININE CLEARANCE (US UNITS)**—CrCl=(140−age) ×(weight in lbs ×0.37)/(Cr in mg/dL×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×10) >Cr in μmol/L [or in US units: (urea in mg/dL/20) >Cr in mg/dL]. Urea reabsorption increases during pre-renal failure, resulting in a disproportionally high serum urea level
- **10–20–30 RULE**—urine Na^+ <10 mmol/L or Cl^- <20 mmol/L and K^+ >30 mmol/L
- **FENA**—$(U_{na}/P_{na})/(U_{cr}/P_{cr})$ x100%, <1%
- **URINALYSIS**—bland, high specific gravity

DISTINGUISHING FEATURES BETWEEN PRE-RENAL FAILURE AND ATN

	Pre-renal	ATN
Urea:Cr ratio (SI)	(Urea × 10) >Cr	(Urea × 20) <Cr
Urea:Cr ratio (US)	Urea >(Cr × 20)	Urea <(Cr × 10)
Increase in Cr	Variable	<44 μmol/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

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_3,

MANAGEMENT

TREAT UNDERLYING CAUSE—fluid resuscitation (**NS** 0.5–1 L IV bolus over 2–4 h), then 100–200 mL/h with frequent volume reassessments

RENAL REPLACEMENT—dialysis (peritoneal, hemodialysis). If needed, usually temporary

TREATMENT ISSUES

CRITERIA FOR DIALYSIS IN ACUTE RENAL FAILURE

★AEIOU★

- **ACIDOSIS**—persistent despite medical treatment
- **ELECTROLYTES**—persistent severe hyperkalemia despite medical treatment
- **INTOXICATION**—ASA, Li, methanol
- **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's
- **HYPERTENSION**—chronic

TUBULAR

- **ACUTE TUBULAR NECROSIS (ATN)**—ischemia, 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, sulfonamide, rifampin, NSAIDs, diuretics
- **INFECTIONS**—pyelonephritis
- **INFILTRATE**—Sjogren's, sarcoidosis
- **IDIOPATHIC**

GLOMERULAR

- **NEPHROTIC**—MCD, MGN, FSGS, MPGN-I rarely if ever cause acute renal failure on their own
- **NEPHRITIC**—IgA, MPGN-II, mesangial proliferative GN, RPGN
  - **ANTI-GBM ANTIBODY**—Goodpasture's, anti-GBM antibody nephritis
  - **IMMUNE COMPLEX**—SLE, HBV, HCV, endocarditis, post-strep/infectious GN, IgA, cryoglobulinemia, shunt nephritis
  - **PAUCI-IMMUNE**—Wegener's, Churg–Strauss, microscopic polyarteritis

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 (recent infections, HBV, HCV, HF, diabetes, hypertension, malignancy, connective tissue disease), medications (ACE inhibitors, ARB, NSAIDs, ASA, cyclosporine, penicillins, cephalosporins, acyclovir, amphotericin)

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. 70)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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, urine eosinophils
- **MICROBIOLOGY**—blood C&S, urine C&S if suspect infection
- **IMAGING**—U/S renal

SPECIAL

- **IMAGING**—CXR, echocardiogram
- **SPECIAL**—renal biopsy

INVESTIGATION ISSUES

DISTINGUISHING FEATURES BETWEEN VARIOUS RENAL ETIOLOGIES

	Urinalysis	Other tests
Vascular	Bland	Peripheral smear (TTP)
	Urinary eosinophils (cholesterol emboli)	p-anca (PAN)
		ANA, ENA (lupus)
Tubular	Muddy brown casts (ATN)	CK (rhabdomyolysis)
		Uric acid (gout)
Interstitial	WBC casts, urinary eosinophils	Systemic eosinophilia
Glomerular	RBC casts	c-anca (Wegener's)
	Acanthocyte (dysmorphic RBC)	p-anca (PAN)
	Oval fat body	Eosinophilia (Churg-Strauss)
	Fatty cast	Anti-GBM (Goodpasture's 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 (hypercalcemia)
- **RENAL**—secondary amyloidosis (λ), light chain deposition disease (κ), myeloma kidney (tubulointerstitial damage due to increased light chain absorption through proximal tubule), Bence Jones/cast nephropathy, plasma cell infiltration, cryoglobulinemia, pyelonephritis, sepsis
- **POST-RENAL**—renal stones (hypercalcemia), neurogenic bladder

NSAIDS-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 → 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 and oxygen free radical generation → acute 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, 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, and volume depletion if possible. If contrast absolutely required, use low (iohexol) or iso-osmolal (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 *or* $NaHCO_3$ 154 mmol/L at 3 mL/kg/h starting 1 h

SPECIFIC ENTITIES (CONT'D)

before until 6 h after contrast exposure; (3) IV *N-acetylcysteine* 150 mg/kg in 500 mL 0.9% NS given 30 min before contrast exposure, followed by 50 mg/kg in 500 mL 0.9% NS IV given over 4 h after (alternatively, *N-acetylcysteine* 600 mg PO BID on day of and day after contrast exposure)

Acute Renal Failure: Post-renal

DIFFERENTIAL DIAGNOSIS

URETHRA—stricture, stenosis
PROSTATE—BPH, prostatitis, cancer
BLADDER—cancer, stones, clots, neurogenic
URETERS (bilateral involvement)
- **INTRALUMINAL**—cancer, stones, clots, papillary necrosis
- **EXTRALUMINAL**—cancer, retroperitoneal fibrosis, pregnancy

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, Cr/urea, urinalysis
- **IMAGING**—U/S abd/pelvis

INVESTIGATIONS (CONT'D)

SPECIAL
- **POST-RESIDUAL VOLUME**—>200 mL suggests obstruction
- **CT ABD/KUB/IVP**—if suspect stones or tumors
- **DIURESIS RENOGRAPHY OR UROGRAPHY**

DIAGNOSTIC ISSUES

RENAL U/S—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

PATHOPHYSIOLOGY OF GLOMERULOPATHIES (CONT'D)

PATHOLOGY TERMS—**focal**=<50% of glomeruli, **diffuse**=>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's syndrome
Recurrent gross hematuria	Thin basement membrane disease, IgA nephropathy, Alport's 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 ≠ nephrotic range proteinuria (proteinuria >3 g/day without other symptoms and signs)

NEPHROTIC SYNDROME

DIFFERENTIAL DIAGNOSIS—minimal change disease, membranous GN, focal segmental glomerulosclerosis, membranoproliferative GN, diabetes, amyloidosis, IgA nephropathy, HIV, drug-associated (NSAIDs, gold, pamidronate)

CLINICAL FEATURES—proteinuria (>3 g/day), edema, hypoalbuminemia, hyperlipidemia, lipiduria, hypercoagulopathy

INVESTIGATIONS—CBCD, lytes, urea, Cr, 24-h urine for protein and Cr, spot urine protein/Cr ratio, renal biopsy (simplification/effacement of visceral podocyte foot processes, classically non-inflammatory)

POOR PROGNOSTIC FACTORS—male, age >50, ↑ creatinine, proteinuria >10 g/day, proteinuria >6 months, hypertension

TREATMENTS—Na restriction, blood pressure control, ACE inhibitor, treatment of dyslipidemia, steroid, cyclophosphamide, anticoagulate if high risk

COMPLICATIONS—ARF/hypovolemia, malnutrition, hyperlipidemia, infections (especially encapsulated bacteria), arterial/venous thrombosis (30–40%), renal vein thrombosis, edema

NEPHRITIC SYNDROME

DIFFERENTIAL DIAGNOSIS—membranoproliferative GN (type 2), rapidly progressive/crescentic GN (αGBM, immune, pauci-immune), IgA nephropathy

CLINICAL FEATURES—hematuria, proteinuria, hypertension

INVESTIGATIONS—CBCD, lytes, urea, Cr, ANA, anti-dsDNA, ENA, p-anca, 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

NEPHRITIC SYNDROME (CONT'D)

SPECIFIC ENTITIES

MINIMAL CHANGE DISEASE (MCD)

- **PATHOPHYSIOLOGY**—T-cell abnormality → ↑ glomerular permeability
- **CAUSES**—primary, secondary (NSAIDs, Li, interferon, NHL, Hodgkin's, 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, cyclosporin
- **PROGNOSIS**—90% steroid responsive, 10% steroid resistant, end-stage renal disease rare

MEMBRANOUS GN (MGN)

- **CAUSES**—primary, secondary (gold, penicillamine, captopril, solid tumors including breast, colon, and lung, Hodgkin's, 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, cyclosporin

SPECIFIC ENTITIES (CONT'D)

- **PROGNOSIS**—40% remission, 30% stable, 30% end-stage renal disease over 10–20 years

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS) (more severe form of **MCD)**

- **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, cyclophosphamide, cyclosporin
- **PROGNOSIS**—large percentage with end-stage renal disease over 15–20 years

MEMBRANOPROLIFERATIVE GN (MPGN)

- **PATHOPHYSIOLOGY**—type 1 = immune complex deposition disease. Type 2 = activation of complement system via C3 nephritic factor (IgG against C3 convertase), with decreased C3 and normal C4
- **CAUSES**—primary, secondary type 1 (HCV, HBV, endocarditis, abscess, infected shunts, CLL, lymphomas, SLE, cryoglobulinemia), secondary type 2 (partial lipodystrophy, sickle cell, complement deficiency)
- **CLINICAL FEATURES**—50% nephrotic (usually type 1), 20% asymptomatic proteinuria/hematuria, 30% acute nephritic (usually type 2)
- **PATHOLOGY**—light microscopy (basement membrane thickening, mesangial cell hypercellularity), immunofluorescence (complements along capillary walls), electron microscopy (type 1 shows discrete deposits in mesangium, type 2 shows deposits as continuous ribbon in glomerular basement membrane)
- **TREATMENTS**—steroid, cyclophosphamide, cyclosporin
- **PROGNOSIS**—40–75% end-stage renal disease over 10–15 years

RAPIDLY PROGRESSIVE GN (RPGN)—ANTI-GLOMERULAR BASEMENT MEMBRANE ANTIBODY DISEASE

- **PATHOPHYSIOLOGY**—antibody against $\alpha 3$ chain of type IV collagen
- **CAUSES**—Goodpasture's syndrome, anti-GBM antibody nephritis
- **CLINICAL FEATURES**—nephritic (hematuria, proteinuria, ARF). 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 for 1 year

RAPIDLY PROGRESSIVE GN (RPGN)—IMMUNE COMPLEX

- **PATHOPHYSIOLOGY**—deposition of circulating immune complex in glomeruli, usually in subendothelial location
- **CAUSES**—SLE, HBV, HCV, endocarditis, post-strep GN, post-infectious GN, IgA nephropathy, cryoglobulinemia, shunt nephritis
- **CLINICAL FEATURES**—nephritic (hematuria, proteinuria, ARF)
- **PATHOLOGY**—immunofluorescence (granular staining)
- **TREATMENTS**—IV pulse steroids followed by PO steroids with IV monthly cyclophosphamide for 1 year

RAPIDLY PROGRESSIVE GN (RPGN)—PAUCI-IMMUNE COMPLEX

- **CAUSES**—Wegener's (c-anca), microscopic polyangiitis (p-anca), Churg–Strauss
- **CLINICAL FEATURES**—nephritic (hematuria, proteinuria, ARF). May have lung involvement
- **PATHOLOGY**—immunofluorescence (no staining)
- **TREATMENTS**—IV pulse steroids followed by PO steroids with PO cyclophosphamide for 1 year

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 (HSP, 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 ARF or severe symptoms

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—ACE inhibitor may slow progression. Steroids, cytotoxic agents
- **PROGNOSIS**—20–40% end-stage renal disease over 20 years

Related Topics
Acute Renal Failure (p. 68)
Chronic Kidney Disease (p. 73)

Chronic Kidney Disease

NEJM 2007 357:13

DIFFERENTIAL DIAGNOSIS

CAUSES OF ACUTE RENAL FAILURE—pre-renal, renal, post-renal (see ACUTE RENAL FAILURE p. 68)

CHRONIC KIDNEY DISEASES

- **RENOVASCULAR DISEASE**—atherosclerosis, hypertensive nephropathy, glomerulosclerosis (with age)
- **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

CLASSIFICATION OF CHRONIC KIDNEY DISEASE

- **STAGE I** (GFR 90–100 mL/min/1.73 m^2, proteinuria)—observe, consider ACE inhibitor
- **STAGE II** (GFR 60–90 mL/min/1.73 m^2)—consider ACE inhibitor, nephrology referral
- **STAGE III** (GFR 30–60 mL/min/1.73 m^2)—nephrology referral
- **STAGE IV** (GFR 15–30 mL/min/1.73 m^2)—consider renal replacement therapy (dialysis or transplantation)
- **STAGE V** (GFR <15 mL/min/1.73 m^2)—dialysis, transplantation, or palliation

RISK FACTORS FOR CHRONIC KIDNEY DISEASE DEVELOPMENT AND PROGRESSION—old age, hypertension, proteinuria (not just a surrogate marker), high-protein diet, dyslipidemia

CLINICAL FEATURES

SIGNS AND SYMPTOMS OF CHRONIC KIDNEY DISEASE

- **VOLUME OVERLOAD**
- **ELECTROLYTE/ACID–BASE BALANCE**—hyperkalemia
- **METABOLIC ACIDOSIS**
- **NORMOCYTIC ANEMIA**

CLINICAL FEATURES (CONT'D)

- **CALCIUM/PHOSPHATE BALANCE**—↓ $1,25(OH)_2$ vitamin D3 synthesis in kidney, ↑ PO_4 due to decreased filtration → ↓ Ca → ↑ PTH → renal osteodystrophy (**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)
- **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**—CBCD, lytes, urea, Cr, glucose, HbA1C, Ca, PO_4, 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

DIAGNOSTIC ISSUES

DISTINGUISHING FEATURES BETWEEN CHRONIC AND ACUTE RENAL FAILURE —previous creatinine (>3 months of elevated creatinine suggests CKD),

DIAGNOSTIC ISSUES (CONT'D)

anemia, small kidneys from renal U/S (except diabetes, amyloidosis, acromegaly, renal vein thrombosis, HIV nephropathy), renal osteodystrophy are all 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)
- **LIPID CONTROL**
- **AVOID NEPHROTOXINS**
- **SMOKING CESSATION**
- **TREAT DIABETES MELLITUS**

TREAT COMPLICATIONS

- **VOLUME OVERLOAD**—low-sodium diet, diuretics
- **HYPERKALEMIA** (K >5.5 mmol/L)—low-potassium diet, *hydrochlorothiazide* 12.5 mg PO daily, *kayexalate* 30 g PO daily-QID, decrease ACE inhibitor
- **METABOLIC ACIDOSIS**—consider $NaHCO_3$ if low pH or HCO_3
- **ANEMIA** (Hb <100 g/L [Hb <10 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 qhs, goal to keep Hb 100–120 g/L [10–12 g/dL]
- **CALCIUM/PHOSPHATE BALANCE**—keep Ca normal, PO_4 <1.5 mmol/L [<4.6 mg/dL], PTH <2–3× normal, dietary phosphate restriction, phosphate binder *$CaCO_3$* 500 mg PO TID, *calcitriol* 0.25–1 μg PO daily, parathyroidectomy

RENAL REPLACEMENT—dialysis (peritoneal, hemodialysis), **renal transplant**

TREATMENT ISSUES

CRITERIA FOR DIALYSIS IN CHRONIC KIDNEY DISEASE—GFR <10 mL/min/1.73 m^2, CrCl <15 mL/min, Cr >1000 μmol/L [>11.3 mg/dL], urea >30 mmol/L [>83 mg/dL], albumin <35 g/L [<3.5 g/dL], uremic symptoms, any acute indications

TREATMENT ISSUES (CONT'D)

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

- **NORMOALBUMINURIA** (<30 mg/day)—lasts 8–10 years, treatment with glycemic/blood pressure/lipid control, smoking cessation
- **MICROALBUMINURIA** (30–300 mg/day)—lasts 5–10 years, same treatment as above plus ACE inhibitor, protein restriction
- **OVERT NEPHROPATHY** (>300 mg/day)—CrCl declines by 2–20 mL/min/year, same treatment as above
- **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. 68)
Diabetes Mellitus (p. 337)
Glomerulonephritis (p. 70)
Hypertension (p. 57)
Multiple Myeloma (p. 178)
Polycystic Kidney Disease (p. 76)

Proteinuria

DIFFERENTIAL DIAGNOSIS

FUNCTIONAL (<1 g/day)—infection, fever, exercise, orthostatic

TUBULAR (0.5–1 g/day)—interstitial nephritis, ATN

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

INVESTIGATIONS

BASIC
- **LABS**—CBCD, 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
- **SULFOSALICYLIC ACID TEST**—detects all proteins
- **SPOT PROTEIN/CR RATIO** (SI Units)—to estimate daily protein excretion in mg

  ♂=ratio×0.14–0.16 mg/kg/day×weight in kg
  ♀=ratio×0.18–0.20 mg/kg/day×weight in kg

INVESTIGATIONS (CONT'D)

- **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

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 NEJM 2003 348:23

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 II, RPGN, IgA nephropathy (see GLOMERULOPATHIES p. 70)
- **HEREDITARY DISORDERS**—Alport's 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

CLINICAL FEATURES (CONT'D)

exercise, urinary tract infections (dysuria, frequency), last menstrual period, past medical history (tumors, renal stones, cystic kidney disease, lupus, Alport's syndrome), medications (ASA, NSAIDs, anticoagulants)
PHYSICAL—vitals (particularly blood pressure), check hearing, abdominal examination (cystic kidney)

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, INR, PTT, urinalysis, urine C&S, urine cytology
- **IMAGING**—KUB, U/S abd, IVP, CT abd

SPECIAL
- **CYSTOSCOPY**—if suspect extra-glomerular bleed
- **KIDNEY BIOPSY**—if suspect glomerular pathology
- **URINE TESTS**—24-h urine calcium, oxalate, and urate

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's syndrome, thin basement membrane disease, Loin pain-hematuria syndrome

ALPORT'S SYNDROME

- **PATHOPHYSIOLOGY**—X-linked defect in α5 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 α3 or α4 chain)
- **CLINICAL FEATURES**—hematuria without proteinuria. Normal GFR

Related Topics
Glomerulonephritis (p. 70)
Polycystic Kidney Disease (p. 76)

Cystic Kidney Diseases

CAUSES

SIMPLE CYST
MALIGNANT CYST
AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE
MEDULLARY SPONGE KIDNEY
MEDULLARY CYSTIC KIDNEY DISEASE

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, Cr/urea, urinalysis
- **IMAGING**—U/S 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**%), 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 $<$30, $>$2 cysts; age 30–60, 2 cysts in each kidney; age $>$**60,** $\geq$4 cysts in each kidney)
- **TREATMENTS**—blood pressure control, ACE inhibitors, dialysis if end-stage renal disease

NEJM 2008 359:14

MEDULLARY CYSTIC KIDNEY DISEASE

- **PATHOPHYSIOLOGY**—genetic abnormality with diffuse tubulointerstitial cysts at corticomedullary border
- **CLINICAL FEATURES**—symptoms include hematuria and hypertension. Frequently progress to end-stage renal disease by age 20–50
- **TREATMENTS**—dialysis if endstage 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
- **DIAGNOSIS**—U/S renal every 6–12 months to help distinguish from cystic malignancy

Metabolic Acidosis

DIFFERENTIAL DIAGNOSIS

ANION GAP (NORMOCHLOREMIC)

- ★**MUDPILE CATS**★
  - **METHANOL**
  - **UREMIA**
  - **DKA**
  - **PARALDEHYDE**
  - **INH AND IRON**
  - **LACTIC ACIDOSIS**
  - **ETHYLENE GLYCOL**
  - **CYANIDE**
  - **ARSENIC**
  - **TOLUENE**
  - **SALICYLATES**
- ★**KULT**★
  - **KETONES**
  - **UREMIA**
  - **LACTIC ACIDOSIS**
  - **TOXINS**

NON-ANION GAP (HYPERCHLOREMIC)

- **HCL GAIN**—drinking HCl
- **HCO_3 LOSS**—**renal** (proximal RTA, acetazolamide), **GI** (diarrhea, ostomy loss)
- ↓ **HCO_3 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**—CBCD, 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. 104)
Overdose (p. 102)
Respiratory Acidosis (p. 18)
Respiratory Alkalosis (p. 18)

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 PCO_2 or HCO_3, irrespective of pH, that may result in acidemia/alkalemia, respectively
   - **Metabolic**—initiated by change in HCO_3
   - **Respiratory**—initiated by change in PCO_2
3. **Check compensation**

	Primary Change	Compensation
	HCO_3	**pCO_2**
MAc	↓ 10	↓ 10–13
MAlk	↑ 10	↑ 5–7
	pCO_2	**HCO_3**
RAlk	↓ 10	↓ 5 (chronic) 2 (acute)
RAc	↑ 10	↑ 3 (chronic) 1 (acute)

Normal pCO_2 = 40 mmHg, HCO_3 = 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 – HCO_3; normal is between 8 and 12 mmol/L
   4a. If anion gap metabolic acidosis, calculate osmolar gap to differentiate between causes **OSMOLAR GAP** = (**G**lucose + **U**rea + $\mathbf{Na}^+ \times 2$) – observed osmolality ★**GUN2**★ (see p. 104 for more details)
   4b. Calculate "delta ratio" (also known as "delta-delta") to check for any superimposed metabolic disorder
   $\Delta AG/\Delta HCO_3 = (AG - 10)/(24 - HCO_3)$

$\Delta AG/\Delta HCO_3$	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
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

DIAGNOSTIC ISSUES (CONT'D)

5. **Any superimposed respiratory disorder?** After adjusting pCO_2 to account for HCO_3 changes (see compensation table above), is there evidence of hypoventilation (↑ pCO_2) or hyperventilation (↓ pCO_2)?

MANAGEMENT

ACUTE—ABC, O_2, IV, intubation, $NaHCO_3$ 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)—urine Na + K − Cl. A negative UNC suggests unmeasured cation, implying that NH_4^+ is present (i.e. type II RTA, not type I RTA). In the presence of acidosis, UNC should be negative (i.e. NH_4^+ present). Therefore, look for GI losses (neGUTive)

RENAL TUBULAR ACIDOSIS - TYPE I (distal)

- **PATHOPHYSIOLOGY**—inability to make NH_4^+. Causes include **H^+/ATPase mutation** (associated with hypokalemia), **back leakage of hydrogen ions due to increased luminal membrane permeability** (Sjogren's syndrome, rheumatoid arthritis, amphotericin B, cirrhosis; associated with hyperkalemia) and **decreased distal tubular Na reabsorption resulting in reduced electrical gradient for proton secretion** (obstructive uropathy, sickle cell anemia; associated with hyperkalemia). Urine pH elevated because of ↓ H^+ in urine. Serum K ↓ in most cases
- **DIAGNOSIS**—+ve UNC, urine pH relatively high despite metabolic acidosis
- **TREATMENTS**—treat underlying cause. HCO_3 and K supplement, or potassium citrate

SPECIFIC ENTITIES (CONT'D)

RENAL TUBULAR ACIDOSIS - TYPE II (proximal)

- **PATHOPHYSIOLOGY**—inability to reabsorb HCO_3 at the proximal tubule. Causes include **Fanconi's syndrome** (multiple myeloma, carbonic anhydrase inhibitor, ifosfamide), **genetic disorders** (Wilson's disease, cystinosis), **vitamin D deficiency,** and **renal transplant**
- **DIAGNOSIS**—low serum K, negative urine net charge. Confirmation is done by HCO_3 challenge → check urine pH every 2 h → measure serum HCO_3 level when urine pH >7 (expect relatively "low" serum HCO_3 in type II RTA). Urinary pH initially ↑ due to HCO_3 loss, but then ↓ as serum HCO_3 becomes low
- **TREATMENTS**—usually self-limiting in adults. HCO_3 supplement has limited utility due to HCO_3 wasting and may even lead to hypokalemia

RENAL TUBULAR ACIDOSIS - TYPE IV

- **PATHOPHYSIOLOGY**—causes include **hyporeninemic hypoaldosteronism** (renal failure, frequently diabetic nephropathy and sometimes acute glomerulonephritis, ACE inhibitors, NSAIDs), **primary aldosterone deficiency** (Addison's, congenital adrenal hyperplasia), and **aldosterone resistance** (amiloride, spironolactone, tubulointerstitial 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
Serum K	↓/↑	↓	↑
Serum HCO_3	Variable	10–20	>17
Urine pH	**>5.3**	Variable	<5.3
UNC	**Positive**	**Negative**	Variable

Metabolic Alkalosis

DIFFERENTIAL DIAGNOSIS

HCO_3 GAIN—HCO_3 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's, Gitelman's, hypomagnesemia

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **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's
  - ↑ **ALDOSTERONE-LIKE**—Cushing's

DIFFERENTIAL DIAGNOSIS (CONT'D)

★CLEVER PD★

- **CONTRACTION**
- **LICORICE**
- **ENDOCRINE**—Conn's, Cushing's, Bartter's
- **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**—CBCD, lytes, urea, Cr, serum osmolality, urinalysis, urine lytes, magnesium, urine osmolality
- **ABG**

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	↓	↑	↓	↑

DIAGNOSTIC ISSUES (CONT'D)

URINE CHLORIDE

- **INCREASED** (>20 mmol/L, "Cl resistant")—diuretic use (decreased Cl reabsorption), Bartter's and Gitelman's syndrome (decreased Cl reabsorption), mineralocorticoid excess (Conn's), Cushing's 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 NH_4 excretion)

MANAGEMENT

ACUTE—ABC, O_2, IV

TREAT UNDERLYING CAUSE—**volume sensitive** (fluids, replete K), **volume insensitive** (spironolactone, amiloride)

SPECIFIC ENTITIES

BARTTER'S SYNDROME—mutation of the Na–K–2Cl transporter in the thick ascending limb of Henle (similar to inhibition by loop diuretics). Characterized by hypercalciuria

GITELMAN'S SYNDROME—mutation of the Na–Cl transporter in the distal tubule (similar to inhibition by thiazide diuretics). Characterized by hypocalciuria

Hyponatremia

NEJM 2000 342:21; NEJM 2007 356:20

DIFFERENTIAL DIAGNOSIS OF HYPOOSMOLAR HYPONATREMIA

HYPOVOLEMIC (VOLUME DEPLETION)

- **RENAL LOSS**—diuretics, hypoadrenalism, hypomagnesemia, Bartter's
- **GI LOSS**—vomiting, diarrhea, third spacing
- **SKIN LOSS**—sweat burns
- **BLOOD LOSS**

EUVOLEMIC

- **NON-SIADH MECHANISMS**
  - **ADRENAL INSUFFICIENCY**
  - **HYPOTHYROIDISM**
  - **PSYCHOGENIC POLYDIPSIA**
  - **LOW-SOLUTE DIET**
- **SIADH MECHANISMS**
  - **PHYSIOLOGIC RESPONSE**—stress, anxiety, pain, nausea

DIFFERENTIAL DIAGNOSIS OF HYPOOSMOLAR HYPONATREMIA (CONT'D)

- **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–Barre 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—Na <135 mmol/L. The serum osmolility should be less than 275 mmol/L for hypoosmolar 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, hypervolemic) 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 (>40 mmol/L), and low uric acid. Also need to rule out hypothyroidism, adrenal insufficiency, diuretic use, and psychogenic polydipsia. See **NEJM 2007 356:20** for more details

CALCULATING CORRECTION RATE

- **CHANGE IN SERUM Na**
  $= (Na_{infusate} - Na_{serum})/(\text{total body water} + 1)$
  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 $\leq$**8 mmol/L** to minimize the risk of central pontine myelinolysis. 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, ½ NS (0.45% NaCl in water) 77 mmol/L, Ringer's 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 oxo cubes/L water daily $\times 3$ days. Hypertonic saline or furosemide if severe (be extremely cautious)

EUVOLEMIC—free water restriction <1 L/days. Demeclocycline. NS or hypertonic saline (3%), plus furosemide if severe. Treat underlying cause

MANAGEMENT (CONT'D)

HYPERVOLEMIC—Na and free water restriction <1 L/day, bed rest. Treat underlying cause

TREATMENT ISSUES

VAPTANS ("**AQUARETICS**")—oral V2 receptor antagonists → block ADH action → water diuresis. For correction of euvolemic and hypervolemic hyponatremia, but requires close monitoring

INDICATIONS FOR HYPERTONIC SALINE—severe symptoms such as seizures

FUROSEMIDE-INDUCED DIURESIS—equivalent to ½ isotonic saline solution. Thus, furosemide can be used to treat hyponatremia, particularly with the concurrent use of normal saline or hypertonic saline

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 central pontine myelinolysis

CENTRAL PONTINE MYELINOLYSIS

- **PATHOPHYSIOLOGY**—within first day of hyponatremia, brain swells as water shifts into cells to 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 after correction and often irreversible. Symptoms include dysarthria, dysphagia, paraparesis, lethargy, coma, and seizures
- **RISK FACTORS**—alcoholics, ♀ on thiazide diuretics, patients with $\downarrow K^+$, and burn victims
- **DIAGNOSIS**—CT head, MRI head
- **TREATMENTS**—dismal prognosis with no effective therapy. Prevention is key

Hypernatremia NEJM 2000 342:20

DIFFERENTIAL DIAGNOSIS

HYPOVOLEMIC—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), **idiopathic**

HYPERVOLEMIC—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

DIAGNOSTIC ISSUES

CALCULATING CORRECTION RATE

- **WATER DEFICIT** (in liters)
  $= (Na_{current}/Na_{goal} - 1) \times$ total body water
- **CHANGE IN SERUM Na**
  $= (Na_{infusate} - Na_{serum})/(\text{total body water} + 1)$
  where total body water $\approx 0.5 \times$ body weight in women and $0.6 \times$ 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, ½NS (0.45% NaCl in water) 77 mmol/L, Ringer's lactate 130 mmol/L, NS (0.9% NaCl in water) 154 mmol/L. Avoid using 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. 347)

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's, renal artery stenosis

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 extremities, respiratory and gastrointestinal muscles. Cramps, paresthesias, 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**

INVESTIGATIONS (CONT'D)

- **HYPERALDOSTERONISM WORKUP**—serum aldosterone and plasma renin activity

DIAGNOSTIC ISSUES

TRANSTUBULAR K GRADIENT—indirect indicator of aldosterone activity

- TTKG = $(U_K/U_{osmo})/(P_K/P_{osmo})$
- TTKG >4 = renal loss (hyperaldosteronism)
- TTKG <2 = GI or non-renal loss
- Note: TTKG only valid if $U_{osmo} > P_{osmo}$ and $U_{Na} > 25$ mmol/L

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 ($MgSO_4$ 5 g IV over 4 h)

TREAT UNDERLYING CAUSE

Hyperkalemia

DIFFERENTIAL DIAGNOSIS

PSEUDOHYPERKALEMIA—hemolysed blood sample, leukocytosis, thrombocytosis

↑ **INTAKE**—rare

SHIFT OUT OF CELL—metabolic acidosis, diabetes (insulin deficit), β-blockade

↑ **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 precordial leads), widen QRS, wide and flat P wave, VF

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, CK, serum osmolality, urinalysis, urine lytes, urine osmo
- **ECG**—consider if K >6.0 mmol/L. May see peaked T waves

SPECIAL

- **ABG/VBG**—quick way to get serum K level
- **HYPOALDOSTERONISM WORKUP**—serum aldosterone and plasma renin activity

DIAGNOSTIC ISSUES

TRANSTUBULAR K GRADIENT—indirect indicator of aldosterone activity

- TTKG = $(U_K/U_{osmo})/(P_K/P_{osmo})$
- TTKG >8 = normal renal response (appropriate aldosterone activity)
- TTKG <7 = suggests hypoaldosteronism in hyperkalemic patient (kidneys not secreting K appropriately
- TTKG <5 = very suggestive of hypoaldosterism in hyperkalemic patient (adrenal insufficiency)

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
- **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**—$NaHCO_3$ 45 mEq IV over 5 min, repeat in 30 min PRN for acidosis

MANAGEMENT (CONT'D)

- **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. **Diuretics** (*furosemide* 40 mg IV, doses up to 200 mg may be needed in ARF). **Dialysis**

TREAT UNDERLYING CAUSE—**discontinue drugs** (K supplements, ACE inhibitors, ARBs, spironolactone, NSAIDs, trimethoprim)

Hypomagnesemia

DIFFERENTIAL DIAGNOSIS

↓ **INTAKE**—malnutrition, malabsorption, maldigestion

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/PO_4**—↓ K, ↓ Ca, PTH resistance, vitamin D deficiency

CLINICAL FEATURES (CONT'D)

- **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, PO_4, 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

TREAT UNDERLYING CAUSE—amphotericin B-induced hypomagnesemia (amiloride)

Hypophosphatemia

DIFFERENTIAL DIAGNOSIS

↓ **INTAKE**—alcoholism, inadequate intake, antacids

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
- **HEMATOLOGIC** (RBC 2,3 DPG falls)—hemolysis, ↓ WBC activity, ↓ clot retraction, thrombocytopenia

Related Topics
Hypocalcemia (p. 352)
Vitamin D Deficiency (p. 352)

INVESTIGATIONS

BASIC

- **LABS**—Ca, Mg, PO_4, PTH, CK, 24-hour urinary PO_4 collection (<100 mg), urine PO_4, urine Cr

DIAGNOSTIC ISSUES

$FePO_4 = (U_{PO4}/U_{Cr})/(P_{PO4}/P_{Cr})$, <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 NEJM 2004 350:7

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

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**—CBCD, lytes, urea, Cr, Ca, PO_4, PTH, uric acid, urinalysis (artifact most times)
- **IMAGING**—unenhanced CT abd/pelvis (sens 96%, spc 100%), KUB (consider EWSL if see stone on film), U/S abd, IVP

SPECIAL

- **URINE TEST**—24-hour urinary Ca/PO_4, 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). **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 daily, or *ampicillin* and *gentamicin*)

PREVENTION—↑ daily fluid intake (>2 L of water/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). **Hyperuricosuria** (dietary uric acid restrictions, *allopurinol* 100 mg PO daily, alkalinization of urine with K citrate or $NaHCO_3$). **Hypomagnesuria** (*Mg gluconate* 500 mg PO TID)

Hypertension

See HYPERTENSION (p. 57)

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—countercurrent exchange, blood pump speed, dialysate speed (500 mL/min), size of membrane, time (4 h 3× week)

VASCULAR ACCESS—temporary (double lumen internal jugular/femoral. Avoid subclavian placement if possible to minimize risk of subclavian stenosis), intermediate (PermCath internal jugular), permanent (AV graft, AV fistula)

ORDERS

- **GOAL WEIGHT DETERMINATION**—symptoms, clinical fluid status, blood pressure
- **FILTER**—low efficiency for new patients, high-flux, high-efficiency filters for most other patients
- **BLOOD PUMP SPEED**—usually 400–450 mL/min for CRF. 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 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 throughout the run. If hyponatremia, set Na at 132–135 mmol/L
- **K^+**—as a general rule, [dialysate K] = 7 mmol/L – [serum K]
- **HCO_3**—25–40 mmol/L (usually 35 mmol/L)
- **Ca^{2+}**—1.25–1.75 mmol/L [5–7 mg/dL] (usually 1.55 mmol/L [6 mg/dL])
- **TEMPERATURE**—35.5°C [95.9°F]
- **HEPARIN**—500 U bolus then 500 U/h if first time. Otherwise, 1000 U bolus then 500 U/h. If high risk (active bleed, HITT, anticoagulated), consider no heparin. Citrate is an alternative at times (HITT)

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. 97 for other causes. Treatments include Trendelenburg position, stopping ultrafiltration, fluid bolus NS 100 mL, and consider ramping Na next time
- **MUSCLE CRAMPS**—due to rapid fluid removal. Give fluid bolus NS 100 mL, 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

ADVANTAGES OF CONTINUOUS RENAL REPLACEMENT 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 molecular (especially in septic patients), better nutrition for patient can be provided

DISADVANTAGES OF CONTINUOUS RENAL REPLACEMENT—requires anticoagulation (heparin, citrate, NS flush q30 min), removes more solute, and requires 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 cycler 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), **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

PERITONEAL DIALYSIS (PD) (CONT'D)

COMPLICATIONS OF PERITONEAL DIALYSIS

- **PERITONITIS**—once every 2 years. Triad of abdominal pain, cloudy dialysate, and >100 WBC/mm^3. Treat with intraperitoneal ceftazidime and vancomycin empirically until cultures available

PERITONEAL DIALYSIS (PD) (CONT'D)

- **MECHANICAL**—blockage (causes include constipation, omental wrap, tube in wrong position), leak, pleural effusion
- **METABOLIC**—hypokalemia, hyperglycemia (glucose in dialysate)
- **MEMBRANE**—lasts 6–8 years as glucose toxic to peritoneal membrane

Notes

Notes

4
CRITICAL CARE
Section Editor: Dr. Wendy Sligl

Intensive Care Issues

ICU ADMISSION CRITERIA

NEED FOR FREQUENT OR CONTINUOUS MONITORING—post-high-risk surgery, high risk for clinical deterioration

HIGH INTENSITY OF NURSING CARE

LIFE SUPPORT THERAPY—mechanical ventilation, vasoactive drugs, continuous renal replacement, artificial liver support

PREVENTATIVE STRATEGIES

VENTILATOR-ASSOCIATED PNEUMONIA—remove endotracheal tube as soon as possible, orotracheal intubation unless contraindicated, hand hygiene, oral and dental hygiene (chlorhexidine rinse), semi-recumbent positioning, rotational bed therapy, subglottic suctioning, drainage of condensate from ventilator circuits, minimize gastric acid suppression therapy (proton pump inhibitors) when possible

GASTROINTESTINAL STRESS ULCERATION—risk factors include mechanical ventilation and/or coagulopathy. Prophylaxis with H_2 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 heparin SC, LMWH, fondaparinux, or pneumatic compression stockings

SEDATION, ANALGESIA, PARALYSIS IN THE ICU

SEDATION/AMNESIA—***propofol*** 0.5 mg/kg/h initial infusion, titrate to 0.5–3.0 mg/kg/h by continuous IV infusion, typical infusion range 0–300 mg/h. Appropriate for short-term sedation, monitor for acidosis and increased CK with prolonged use, rapid onset, short duration; ***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 q2–4h 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 μg q5min IV load to effect, then 1–4 μg/kg/h by continuous IV infusion, typical infusion range 50–300 μg/h, 100× more potent than morphine. Used in patients with hemodynamic instability, rapid onset, short duration; ***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, undergoes Hoffman degradation; ***succinylcholine*** 0.5–1.5 mg/kg IV, onset 1 min, duration ~10 min, metabolized by pseudocholinesterase, many contraindications

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–Barre, motor neuron disease, compression, hypophosphatemia

NEUROMUSCULAR JUNCTION—blocking agents, Eaton–Lambert, 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 (NEJM 2006 354:e13)

- **LANDMARK**—palpate radial artery immediately proximal to scaphoid. Insert 20-gauge (48 mm length) catheter at 30°

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_4,

PROCEDURES (CONT'D)

FEMORAL ARTERIAL LINE INSERTION

- **LANDMARK**—femoral artery is midway between ASIS and pubic symphysis. Puncture and insert cook catheter, *never dilate an artery!*

FEMORAL CENTRAL VENOUS CATHETER (NEJM 2008 358:E30)

- **LANDMARK**—femoral artery is midway between ASIS and pubic symphysis. Femoral vein is medial to artery. 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%)

SUBCLAVIAN CENTRAL VENOUS CATHETER (NEJM 2007 357:E26)

- **LANDMARK**—subclavian vein is directly underneath clavicle. Insert introducer needle through skin at 20° 2–3 cm beneath midway of clavicle toward sternal angle. When needle hits clavicle, apply downward pressure 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%), infections (0.12%)
- **REMOVAL**—place patient in Trendelenburg position and ask him/her to perform a Valsalva maneuver when removing the catheter to prevent air embolism

INTERNAL JUGULAR CENTRAL VENOUS CATHETER (NEJM 2007 356:E21)

- **LANDMARK**—locate carotid pulse. Internal jugular is immediately lateral to it. 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
- **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 when removing the catheter to prevent air embolism

NEJM 2003 348:12

CENTRAL VENOUS SATURATION

ARTERIAL OXYGEN CONTENT (C_aO_2)

- $C_aO_2 = O_2$ carried by hemoglobin $+ O_2$ dissolved in blood
- $C_aO_2 = 1.36 \times Hb \times SaO_2 + 0.003 \times P_aO_2$ where S_aO_2 = arterial Hb saturation

VENOUS OXYGEN CONTENT (CvO_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 ($S_{cv}O_2$ 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
- $VO_2 = CO \times (C_aO_2 - C_vO_2) \cong$ constant (the body normally extracts ~25% of the delivered oxygen except in fever, sepsis, hyperthyroidism, i.e. VO_2/DO_2=0.25)

INTERPRETATION

- As $CO \times (C_aO_2 - C_vO_2) \cong$ constant, $\downarrow C_vO_2$ suggests $\downarrow$ CO
- S_vO_2 is about 75% saturated. A mixed venous saturation of <50% is alarming, <25% is usually unsustainable

PROGNOSTIC ISSUES

ACUTE PHYSIOLOGIC AND CHRONIC HEALTH EVALUATION (APACHE) II SCORE—web-based programs are available. The latest version is APACHE IV

- **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

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 long-term ventilatory support

CARDIOPULMONARY RESUSCITATION

CONDITIONS ASSOCIATED WITH NEGLIGIBLE CHANCE OF SURVIVING CPR—decompensated diseases (cancer, sepsis, pre-arrest hypotension or

CARDIOPULMONARY RESUSCITATION (CONT'D)

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)

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). If resuscitated promptly, 95% of survivors will return to their baseline level of function after CPR, but 5% will be left in a chronic vegetative state. Survival to discharge 1–5% for out-of-hospital CPR and 15% for in-hospital CPR

BRAIN DEATH

EXAMINATION OF THE UNRESPONSIVE PATIENT

- **VITALS**—include GCS
- **5N**—neurological, noggin, neck, nose, needle
- **EYES**—fundoscopy, pupil reflex, corneal reflex, oculocephalic reflex, oculovestibular reflex
- **OTHERS**—gag 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=localize to pain; 6=obey commands
- **CONSIDER INTUBATION**—if GCS <8, as unable to protect airway

OCULOCEPHALIC REFLEXES

- **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 had brain stem injury or was psychogenic
- **CALORIC TESTING**—instillation of ice-cold water into the ear canal on one side. Conjugate eye movement to the irrigated side is expected in the comatose patient (without nystagmus), while it may be absent or asymmetric if the patient had brain stem injury. In a conscious patient, nystagmus will be seen with the slow phase toward irrigated side and the fast phase 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)

BRAIN DEATH (CONT'D)

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, absence of metabolic causes for encephalopathy
- **PHYSICAL**—core temperature ≥34°C [≥93.2°F], absence of motor response to painful stimulus, absence of brain stem reflexes (corneal, pupillary, gag, cough, doll's eyes, calorics), apnea testing
- **IMAGING**—perfusion brain scan (most sensitive test), cerebral angiogram, EEG, transcranial doppler ultrasound
- **CRITERIA**—need both history and physical features to confirm brain death. If apnea testing cannot be performed or indeterminate, need imaging test to verify
- **BRAIN DEATH MIMICS**—locked-in syndrome (focal injury to pons), hypothermia (light reflex lost 28–32°C [82.4–89.6°F], other brain stem reflexes lost <28°C [82.4°F]), drug intoxication, Guillain–Barre syndrome

Related Topics
Dialysis Issues (p. 85)
Critical Illness Neuromuscular Disorders (p. 332)
Palliative Care (p. 389)
Resuscitation Status (p. 399)

APNEA TESTING

1. 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 8 min. Reconnect ventilator immediately and draw ABG if SBP <90 mmHg, marked decrease in SaO_2, or arrhythmia
4. Apnea present if respiratory movements are absent, $PaCO_2$ ≥60 mmHg (and increased ≥20 mmHg above baseline) and pH ≤7.28

BRAIN DEATH (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT DEAD, VEGETATIVE, OR SEVERELY NEUROLOGICALLY IMPAIRED (ASSESSING OUTCOME FOR COMATOSE SURVIVORS OF CARDIAC ARREST)?

	LR+	LR−
Clinical signs that predict death or poor neurological outcome		
Absent corneal reflexes at 24 h	12.9	0.60
Absent pupillary response at 24 h	10.2	0.8
Absent withdrawal response to pain at 24 h	4.7	0.2
No motor response at 24 h	4.9	0.6
No motor response at 72 h	9.2	0.7

APPROACH—"simple physical examination maneuvers strongly predict death or poor outcome in comatose survivors of cardiac arrest. The most useful signs occur at 24 hours after cardiac arrest and earlier prognosis should not be made by clinical examination alone. These data provide prognostic information, rather than treatment recommendations, which must be made on an individual basis incorporating many other variables"

JAMA 2004 291:7

Hypoxemia

DIFFERENTIAL DIAGNOSIS

R TO L SHUNT (unresponsive to supplemental O_2, V/Q <1)—ARDS, HF, pneumonia, alveolar hemorrhage, atelectasis, pulmonary arteriovenous malformation, intracardiac shunt (ASD, VSD, PFO)

V/Q MISMATCH (V/Q >1)—pneumonia, ARDS, asthma, COPD, fibrosis, pulmonary embolism, tumor-filled alveoli, atelectasis, HF

DIFFUSION DEFECTS—interstitial lung disease, PJP, atypical pneumonia

HYPOVENTILATION (A-a normal)

- **CNS**—sedating drugs, tumor, stroke, sleep apnea
- **NEUROMUSCULAR**—botulism, Guillain–Barre, ALS, myxedema
- **UPPER AIRWAY OBSTRUCTION**—epiglottitis, laryngospasm
- **LOWER AIRWAY OBSTRUCTION**—COPD, asthma
- **DEAD SPACE VENTILATION**—infection

LOW O_2 PARTIAL PRESSURE (A-a normal)—high altitude

PATHOPHYSIOLOGY

DEFINITION OF HYPOXEMIA—P_aO_2 <60 mmHg. Note that hypoxia refers specifically to decreased oxygen supply to tissues and organs

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK, lactate
- **IMAGING**—CXR, CT chest
- **ABG**
- **ECG**

DIAGNOSTIC ISSUES

OXIMETRY

- **NORMAL**—>90% is normal. Dyspnea may occur ~85%. Pulmonary hypertension may develop from chronic alveolar hypoxia if saturations <80%
- **ACCURACY**—between 70 and 100% saturation error is ±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)

DIAGNOSTIC ISSUES (CONT'D)

ALVEOLAR-ARTERIAL (A-a) O_2 GRADIENT

- **NORMAL**—A-a gradient $<$age/4 + 4, or $<$0.4 $\times$ age. Usually $<$15 mmHg in young, up to $\sim$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 $\approx$ 760 mmHg if at sea level
- **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 $\times$ 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, and/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 $<$50 mmHg even with F_iO_2 $>$50)—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
HEMORRHAGE—pulmonary embolism, pulmonary contusion, bleeding diathesis, DIC, anticoagulation, vasculitis (Wegener's granulomatosis, Goodpasture's, SLE)

PATHOPHYSIOLOGY

DEFINITION OF ARDS

- **ACUTE ONSET**
- **BILATERAL ALVEOLAR INFILTRATES**—usually asymmetric/patchy, peripheral $>$central
- **HYPOXEMIA**—P_aO_2/F_iO_2 $\leq$200
- **ABSENCE OF LEFT ATRIAL HYPERTENSION**—historically defined as pulmonary arterial wedge pressure $\leq$18 mmHg; however, can rule out left ventricular dysfunction non-invasively with echocardiography

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

PATHOPHYSIOLOGY (CONT'D)

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_aO_2/F_iO_2 ratio is low. V/Q mismatch and hypoventilation may also contribute
CAUSES—over 80% of ARDS are caused by infections, aspiration, and trauma

- **PULMONARY**—pneumonia (bacterial, viral, fungal, PJP), aspiration, drowning, inhalation injury (O_2, smoke, NO_2), reperfusion injury (post-lung transplant or cardiopulmonary bypass)
- **GI**—acute pancreatitis
- **CNS**—neurogenic (intracerebral hemorrhage)
- **SYSTEMIC**—sepsis, transfusion reaction, major trauma, drugs (heroine, cocaine, aspirin, chemotherapy)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, troponin/CK, urinalysis, lactate
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/C&S/AFB, urine C&S
- **IMAGING**—CXR, CT chest, echocardiogram
- **ABG**
- **ECG**
- **SWAN–GANZ CATHETERIZATION**

DIAGNOSTIC AND PROGNOSTIC ISSUES

ACUTE LUNG INJURY—milder form of ARDS with $P_aO_2/F_IO_2 \leq 300$

PROGNOSIS OF ARDS—overall mortality rate ~45%. Mortality increases with additional organ failure (>99% if three system failures)

MANAGEMENT

ABC—O_2 to keep sat >90%, IV

MECHANICAL VENTILATION

- **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 $\leq$30 cmH_2O
- **PEEP**—should be employed to keep FiO_2 in presumed non-toxic range (<0.60). Increase PEEP by increments of 3–5 cm (maximum = 15–20 cm) to increase functional residual capacity (may be harmful)
- **RECRUITMENT**—recruitment maneuvers may be used to keep alveoli open; e.g. 40 cmH_2O PEEP for 40 s

MANAGEMENT (CONT'D)

- **PERMISSIVE HYPERCAPNIA**—generally tolerate pH >7.25, may need to run HCO_3 infusion to maintain pH
- **SALVAGE/ALTERNATE MODES OF VENTILATION**—APRV (airway pressure release ventilation), HFOV (high-frequency oscillatory ventilation)

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 still 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). **Nitric oxide** (selectively dilates pulmonary vessels of ventilated alveoli, improving V/Q matching. Reduces pulmonary artery pressures and intrapulmonary shunting with an increase in P_aO_2/F_IO_2)

TREAT UNDERLYING CAUSE

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–Barre
- **LACK OF RESPIRATORY DRIVE**—neurologic disease, drug overdose

LACK OF RESPIRATORY DRIVE—hypoxic brain injury, drug overdose

NON-INVASIVE POSITIVE PRESSURE VENTILATION (NIPPV)

- **CONDITIONS IN WHICH NIPPV IS USED**—COPD, HF, asthma, postoperative respiratory failure, post-extubation 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 possible use if due to ↑ PCO_2), respiratory arrest, facial trauma/surgery/burn, airway obstruction, copious secretions, aspiration risk, GI bleeding, gastroesophageal surgery, esophageal rupture, hemodynamic instability, co-existent organ failure, massive 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 $\leq$8), impending airway occlusion, therapeutic hyperventilation. In general, intubation if BIPAP contraindicated or failed, or clinical status severe and likely require longer term ventilation
- **TUBES**—endotracheal tubes, tracheostomy tubes (see ARTIFICIAL AIRWAYS)

TERMINOLOGY

- **RESISTANCE**—restriction that inhibits flow of gas in airways. May result in increased P_{peak} or decreased V_e
- **COMPLIANCE**—ease with which lungs expand. Normal ~50 mL/cmH_2O
- **TIDAL VOLUME** (VT)—amount of air delivered per breath. Normal ~8 mL/kg (500 mL)
- **MINUTE VOLUME** (Ve)—amount of air delivered per minute. Ve (mL/min)= VT × RR

MECHANICAL VENTILATION (CONT'D)

- **POSITIVE END-EXPIRATORY PRESSURE** (PEEP)—maintenance of positive pressure throughout 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 cmH_2O. >15 cmH_2O may cause barotrauma
- **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. Happens about halfway through inspiration phase
- **PLATEAU PRESSURE** (P_{plat})—pressure to prevent lungs from deflating at end inspiration. Related to lung/chest wall compliance. Normal is 33 ± 9 cmH_2O
- **RAPID SHALLOW BREATHING INDEX** (RSBI)—index used for weaning. The lower the better (<70 is excellent, <100 is good). RSBI = RR/tidal volume (measured in liters)

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 $\leq35^\circ$
- **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 (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

ARTIFICIAL AIRWAYS (CONT'D)

ENDOTRACHEAL TUBES (NEJM 2007 356:e15)—inserted nasally or orally, with aid of laryngoscope or bronchoscope. 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)

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 O_2 (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, awake enough to protect airway, on minimal F_IO_2 (<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 cmH_2O (almost no support) to 30 cmH_2O (max). Normal = 14–16 cmH_2O. 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_iO_2—range 0.21–1.0. Normal = 0.4 or keep saturation >90%

SENSITIVITY—determines the degree of patient effort required to trigger a positive pressure breath

PEEP/EPAP—generally start at 5 cmH_2O, max 15–20 cmH_2O (usually in ARDS)

VENTILATORY MODES

- **ASSIST CONTROL** (AC)—mandatory ventilator control breaths at set rate. Patient may breathe spontaneously (i.e. trigger the ventilator, "assist" breaths) with 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 level of volume)
- **PRESSURE SUPPORT** (PS)—set pressure, patient-initiated inspiration (no backup rate, ventilator only boosts airflow to pre-determined level of pressure)
- **SYNCHRONIZED INTERMITTENT MANDATORY** (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) continually to maintain the tidal volume set
- **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 CO_2 elimination. Used in refractory hypoxemia due to ALI/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. Often used in patients with refractory hypoxemia due to ALI/ARDS who fail conventional ventilation
- **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 NIPPV (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 cmH_2O, up to 20 cmH_2O) and expiratory positive airway pressure phase (EPAP, start at 6 cmH_2O, up to 10 cmH_2O). IPAP leads to ↑ airflow which ↑ Ve and helps to ↓ PCO_2, whereas EPAP leads to ↑ FRC and mainly ↑ PO_2. May be used in NIPPV (more common) or intubated patients

WEANING VENTILATION

CRITERIA FOR WEANING VENTILATED PATIENTS

- **REVERSAL OF INITIAL DISEASE PROCESS**—complete reversal not necessary. Ideally, stable chest wall and good pain control. Minimal secretions, minimal sedation, no metabolic acidosis, clear CXR, adequate hemoglobulin, adequate nutrition
- **F_iO_2 SETTING**—effective oxygenation at F_iO_2 0.5 or less
- **PEEP SETTING**—effective gas exchange at PEEP 7.5 cmH_2O or less
- **MINUTE VENTILATION SETTING**—maintain normal pH at Ve 10–12 Lpm or less
- **SPONTANEOUS PARAMETERS**—while off ventilator, able to generate own parameters. VT >5–7 mL/kg, Ve <10 L, VC=12–15 mL/kg, NIF (negative inspiratory force) >−20 cmH_2O, RSBI <100 (even better if <70)

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**—PSV maximum and slowly decreasing to minimal 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 *S. aureus* (including MRSA), Enterobacteriaceae, *Pseudomonas aeruginosa*. Other common microorganisms include *Stenotrophomonas*, *Acinetobacter*, anaerobes

DIAGNOSIS—diagnosis can be difficult. Clinical scores can be used to aid in diagnosis

TREATMENTS

- **EMPIRIC THERAPY**—anti-pseudomonal carbapenem or β-lactam/β-lactamase inhibitor *plus* aminoglycoside or respiratory fluoroquinolone. Add vancomycin or linezolid if high rates of MRSA. De-escalate therapy as soon as possible when culture results known
- **DURATION OF THERAPY**—depends on the microorganism, severity of infection, patient comorbidities and response to therapy, but short courses generally adequate (7–8 days)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE VENTILATOR-ASSOCIATED PNEUMONIA?

	LR+	LR−
Physical and investigations		
Fever	1.2	0.86
Leukocytosis	1.3	0.74
Purulent sputum	1.3	0.63
≥2 of fever/↑ WBC/purulent sputum	2.8	0.41
Crepitation on auscultation	1.2	0.68
Hypoxemia	1.1	0.91
Radiographic features		
New infiltrate on radiograph	1.7	0.35
Air bronchogram	3.8	0.29
Silhouette sign	1.2	0.63
Alveolar infiltrate	1.2	0.47
Fissure abutment	1.9	1.0
Atelectasis	0.77	1.1
Pulmonary secretion analysis		
>50% neutrophils	2	0.09
Intracellular (PMN) bacteria	1.0	1.0
Positive Gram stain		
Blind bronchial aspirate	2.1	0.60
Mini-BAL fluid	5.3	0.5
BAL fluid	18	0.56
Culture		
Blind bronchial asp. ($>10^5$ CFU/mL)	9.6	0.42
BAL fluid ($>10^4$ CFU/mL)	1.4	0.78
Clinical pulmonary infection score		
Score >6	2.1	0.38

APPROACH—"while no single sign is diagnostic of VAP, the appearance of a new infiltrate on CXR should prompt one to check for fever, purulent sputum and leukocytosis (VAP becomes more likely when 2 or more of these signs are positive). Analysis of pulmonary secretions can further refine the diagnosis of VAP. The absence of CXR infiltrate moderately decreases the chance of VAP"

JAMA 2007 297:14

Shock

DIFFERENTIAL DIAGNOSIS

★SHOCK★

SEPTIC—pneumonia, bacteremia, UTI, intra-abdominal infection, meningitis, necrotizing fasciitis

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

DIFFERENTIAL DIAGNOSIS (CONT'D)

KLASSIFIED CAUSES

- **MEDICATIONS**—antihypertensives, AV nodal blocking agents
- **ANAPHYLACTIC**
- **LIVER**—hepatic failure
- **ENDOCRINE**—adrenal insufficiency, myxedema
- **SPINAL**—cord compression

PATHOPHYSIOLOGY

DEFINITION—hypotension leading to cellular hypoperfusion, hypoxia, lactic acidosis, and subsequent

PATHOPHYSIOLOGY (CONT'D)

organ failure (oliguria, hepatic and GI dysfunction, altered mental status)

IT'S SIMPLE MATH

- **BP** = CO × SVR = (SV × HR) × SVR, where CO = cardiac output and HR = heart rate
- **STROKE VOLUME** (SV)—decreases in cardiogenic, hypovolemic, adrenal, hypothyroidism, and obstructive shock
- **SYSTEMIC VASCULAR RESISTANCE** (SVR)—decreases in distributive shock (septic, anaphylactic, neurogenic, hepatic)

CLINICAL FEATURES

HISTORY—pay particular attention to risk factors for sepsis, blood loss, MI, or pulmonatry embolism; past medical history; medications

PHYSICAL—vitals. Assess volume status, cardiac and respiratory function, and extremities. Look for evidence of end-organ damage

ASSESSMENT OF VOLUME STATUS

- **VITALS**—postural heart rate and blood pressure
- **SKIN**—skin turgor (inner aspect of thigh, sternum), oral mucosa
- **CARDIOPULMONARY**—JVP or CVP, crackles, S_3
- **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**—CBCD, lytes, urea, Cr, INR, PTT, AST, ALT, ALP, bilirubin, Ca, Mg, PO_4, TSH, D-dimer, lactate, CK, troponin, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum C&S, urine C&S
- **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, primary pulmonary hypertension, valvular disease, intracardiac shunts, cardiac tamponade, pulmonary embolus), hemodynamic monitoring (complicated AMI, multi-organ system failure, post-cardiac surgery),

DIAGNOSTIC ISSUES (CONT'D)

treatment (aspiration of air emboli). No mortality difference with use of PA catheter

- **CONTRAINDICATIONS**—tricuspid or pulmonary mechanical valve, tricuspid or pulmonary valve endocarditis, right heart mass (thrombus and/or tumor)
- **SITES OF ENTRY**—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
  - **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) = 900–1200 dynes/s/cm^2
  - **CARDIAC INDEX** = 2.4–4.2 L/min/m^2, CO = 4–7 L/min
  - **DO_2** = 400–650 mL/min/m^2
  - **VO_2** = 125–175 mL/min/m^2
- **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]	↓	↑	↑	↑

[a]In 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. 372)
Myocardial Infarction (p. 26)
Sepsis (p. 99)
Tamponade (p. 32)

MANAGEMENT

ACUTE—ABC, O_2, cardiac and oximetry monitoring, **IV fluid resuscitation** (1–5 L), **ICU consult**, consider intubation/mechanical ventilation, **inotropes/vasopressors** (*Norepinephrine* 1–30 μg/min IV. *Vasopressin* 0.01–0.04 U/min IV. *Epinephrine* 1–20 μg/min IV. *Ephedrine* 5–25 mg IV q5–10min until blood pressure stable. *Phenylephrine* 20–200 μg/min IV. *Dobutamine* 2.5–15 μg/kg/min IV. *Milrinone* 0.375–0.75 μg/kg/min IV. *Dopamine* start 1–4 μg/kg/min IV, titrate to maximum 20 μg/kg/min. *Midodrine* 5–10 mg PO TID). **Correct coagulopathy** (transfuse PRBC, FFP, cryoprecipitate)

TREAT UNDERLYING CAUSE

TREATMENT ISSUES

INOTROPES/VASOPRESSORS

- **PHYSIOLOGY**—α1 = peripheral vasoconstriction = ↑ peripheral vascular resistance = treatment for sepsis; β1 = inotropic and chronotropic effect = ↑ cardiac output = treatment for heart failure; β2 = peripheral vasodilation = counter α1 effect

Agent	Mechanism of action	Special note
Norepinephrine	α1 mainly, β1 → ↑ PVR, ↑ CO	First line for septic shock
Vasopressin	V1, V2 → dilates renal, pulmonary, cerebral, coronary arteries and constricts others	Second line for sepsis; AE: Gut ischemia, skin necrosis
Epinephrine	β1, β2, α1 → ↑ CO, ↑ PVR	Salvage for sepsis, first line for anaphylaxis; AE: ischemia
Phenylephrine	α1 → ↑ PVR	Sepsis, counteract spinal/epidural anesthesia
Ephedrine	β1, β2, α1 → ↑ CO, ↑ PVR	Bolus therapy pending CVC placement for continuous vasopressor therapy
Dobutamine	β1, β2 → ↑ CO, ↓ PVR	First line for cardiogenic shock
Milrinone	Phosphodiesterase inhibitor → ↑ CO, ↓ PVR	First line for cardiogenic shock with pulmonary HTN
Dopamine 1–2 μg/kg/min	DA → dilates renal, mesenteric, cerebral arteries and airways	↑ renal perfusion/GFR (controversial)
Dopamine 5–10 μg/kg/min	DA, β1 → ↑ CO	HF/sepsis; AE: tachycardia
Dopamine >10 μg/kg/min	α1 → ↑ PVR	Sepsis/HF; AE: tachycardia
Midodrine	α1 → ↑ PVR	Sepsis; oral

where AE=adverse effects, CO=cardiac output, CVC=central venous catheter, DA=dopamine, HF=heart failure, HTN=hypertension, PVR=peripheral vascular resistance

Sepsis and Septic Shock

NEJM 2006 355:16
Surviving Sepsis Campaign Guidelines Crit Care Med 2008 36:1

PATHOPHYSIOLOGY

DEFINITIONS

- **SIRS**—≥2 of temperature >38.3°C [>100.9°F] or <36°C [<96.8°F], heart rate >90 beats min, respiratory rate >20 or P_aCO_2 <32 mmHg, WBC >12×10^9/L or <4 ×10^9/L or >10% bands

PATHOPHYSIOLOGY (CONT'D)

- **SEPSIS**—SIRS plus documented or suspected infection
- **SEVERE SEPSIS**—sepsis-associated hypoperfusion leading to lactic acidosis, oliguria, or acute alteration of mental status (i.e. sepsis plus organ dysfunction)

PATHOPHYSIOLOGY (CONT'D)

- **SEPTIC SHOCK**—sepsis-induced hypotension (i.e. SBP <90 mmHg) despite adequate fluid resuscitation or vasopressor dependence.

SIMPLIFIED MECHANISM OF INJURY—infection → systemic inflammation (SIRS) → complement activation, ↓ fibrinolytics → endothelial dysfunction, microvascular coagulopathy and thrombosis → organ failure. Too little or too much host response

MECHANISM OF ACUTE KIDNEY INJURY IN SEPSIS

1. Hypotension, increased catecholamines and vasopressor resistance to norepinephrine and angiotensin II → renal ischemia → acute kidney injury
2. Hyperglycemia → white cell dysfunction and inflammation → acute kidney injury
3. Disseminated microvascular coagulation → glomerular and vascular microthrombosis → acute kidney injury

BAND CELLS—neutrophils with unsegmented nuclei, a developmental stage immediately preceding the mature segmented form

- **LEFT SHIFT**—band cell count $>0.7\times10^9$/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 myelogenous leukemia, agnogenic myeloid metaplasia, or one of the various forms of acute leukemia)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, albumin, troponin, CK, INR, PTT, lactate, urinalysis, random cortisol
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S
- **IMAGING**—CXR
- **ABG**

SPECIAL

- **$ScvO_2$ MONITORING**—with internal jugular or subclavian central line insertion
- **LUMBAR PUNCTURE**—if altered level of consciousness
- **THORACENTESIS**—if significant pleural effusion(s)
- **PARACENTESIS**—if ascites

MANAGEMENT

ACUTE—ABC, **O_2**, **IV**, consider intubation/mechanical ventilation

MANAGEMENT (CONT'D)

RESUSCITATION (early goal-directed therapy)—**fluids** (Ringer's lactate or NS 3–10 l IV, consider colloids such as PRBC, albumin, hydroxyethyl starches) and **vasopressors/inotropes** (*norepinephrine* 1–30 mcg/min IV, *vasopressin* 0.01–0.04 U/min IV, *dobutamine* 2.5–15 μg/kg/min IV) during first 6 h to maintain CVP 8–12 mmHg, MAP ≥65 mmHg or SBP >90 mmHg, urine output ≥0.5 mL/kg/h and central venous or mixed venous saturation ≥70%

NEJM 2001 345:19

ANTIMICROBIALS—early **empiric antimicrobials, should be administered ASAP, order STAT.** If suspect pulmonary source, macrolide plus β-lactam for community-acquired pneumonia, anti-pseudomonal plus aminoglycoside or fluoroquinolone ± vancomycin (if high-level MRSA endemicity) for nosocomial pneumonia. If suspect urinary source, third-generation cephalosporin, fluoroquinolone, or aminoglycoside. If suspect intra-abdominal source, β-lactam/β-lactamase inhibitor or carbapenem. **Tailor antimicrobials** once organism(s) identified. Know your local epidemiology

SOURCE CONTROL—absolutely imperative. Must drain abscesses and debride devitalized tissues to achieve source control

GLYCEMIC CONTROL—**insulin infusion** to keep serum glucose <10 mmol/L [<180 mg/dL], maintaining euglycemia *may* improve outcomes; however, must avoid hypoglycemia

ACTIVATED PROTEIN C—for patients at high risk of death (APACHE score ≥25, sepsis-induced multiple organ failure, septic shock, or sepsis-induced ARDS, with no absolute contraindications related to bleeding risk, or relative contraindications that outweigh potential benefit). Decreased mortality from 30.8% to 24.7%, but increased bleeding rate from 2% to 3.5%

NEJM 2002 347:13

STEROIDS—controversial as no reduction in mortality but hasten time to shock reversal, administer ***hydrocortisone*** 50 mg IV q6h in patients with vasopressor-dependent shock

BLOOD PRODUCTS—in septic shock patients with low $S_{cv}O_2$ during the first 6 h of resuscitation, the target hematocrit should be 30%. 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** (*ranitidine* 50 mg IV q8h or 150 mg PO/NG q12h)

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

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
- **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 (↓ O_2 delivery, ↑ metabolic rate), lactate accumulates and causes metabolic acidosis

PATHOPHYSIOLOGY (CONT'D)

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**—CBCD, 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. CSF, pleural, pericardial, ascites)
- **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, O_2 to keep sat >94%, IV, HCO_3 bolus (1–2 amps), or infusion if extremely low pH (<7.2)

TREAT UNDERLYING CAUSE

Rhabdomyolysis

DIFFERENTIAL DIAGNOSIS

SKELETAL MUSCLE DAMAGE

- **MEDICATIONS**—alcohol, cocaine, statins, neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia
- **HYPERACTIVITY**—seizures, exertion
- **IMMOBILITY**
- **COMPARTMENT SYNDROME**
- **TRAUMA OR SURGERY**
- **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

PATHOPHYSIOLOGY (CONT'D)

hypercalcemia in 20% of patients when rhabdomyolysis resolves

COMPLICATIONS—acute kidney injury, DIC

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, Cr, CK, AST, ALT, Ca, PO_4, Mg, uric acid, troponin, urine myoglobin

DIAGNOSTIC ISSUES

MONITORING IN RHABDOMYOLYSIS—CK, urine output, Cr, Ca, PO_4 should be checked regularly (q4–24 h) until CK normlized

MANAGEMENT

ACUTE—**ABC**, O_2 to keep sat >90%, **IV**

PREVENT COMPLICATIONS—**NS** 3–4 L in first 3–4 h bolus, then 300 mL/h or more to prevent acute

MANAGEMENT (CONT'D)

kidney injury. However, if acute kidney injury already established be careful not to cause fluid overload. **Alkaline diuresis** (add 3 amps $NaHCO_3$ to 1 L D5W to keep 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 dopaminergic agonists, such as levodopa therapy in Parkinson's 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 dantrolene, bromocriptine, and amantadine

SPECIFIC ENTITIES (CONT'D)

SEROTONIN SYNDROME

- **PATHOPHYSIOLOGY**—overstimulation of central and peripheral serotonin receptors, usually related to overdose of SSRIs or drug interactions that increase serotonergic neurotransmission (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. In mild cases, symptoms usually resolve within 24 h. Consider cyproheptadine in select cases

Toxicology

APPROACH TO OVERDOSE

BASIC—ABC, O_2, IV, monitor, vitals (HR, RR, BP, temp, O_2 sat, blood sugar, GCS)

INVESTIGATIONS

- **BLOOD TESTS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, Ca, Mg, PO_4, βhCG, 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, e.g. narcotics, benzodiazepines, cocaine, amphetamines, cannabinoids)
- **IMAGING**—CXR, CT head
- **ECG**
- **ABG**

HISTORY (brief)—collateral important, inquire about depression

PHYSICAL (brief)—pupils, lungs, heart, GI, skin

ANTICHOLINERGIC SYNDROMES

CAUSES—tricyclic antidepressants, 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, LSD, PCP, methamphetamine, phenylpropanolamine, ephedrine, pseudoephedrine, methylphenidate, nicotine, theophylline

CLINICAL FEATURES—**common** (fever, tachycardia, hypertension, *diaphoresis*, delusions, paranoia,

SYMPATHOMIMETIC SYNDROMES (CONT'D)

mydriasis, hyperreflexia), **serious** (seizures, coma, arrhythmias, cardiovascular collapse)

TREATMENTS—**supportive** measures, **sedation** with benzodiazepines. **Avoid** β-blockers (unopposed α effect)

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 on p. 105

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 via conjugation with glutathione. With acetaminophen overdose, NAPQI accumulates due to depletion of glutathione 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 140's**★ toxic dose = **140** mg/kg, 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 1L 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, and transaminases) 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**

KING'S COLLEGE CRITERIA FOR LIVER TRANSPLANTATION IN TYLENOL OVERDOSE ★The rule

ACETAMINOPHEN OVERDOSE (CONT'D)

of 3's★—either pH <7.**3** or grade **III**/IV encephalopathy plus Cr >**3**00 μmol/L [>**3.3** mg/dL] plus INR >**6.5** (~5% survival with medical therapy alone)

NEJM 2008 359:3

SALICYLATE OVERDOSE

CAUSES (★**The rule of 3's**★)—a single dose of 10–**3**0 g (**3**0 tablets of **3**25 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). **Alkalinize** serum and urine; maintain urine pH 8–8.5 (***NaHCO*$_3$** 1–3 amps IV push, then 3 amps of $NaHCO_3$ 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)

OPIATE, SEDATIVE OR ETHANOL INTOXICATION SYNDROMES

CAUSES—narcotics, 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 opiates), **flumazenil** (if benzodiazepines), **urinary alkalinization** (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

β-BLOCKER OVERDOSE (CONT'D)

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 or sotalol, **insulin/glucose infusions, atropine, or pacing** not usually effective

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

CLINICAL FEATURES—**common** (hypotension, arrhythmias, delirium, hypokalemia, lactic acidosis, hyperglycemia)

TREATMENTS—**supportive** measures. **Fluid** resuscitation. **IV calcium** (*calcium gluconate* 10% 50 mL or *calcium chloride* 10% 20 mL). **Glucagon**. **Insulin/glucose infusions**

LITHIUM TOXICITY

CAUSES—usually related to chronic drug accumulation, although acute overdose may occur. Common risk factors include 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 diabetes insipidus, leukocytosis, and goiter

TREATMENTS—**supportive** measures, gastric lavage if within 60 min of ingestion, **hypotonic solution** infusion, 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)

Related Topics
ABG (p. 77)
Alcohol Abuse (p. 105)
Delirium/Coma (p. 380)
ECG (p. 62)
Seizures (p. 309)

DIAGNOSTIC ISSUES FOR OVERDOSE

OSMOLAR GAP—measured osmolality – calculated osmolality, where $Osmo_{calc}$ ★**GUN2**★

- **$Osmo_{calc}$** = (**G**lucose in mmol/L) + (**U**rea in mmol/L) + 2×(**N**a mmol/L)
- or in US units: **$Osmo_{calc}$** = (**G**lucose in mg/dL)/18 + (**U**rea in mg/dL)/2.8 + 2×(**N**a mEq/L)
- **NORMAL OSMOLAR GAP**—typically −2 to +6 mOsm/kg
- **INCREASED OSMOLAR GAP AND ANION GAP**—ethylene glycol, methanol, diabetic or alcoholic ketoacidosis, lactic acidosis, chronic renal failure (other small solutes), severe lactic acidosis ("idiogenic osmole"), severe 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 – HCO_3. 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. 77). 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). A "normal" AG may actually be elevated in the setting of hypoalbuminemia

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

MANAGEMENT OF OVERDOSES

1. **ACUTE**—ABC, **O_2**, IV, **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 hour 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

MANAGEMENT OF OVERDOSES (CONT'D)

charcoal not indicated (e.g. iron, lithium, cyanide). **Whole bowel irrigation** (*Polyethylene glycol* 2 L/hour, up to 10 L). **Skin** (remove clothing, cleanse). Ipecac not recommended

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 (ethanol, isopropanol, acetone, methanol, ethylene glycol), lithium, procainamide, theophylline, salicylates, heavy metals, trichloroethanol, atenolol, or sotalol
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 1L D5W IV over 16 h. Alternatively, *N-acetylcysteine* 140 mg/kg PO/NG, followed by 70 mg/kg q4h for 17 doses). **Opiates** (*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

MANAGEMENT OF OVERDOSES (CONT'D)

3 mg). **Methanol/ethylene glycol** (*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]. *Fomepizole* 15 mg/kg IV, followed by 10 mg/kg q12h until ethylene glychol level <3.2 mmol/L [<20 mg/dL]). **Digitalis** (*Digibind* 10–20 vials IV if life-threatening arrhythmia). **Calcium channel blockers** ($CaCl_2$ 1 g over 5 min, repeat if life-threatening disease). **β-blockers** (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 ×2, then 500 mg q4–12hr 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 imbalance, arrhythmias, hypotension, seizures, and others. Consider ICU/CCU consultation where appropriate
6. **PSYCHIATRY CONSULT WHEN STABLE**

Alcohol Withdrawal and Complications of Alcoholism

PATHOPHYSIOLOGY

ALCOHOLIC 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)

AT RISK FOR ALCOHOLISM—>14 drinks/week or >4 drinks/session for men and >7 drinks/week or >3 drinks/session for women. Alcoholic cirrhosis requires >80 g/day (8 beers, 1 bottle of wine, or 250 mL of hard liquor) for 10–20 years

COMPLICATIONS OF ALCOHOLISM

- **ACUTE INTOXICATION**
- **ACUTE WITHDRAWAL**—minor withdrawal, seizures, hallucinations, delirium tremens
- **CHRONIC ALCOHOLISM**
  - **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

PATHOPHYSIOLOGY (CONT'D)

- **HEMATOLOGY**—macrocytic anemia, thrombocytopenia, splenomegaly
- **CANCER**—oral cavity, esophagus, pharynx, larynx, liver, breast
- **ENDOCRINE**—alcoholic hypoglycemia and ketosis, pseudo-Cushing's, hyperuricemia, hypogonadism
- **SOCIAL**—accidents, domestic violence, fetal alcohol syndrome

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN ALCOHOL PROBLEM?

CAGE—**C**ut down, **A**nnoyed by criticisms, **G**uilty about drinking, **E**ye-opener. LR+ for heavy drinking (>8 drinks/day): 0=0.14, 1=1.5, 2=4.5, 3=13.2, 4=101

OTHERS—MAST, AUDIT

APPROACH—"use CAGE for screening heavy drinking (>8 drinks/day). Score of 0 has good NPV at low prevalence of disease. Scores of 3 or 4 strongly support diagnosis of alcohol abuse. Scores of 1 or 2 must be interpreted with caution. Note that CAGE is relatively insensitive in detecting hazardous drinking but lower amounts or drinking in pregnancy"

JAMA 1994 272:22

CLINICAL FEATURES (CONT'D)

DSM IV 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: autonomic hyperactivity (e.g. sweating, tachycardia), tremor, insomnia, nausea or vomiting, transient visual, tactile, or auditory hallucinations or illusions, psychomotor agitation, anxiety, grand mal seizures
C. Symptoms causing clinically significant distress or impairment in social or occupational function
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
- **SYMPTOMS**—usually visual, although auditory and tactile phenomena may also occur. Unlike DT, there is usually no decreased level of consciousness/global confusion

WITHDRAWAL SEIZURES

- **TIMING**—usually occur within 48 h after the last drink; however, may occur after only 2 h of abstinence
- **SYMPTOMS**—generalized tonic–clonic convulsions. Predominantly seen in patients with a long history of chronic alcoholism. Be wary of intracerebral hemorrhage with focal seizures

DELIRIUM TREMENS (DT)

- **TIMING**—typically begin between 48 h 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**—age >30, history of sustained drinking, history of previous delirium tremens, concurrent illness, greater number of days since the last drink

INVESTIGATIONS

BASIC

- **LABS**—CBCD (macrocytosis, cytopenias), lytes, urea, Cr, glucose, TSH, AST, ALT (AST/ALT >2), ALP, bilirubin, GGT, Ca, Mg, PO_4, osmolality
- **MICROBIOLOGY**—blood C&S, urinalysis, urine C&S (if delirious)
- **IMAGING**—CXR
- **ECG**
- **ABG**
- **URINE DRUG SCREEN**

INVESTIGATIONS (CONT'D)

SPECIAL

- **CARBOHYDRATE DEFICIENT TRANSFERRIN**—sens 60–70%, spc 80–90%
- **HEAD CT**—if significant or prolonged delirium, focal neurologic deficits, or focal seizures

ACUTE MANAGEMENT OF ALCOHOL WITHDRAWAL

ACUTE—**ABC**, O_2 to keep sat >94%, **IV** (NS 1 L 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* 1–2 mg IV q5min until patient calm, then put on high-risk protocol
- **HIGH RISK FOR WITHDRAWAL** (fixed schedule dosing)—*chlordiazepoxide* 50–100 mg PO q6h and PRN ×1 day, then 25–50 mg q6h and PRN ×2 days. Alternatively, consider CIWA-Ar scale below
- **LOW RISK FOR WITHDRAWAL** (as needed dosing)—*diazepam* 10–20 mg PO q2h or *lorazepam* 1–2 mg PO q1h until no symptoms then PRN doses
- **AGITATION**—add *haloperidol* 0.5–5 mg PO/IM/IV q1–4h PRN (but may lower seizure threshold)
- **TREMORS**—**β-blockers**

NUTRITIONAL SUPPLEMENT—**thiamine deficiency** (*thiamine* 100 mg IV/IM ×5 days must be given before any glucose solution, or may worsen Wernicke encephalopathy). ***Multi-vitamin*** 1 tab PO daily. Replace K and Mg 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*** 25 mg PO daily ×1 week, then 50 mg PO daily for at least 3–4 months, coupled with psychosocial intervention may be used for alcohol dependence. **Disulfiram**, which causes a highly unpleasant sensation when patient consumes alcohol, may also be used

TREATMENT ISSUES FOR ALCOHOL WITHDRAWAL

REVISED CLINICAL INSTITUTE WITHDRAWAL ASSESSMENT FOR ALCOHOL (CIWA-A R) SCALE

- **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, or numbness, or do you feel like bugs are crawling on or under your skin?"

TREATMENT ISSUES FOR ALCOHOL WITHDRAWAL (CONT'D)

- **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 $\geq$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'S ENCEPHALOPATHY**—encephalopathy (profound disorientation, indifference, inattentiveness, delirium, altered level of consciousness), oculomotor dysfunction (nystagmus, lateral rectus palsy, and conjugate gaze palsies), gait ataxia
- **KORSAKOFF'S AMNESIA** (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 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 due to crystalline nephropathy
- **TREATMENTS**—**supportive** measures. **NG suction** may be helpful if recent ingestion (but not activated charcoal). ***NaHCO$_3$*** 1–2 amps IV bolus, then 3 amps in 1 L D5W at 250 mL/h (if metabolic acidosis pH $<$7.3. Helps to minimize tissue penetration and damage). **Alcohol dehydrogenase inhibition** (*fomepizole* 15 mg/kg IV, followed by 10 mg/kg q12h) or **continuous ethanol** (IV 8 mL/kg 10% ethanol in D5W over 30 min then 1.5–2 mL/kg/h to maintain serum ethanol $>$21 mmol/L, increase rate to 3 mL/kg/h on dialysis; alternatively PO 1 mL/kg 95% ethanol then 0.15 mL/kg/h $\approx$ 4 oz Scotch loading dose with 2 oz q1h maintenance). **Cofactor therapy** includes *folic acid* 50 mg IV q4h until methanol no longer measurable (accelerates formic acid $\rightarrow$ $CO_2 + H_2O$); *thiamine* 100 mg IV q6h and *pyridoxine* 50 mg IV q6h until ethylene glycol no longer measurable (accelerates glycoxylate $\rightarrow$ 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 multi-vitamin as supportive measures

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

CAUSES (CONT'D)

- **METABOLIC**—anorexia nervosa, malnutrition

ALTERED REGULATION

- **CENTRAL**—stroke, Parkinson's 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 be mild (34–35°C [93–95°F]), moderate (30–34°C [86–93°F]), or severe (<30°C [<86°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 complications (frostbite). 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**—CBCD, lytes, urea, Cr, glucose, CK, troponin, AST, ALT, ALP, bilirubin, TSH, urinalysis
- **MICROBIOLOGY**—blood cultures
- **ECG**—Osborn wave (elevated J point), prolonged RR, PR, QRS, and QT intervals

MANAGEMENT

ACUTE—**ABC**, O_2 to keep sat >94%, **IV**. 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 lightening, 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 CBCD, lytes, urea, Cr, glucose, CK, appropriate imaging, drug and alcohol levels, urinalysis, CXR, ABG, ECG
- **TREATMENTS**—ABC, O_2, 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 CBCD, lytes, urea, Cr, glucose, osmolality, drug and alcohol levels, urinalysis, CXR, ABG, and ECG
- **TREATMENTS**—ABC, O_2, 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 and possible ARDS), and systemic toxins (CO, CN)

CLINICAL FEATURES

HISTORY—exposure to smoke (duration, substance, environment, deaths at the scene), dyspnea, chest pain, confusion, loss of consciousness, burns, other injuries, past medical history (respiratory disorders), medications

CLINICAL FEATURES (CONT'D)

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**—CBCD, lytes, urea, Cr, glucose, carboxyhemoglobin level, cyanide level, methemoglobin level (↓ with cyanide poisoning), lactate (↑ with cyanide poisoning)
- **IMAGING**—CXR
- **ECG**
- **ABG**—to determine PaO_2, $PaCO_2$, and CO-Hb levels
- **LARYNGOSCOPY/BRONCHOSCOPY**—if significant burns

MANAGEMENT

ACUTE—**ABC**, high flow O_2 to keep sat >94%, **IV**. Consider early **intubation** if severe injury/symptoms. Salbutamol and ipratropium

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 O_2
- **CLINICAL FEATURES**—nausea, malaise, headache, dyspnea, angina, confusion, coma
- **TREATMENTS**—100% O_2 (decreases $t_{½}$ of CO from 4 h to 1.5 h). Hyperbaric oxygen may be used in selected patients (CO >25%, end-organ ischemia, or loss of consciousness)

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 antidote kit (inhaled amyl nitrite, intravenous sodium nitrite, sodium thiosulfate)

Anaphylaxis

See ANAPHYLAXIS (p. 372)

Notes

5
GASTROENTEROLOGY

Section Editor: Dr. Winnie Wong

Nausea and Vomiting

DIFFERENTIAL DIAGNOSIS

NEUROLOGIC

- **ORGANIC**—infections, tumors, multiple sclerosis, vestibular nerve or brain stem lesions
- **DRUGS**—chemotherapy, SSRI, opioids, antibiotics
- **PSYCHIATRIC**—anorexia nervosa, bulimia nervosa, rumination

GASTROINTESTINAL

- **INFECTIONS**—acute gastroenteritis, food poisoning, pyelonephritis, pneumonia
- **NEOPLASTIC**—gastric, ovarian, paraneoplastic, renal
- **OBSTRUCTION**—stomach, small bowel, colon, functional, gastric volvulus
- **POSTOP**—vagotomy, gastrectomy, fundoplication
- **PEPTIC ULCER DISEASE**—esophagus, stomach, duodenum
- **GASTROPARESIS**—ischemic, diabetic, amyloidosis, scleroderma, drugs
- **OTHERS**—eosinophilic gastroenteritis, hepatobiliary disease, pancreatic disease, peritoneal irritation

METABOLIC

- **ENDOCRINE**—diabetes, adrenal insufficiency, hypercalcemia, hyperthyroidism, hyperemesis gravidarum
- **OTHERS**—uremia, pregnancy

IDIOPATHIC

PATHOPHYSIOLOGY

REFLEX PATHWAY

- **AFFERENT**—(1) **humoral** 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 **GI tract** 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

PATHOPHYSIOLOGY (CONT'D)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, Ca, Mg, PO_4, AM cortisol, urinalysis
- **MICROBIOLOGY**—urine C&S
- **IMAGING**—CXR, AXR

SPECIAL

- **GASTROSCOPY**
- **CT HEAD**

MANAGEMENT

SYMPTOM CONTROL

- **H1 ANTAGONISTS**—*dimenhydrinate* 50 mg PO/PR q4h, *diphenhydramine* 25–50 mg PO/IV/IM q6h, *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 q6–8h, *chlorpromazine* 10–25 mg PO q4–6h), **butyrophenones** (*droperidol* 1.25–5 mg IM q4 h, haloperidol 0.5–1 mg IV/PO q4h)
- **5HT3 ANTAGONISTS**—*ondansetron* 8 mg PO/IV daily-BID, *granisetron* 2 mg PO or 1 mg IV, *dolasetron* 100 mg PO/IV daily
- **M1 ANTAGONISTS**—*scopolamine* 1.5 mg TD q72h
- **STEROID**—*dexamethasone* 4 mg BID–TID PO/SC/IV
- **TUBE FEED**—NJ tube, G tube

TREAT UNDERLYING CAUSE

Related Topics
Chemotherapy-Induced Nausea and Vomiting (p. 229)
Nausea and Vomiting in the Palliative Setting (p. 395)

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_5,

Dysphagia

DIFFERENTIAL DIAGNOSIS

OROPHARYNGEAL (upper esophagus and pharynx, or upper esophageal sphincter dysfunction)

- **NEUROLOGICAL**—stroke, multiple sclerosis, Parkinson's, dementia, amyotrophic lateral sclerosis, Guillain–Barre, myasthenia gravis, cerebral palsy, Huntington's, tardive dyskinesia, brain stem tumors, trauma
- **MYOPATHIC**—myotonic dystrophy, dermatomyositis, connective tissue disease, sarcoidosis, paraneoplastic
- **STRUCTURAL**—cricopharyngeal bar, Zenker's diverticulum, cervical webs, oropharyngeal tumors, osteophytes and skeletal abnormality, congenital abnormality
- **INFECTIOUS**—syphilis, Lyme disease, botulism, mucositis
- **METABOLIC**—Cushing's, thyrotoxicosis, Wilson's, amyloidosis
- **IATROGENIC**—chemotherapy, neuroleptics, post-surgical, radiation

ESOPHAGEAL (body of esophagus, lower esophageal sphincter, cardia)

- **STRUCTURAL**—**tumors** (benign, malignant), **esophagitis/stricture** (reflux, caustic/erosive, infectious, eosinophilic, pill, radiation), tylosis, diverticula, **iatrogenic** (post-surgery, radiation), esophageal ring/web, **extrinsic compression** (enlarged aorta, left atrium, mediastinal mass, osteophytes, subclavian artery)
- **MOTILITY**—achalasia, scleroderma, Chagas disease, diffuse esophageal spasm, hypertensive lower esophageal sphincter, nutcracker esophagus, non-specific esophageal motility disorders
- **FUNCTIONAL**

CLINICAL FEATURES

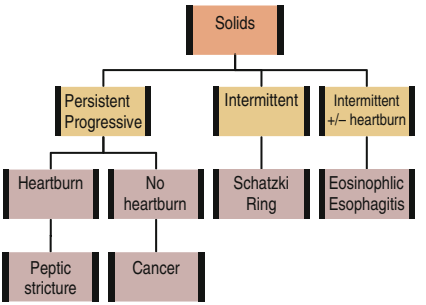
DIAGNOSTIC CLUES—history of heartburn may suggest GERD leading to erosive esophagitis, peptic stricture, or esophageal adenocarcinoma. History of atopic diseases especially in a young adult with recurrent dysphagia may suggest eosinophilic esophagitis. Also check for odynophagia, regurgitation, hematemesis, coffee ground emesis, respiratory symptoms, and weight loss

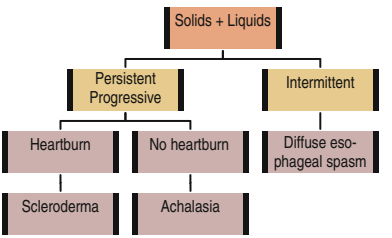
PRACTICAL APPROACH TO DYSPHAGIA

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

CLINICAL FEATURES (CONT'D)

2. Difficulty swallowing both solids and liquids? If yes, consider motility disorders and proceed to step 3. If progressing from solids to liquids, consider structural disorders and proceed to step 4
3. For motility disorders, is the dysphagia progressive? If yes, consider achalasia or scleroderma. If intermittent, consider diffuse esophageal spasm or non-specific esophageal motility disorder
4. For structural disorders, is the dysphagia progressive? If yes, consider tumors and peptic stricture. If intermittent, consider esophageal ring
5. Any caustic ingestion history?





INVESTIGATIONS

BASIC

- **IMAGING**—barium swallow (esophageal), videofluoroscopy (oropharyngeal)
- **SWALLOWING ASSESSMENT**—occupational therapy or speech pathology

SPECIAL

- **GASTROSCOPY**—for esophageal lesions and biopsy for eosinophilic esophagitis
- **ESOPHAGEAL MANOMETRY**—definitive for achalasia, useful for diffuse esophageal spasm

INVESTIGATIONS (CONT'D)

- **pH MONITORING**—for GERD, especially if gastroscopy normal
- **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 lack of peristalsis in the body of the esophagus and incomplete relaxation of the lower esophageal sphincter on manometry
- **DIAGNOSIS**—endoscopy is essential for ruling out malignancy. Barium swallow (beak-like narrowing), esophageal manometry (definitive)

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—endoscopic intrasphincteric injection of botulinum toxin, pneumatic dilation, and surgical myotomy

INFECTIOUS ESOPHAGITIS

- **PATHOPHYSIOLOGY**—common organisms include *Candida albicans*, CMV, and HSV. Happens more likely in immunocompromised host
- **DIAGNOSIS**—gastroscopy and biopsy/viral cultures

EOSINOPHILIC ESOPHAGITIS

- **PATHOPHYSIOLOGY**—food allergens and genetic factors leading to eosinophilic infiltration and stricture
- **DIAGNOSIS**—gastroscopy and biopsy
- **TREATMENTS**—dilatation, dietary modification, swallowed inhaled steroids, and oral steroids

Related Topics
Esophageal Cancer (p. 195)
Stroke (p. 299)

Dyspepsia

DIFFERENTIAL DIAGNOSIS

NON-GASTRIC CAUSES—cardiac (myocardial infarction), pulmonary (pneumonia), hepatobiliary (biliary colic), pancreatic (pancreatitis), colonic (irritable bowel disease), musculoskeletal, dietary indiscretion

PEPTIC ULCER DISEASE (PUD, 10–20%)—*H. pylori*, ASA, NSAIDs (COX-2 inhibitors slightly decreased risk), cancer, Zollinger–Ellison, smoking

MEDICATION SIDE EFFECTS—NSAIDs, ASA, theophylline, calcium channel blockers, erythromycin, metronidazole, bisphosphonates, orlistat, acarbose, iron, potassium supplements

GASTROESOPHAGEAL REFLUX DISEASE (GERD, 20%)

★ACIDS★

- **A**cid hypersecretion—Zollinger–Ellison disease
- **A**lcohol abuse
- **C**onnective tissue disease—scleroderma
- **I**nfections of esophagus—CMV, HSV, candidiasis
- **D**iabetic gastroparesis
- **D**rug therapy
- **S**moking

NON-ULCER DYSPEPSIA (50%)—cause unclear. Diagnosis of exclusion (rule out organic cause and irritable bowel disease)

PATHOPHYSIOLOGY

COMPLICATIONS OF PUD—perforation, hemorrhage, gastric outlet obstruction, pancreatitis

PATHOPHYSIOLOGY (CONT'D)

COMPLICATIONS OF GERD—esophageal complications include esophagitis, esophageal ulcer, esophageal stricture, and Barrett's syndrome. Extra-esophageal complications include asthma, aspiration, chronic cough, hoarseness, chronic laryngitis, and dental erosions

CLINICAL FEATURES

SYMPTOM DEFINITIONS

- **DYSPEPSIA**—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

RATIONAL CLINICAL EXAMINATION SERIES: CAN THE CLINICAL HISTORY DISTINGUISH BETWEEN ORGANIC AND FUNCTIONAL DYSPEPSIA?

	LR+	LR−
Organic dyspepsia		
Diagnosis reached by the clinician or computer model	1.6	0.46
Peptic ulcer disease		
Diagnosis reached by the clinician or computer model	2.2	0.45

CLINICAL FEATURES (CONT'D)

	LR+	LR−
Esophagitis		
Diagnosis reached by the clinician or computer model	2.4	0.5

APPROACH—"functional dyspepsia is defined as pain or discomfort centered in the epigastrium with a normal endoscopy. Neither clinical impression nor computer models that incorporated patient demographics, risk factors, history items and symptoms adequately distinguished between organic and functional disease in patients referred for endoscopic evaluation of dyspepsia"

JAMA 2006 295:13

PRACTICAL APPROACH TO DYSPEPSIA

1. Consider **non-gastric causes** of dyspepsia (cardiac, pulmonary, hepatobiliary, colonic, musculoskeletal, medications, and dietary indiscretion) and investigate those causes if likely. Otherwise proceed to step 2
2. If **age >50 or alarm symptoms ★Very BAD★** (**V**omiting, **B**leed/anemia, **A**bdominal mass/weight loss, **D**ysphagia), refer for gastroscopy to check for gastric cancer. Otherwise proceed to step 3
3. If **ASA or NSAIDs** use, stop medications if possible. If not, consider proton pump inhibitor/H_2 blocker trial and proceed to step 4
4. If **GERD predominant symptoms** (heartburn, regurgitation), treat as GERD. Otherwise, proceed to step 5
5. If ***H. pylori* urea breath test positive**, treat with triple therapy. Otherwise, proceed to step 6
6. If none of the above, diagnosis of **non-ulcer dyspepsia**

Canadian Dyspepsia Working Group. Can J Gastroenterol 2005 19:5

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, glucose, AST, ALT, ALP, bilirubin, lipase, Ca, albumin, fecal occult blood
- **IMAGING**—upper GI series, U/S abd, CT abd

SPECIAL

- **UREA BREATH TEST**
- ***H. PYLORI* SEROLOGY**
- **24-H ESOPHAGEAL PH MONITORING**
- **ENDOSCOPY WITH BIOPSY**—urease test, C&S for *H. pylori*
- **PROTON PUMP INHIBITOR TEST**—sens 78% for GERD

MANAGEMENT

PEPTIC ULCER DISEASE—avoid NSAID use. Antisecretory treatment (*ranitidine* 150–300 mg PO BID, *omeprazole* 20–40 mg PO daily, *lansoprazole* 15–30 mg PO daily, *pantoprazole* 40 mg PO BID). ***H. pylori* eradication** (**★CAO★**: *clarithromycin* 500 mg PO BID, *amoxicillin* 1 g PO BID, *omeprazole* 40 mg PO daily ×10 days; **★CMO★** (if penicillin allergy): *clarithromycin* 500 mg PO BID, *metronidazole* 250 mg PO QID, *omeprazole* 40 mg PO daily ×10 days; **★BMT★** (if macrolide allergy or failed first line): *bismuth* 30 mL PO QID, *metronidazole* 250 mg PO QID, *tetracycline* 500 mg PO QID ×2 weeks)

GERD—lifestyle changes (avoid coffee, alcohol, chocolate, high-fat meals, acidic or spicy foods. More frequent, smaller portions, weight loss, smoking cessation, elevate bed, loose garments). **Antisecretory treatment** (proton pump inhibitors more effective than H2 blockers for esophagitis. Use antacids as breakthrough). **Nissen fundoplication**

NON-ULCER DYSPEPSIA—lifestyle changes (avoid alcohol, caffeine, tobacco). **Antisecretory treatment** (see above). ***H. pylori* eradication** (may or may not relieve symptoms). **Promotility agent** (domperidone)

Related Topics
Esophageal Cancer (p. 195)
Gastric Cancer (p. 197)
Gastric Lymphoma (p. 173)

SPECIFIC ENTITIES

GERD

- **CAUSES**—obesity, lower esophageal sphincter pressure, decreased esophageal peristalsis, gastric acid hypersecretion, delayed gastric emptying, and overeating
- **PATHOPHYSIOLOGY**—reflux of stomach contents, leading to a multitude of symptoms including heartburn, regurgitation, dysphagia, chest pain, complicated by esophagitis, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma
- **CLINICAL FEATURES**—esophageal (heartburn, regurgitation), extra-esophageal (wheeze, cough, pneumonia, waterbrash, hoarseness, sore throat, globus, dental erosions)
- **DIAGNOSIS**—clinical based on symptoms (≥2/week). Endoscopy to look for complications and rule out other potential diagnoses

NEJM 2008 359:16

NSAIDS-INDUCED GASTROPATHY

- **PATHOPHYSIOLOGY**—NSAIDs inhibit COX-1 (normally protective effect through mucus secretion,

SPECIFIC ENTITIES (CONT'D)

bicarbonate secretion, mucosal circulation) and COX-2 (inducible inflammatory activity, also in kidneys). It also has direct toxic mucosal effect → dose related but even low dose baby ASA may contribute to ulcer formation. Overall ~20% patients on NSAIDs develop ulcers. Risk factors include age >60, pre-existing peptic ulcer, multiple NSAIDs, high-dose NSAIDs, concomitant glucocorticoid or anticoagulant therapy

- **TREATMENTS**—primary prophylaxis includes misoprostol and proton pump inhibitor. If ulcer developed while on NSAIDs but must continue, should give proton pump inhibitor

BARRETT'S ESOPHAGUS

- **PATHOPHYSIOLOGY**—prolonged heartburn → intestinal squamous metaplasia (abnormal salmon-colored mucosa extending proximally from the gastroesophageal junction to the normal pale esophageal mucosa) → dysplasia → adenocarcinoma of esophagus and gastric cardia. Barrett's develops in 5–8% of patients with GERD. Transformation to low-grade dysplasia 4%/year, high-grade dysplasia 1%/year and cancer 0.5%/year
- **DIAGNOSIS**—screen with surveillance endoscopy every 2–3 years if age >50 or GERD >5 years. Mucosal biopsy after the initial diagnosis of Barrett's esophagus to look for dysplasia. Once diagnosed with Barrett's, endoscopy with biopsy every 1–3 years, 6–12 months if low-grade dysplasia

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—high-grade dysplasia should be evaluated for esophagectomy or ablative therapy

GASTROPARESIS

- **CAUSES**—systemic diseases (diabetes, scleroderma), drugs (anticholinergic agents, narcotics), idiopathic
- **PATHOPHYSIOLOGY**—impairment of gastric emptying due to dysfunction of the neuromuscular unit → dyspepsia, bloating, nausea, vomiting, and weight loss
- **DIAGNOSIS**—nuclear medicine solid-phase gastric emptying study, barium swallow, gastroscopy
- **TREATMENTS**—frequent, small, low-fat, low-fiber feedings, prokinetic agents (*metoclopramide* 10 mg PO TID ac meals, *erythromycin* 250 mg PO TID ac meals, *domperidone* 10 mg PO QID), nutritional support

NEJM 2007 356:8

HELICOBACTER PYLORI

- **PATHOPHYSIOLOGY**—chronic inflammation → causative role in 50–80% of duodenal ulcers, 40–60% of gastric ulcers, 80% of gastric cancers, and 90% of gastric lymphomas
- **DIAGNOSIS**—urea breath test (sens 90%, spc 95%. Particularly good in post-treatment setting), serology (sens 90%, spc 80%) is of limited value as it tests for IgG which only indicates previous exposure, endoscopy (culture, histologic assessment, 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, peritonitis

GU—pyelonephritis, renal colic, cystitis, prostatitis, testicular torsion, inguinal hernia

GYNECOLOGIC—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's disease, diabetic ketoacidosis, uremia, hypercalcemia, porphyria, familial Mediterranean fever

OTHERS—myocardial infarction, pneumonia, splenic injury, shingles, musculoskeletal

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), N&V, bleeding, fever, inquire about last menstrual period and pregnancy if female, past medical history (CAD, diabetes, hypertension, renal stones), medication history (analgesics)

PHYSICAL—vitals, respiratory and cardiac examination, abdominal examination, CVA tenderness, pelvic and rectal examination and test for fecal occult blood

APPENDICITIS SEQUENCE—vague pain initially located in the epigastric or periumbilical region; anorexia, nausea, or unsustained vomiting; migration of the initial pain to the RLQ; low-grade fever

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE APPENDICITIS?

	Sens	Spc	LR+	LR−
History				
Migration of pain to RLQ	64%	82%	3.18	0.5
RLQ pain	81%	53%	8.0	0.15
Pain before vomiting	100%	64%	2.76	–
No similar pain previously	81%	41%	1.5	0.32
Physical				
Rigidity	27%	83%	3.76	0.82
Fever	67%	79%	1.94	0.58
Rebound tenderness	63%	69%	3.7	0.4
Psoas sign	16%	95%	2.38	0.90
Obturator sign	–	–	–	–
Rectal exam	–	–	–	–

APPROACH—"migration of pain, RLQ pain and pain before vomit suggest appendicitis. Rigidity, positive psoas sign, fever and rebound tenderness increase likelihood of appendicitis. Absence of above and similar pain previously suggest appendicitis is less likely"

JAMA 1996 276:19

CLINICAL FEATURES (CONT'D)

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's 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's 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. 139)

EXAMINATION OF ABDOMINAL MASSES

- **RIGHT UPPER QUADRANT MASS**—**liver** (downward with inspiration, left lobe, bruit/venous hum), **right kidney** (downward with inspiration, ballotable, palpable upper border), **gallbladder** (downward with inspiration, smooth and regular), **colon or gastroduodenal** (does not move with inspiration, ill-defined mass, high-pitch bowel sounds), **lymphoma** (does not move with inspiration, usually more central)
- **LEFT UPPER QUADRANT MASS**—**spleen** (downward and medially with inspiration, notch, bruit), **left kidney** (downward with inspiration, ballotable, palpable upper border), **colon** (splenic flexure), **gastric or pancreatic** (ill-defined mass, difficult to clearly differentiate these masses on examination), **lymphoma** (does not move with inspiration, usually more central)
- **RIGHT LOWER QUADRANT MASS**—**colon, distal small bowel, or appendix** (lower GI masses are ill-defined and difficult to clearly differentiate on examination), **ovary, uterus, fallopian tube** (pelvic structures require bimanual examination), **lymphoma** (does not move with inspiration, usually more central)
- **LEFT LOWER QUADRANT MASS**—**colon, distal small bowel, or appendix** (lower GI masses are ill-defined and difficult to clearly differentiate on examination), **ovary, uterus, fallopian tube** (pelvic structures require bimanual examination), **lymphoma** (does not move with inspiration, usually more central)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, lipase, amylase, lactate, INR, PTT, Ca albumin, urinalysis, urine βhCG (if women age <40)
- **MICROBIOLOGY**—urine C&S, stool C&S, fecal occult blood
- **IMAGING**—CXR, AXR, U/S abd/pelvic

SPECIAL

- **IMAGING**—IVP, barium contrast, CT abd
- **ECG**—if suspect cardiac involvement
- **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 also see outside of bowel wall, suggests free air outside bowel)
- **SMALL BOWEL**—more central location, valvulae closer together, thin and cross completely. Dilated if >3 cm [1.2 in.]
- **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)
- **STOOL IN BOWEL**—cannot distinguish from abscess
- **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 (decreased fat)
- **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, O_2, IV hydration. **NPO**, NG if severe N&V/obstruction. ***Morphine*** 2.5–5 mg SC q4h PRN and 1–2 mg IV q1h PRN. ***Dimenhydrinate*** 50 mg IM/IV q6h PRN

TREAT UNDERLYING CAUSE—**early surgical consult**. **Antibiotics** if fever or suspect peritonitis (*cefazolin* 1 g IV q8h, *gentamicin* 6 mg/kg IV q24h, *metronidazole* 500 mg IV q12h)

SPECIFIC ENTITIES

GALLSTONE DISEASE SPECTRUM—asymptomatic (70%), biliary colic (20%, intermittent obstruction), acute cholecystitis (cystic duct obstruction), choledocholithiasis (common bile duct obstruction), ascending cholangitis (stasis and infection of biliary tract. May be secondary to choledocholithiasis. See p. 139 for more details), gallstone pancreatitis (pancreatic duct obstruction), gallstone ileus, gallbladder cancer

ACUTE CHOLECYSTITIS

- **PATHOPHYSIOLOGY**—abnormalities of bile acid secretion, mucus generation, and gallbladder motility → gallstone formation → migrate to obstruct the cystic duct and even common bile duct/pancreatic duct → gallbladder inflammation and sometimes 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 (Aboriginal, Hispanic), TPN, and rapid weight loss

SPECIFIC ENTITIES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ACUTE CHOLECYSTITIS?

HISTORY—RUQ pain, N&V, anorexia, fever

PHYSICAL—Murphy sign (arrest of inspiration while palpating the gallbladder during a deep breath), guarding, rigidity, RUQ mass, rebound, rectal tenderness

	Sens	Spc	LR+	LR−
Murphy sign	65%	87%	2.8	0.5
RUQ tenderness	77%	54%	1.6	0.4

INVESTIGATIONS—leukocytosis, ALP >120 U/L, elevated ALT or AST, elevated bilirubin

APPROACH—"no single clinical finding or laboratory test carries sufficient weight to establish or exclude cholecystitis without further testing (i.e. ultrasound). Clinical gestalt (without ultrasound) is estimated to have LR+ 25–30, bringing the probability of cholecystitis from 5% pretest to 60% post test. The evaluation of patients with abdominal pain suggestive of cholecystitis will continue to rely heavily on clinical gestalt and diagnostic imaging"

JAMA 2003 289:1

- **DIAGNOSIS**—U/S abd, endoscopic U/S, ERCP, percutaneous transhepatic cholangiography, MRCP, HIDA/DISIDA, CT scan
- **TREATMENTS**—supportive measures include NPO, IV fluids, pain control (NSAIDs, opioids), antiemetics and antibiotics (*cefuroxime* 250–500 mg IV BID, or *ciprofloxacin* 400 mg IV q12h plus *metronidazole* 500 mg IV q12h). Cholecystectomy (laparoscopic, open) or percutaneous cholecystomy to facilitate drainage. If biliary pain despite cholecystectomy, consider possibility of a retained common bile duct stone, sphincter of Oddi dysfunction, or functional pain

NEJM 2008 358:26

ACUTE MESENTERIC ISCHEMIA

- **PATHOPHYSIOLOGY**—embolism in the celiac or superior mesenteric artery from valvular heart disease or atrial fibrillation → sudden and severe periumbilical pain out of proportion with physical findings, N&V, leukocytosis, ↑ lactate, ileus
- **DIAGNOSIS**—high clinical suspicion
- **TREATMENTS**—immediate surgery

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 → hematochezia, diarrhea, abdominal pain
- **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

SPECIFIC ENTITIES (CONT'D)

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 U/S (sens 90% for stenosis of >50%), CT, or mesenteric angiography
- **TREATMENTS**—angioplasty, surgical revascularization

Upper GI Bleed

NEJM 2008 359:9

DIFFERENTIAL DIAGNOSIS

PEPTIC ULCER DISEASE (PUD)—gastric, duodenum
INFLAMMATION—**esophagitis** (CMV, medications), **gastritis** (acute, chronic), **inflammatory bowel disease** (Crohn's)
VARICES—esophagus, stomach
TUMORS—esophagus, stomach, duodenum
STRUCTURAL—Mallory–Weiss tear, Boerhaave's syndrome, Dieulafoy's lesion, arteriovenous malformation, aortoduodenal fistula, hemobilia
OTHERS—epistaxis, hemoptysis

CLINICAL FEATURES

HISTORY—volume of hematemesis, melena, and hematochezia, vomiting, past medical history (PUD, *H. pylori* infection, alcohol-related disorders, liver cirrhosis with varices, renal failure, metastatic cancer, heart disease/HF), medication history (anticoagulants, NSAIDs)

PHYSICAL—acute bleeding, sinus tachycardia, supine hypotension (SBP <95 mmHg), postural pulse increase >30/min or dizziness, anemia (conjunctival, facial or palmar pallor), cirrhosis (facial telangiectasia, palmar erythema, spider angiomas, gynecomastia, abdominal wall veins, white nails, peripheral edema). Perform a rectal examination and test for fecal occult blood. Examine vomitus or nasogastric aspirate and test for occult blood

CLINICAL FEATURES (CONT'D)

BLACK STOOL THAT MAY MIMIC MELENA—bismuth subsalicylate, iron, spinach, charcoal

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 dizzines	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)

Related Topic
Shock (p. 97)

HYPOVOLEMIA DUE TO VOMITING, DIARRHEA, DECREASED INTAKE, DIURETICS

	Sens	Spc	LR+	LR−
Symptoms				
Postural pulse increment ≥30/min	43%	75%	1.71	0.8
Postural hypotension ≥20 mmHg	29%	81%	1.5	0.9
Dry axilla	50%	82%	2.8	0.6
Dry oral/nasal mucous membrane	85%	58%	2.0	0.3
Dry tongue	59%	73%	2.1	0.6

CLINICAL FEATURES (CONT'D)

	Sens	Spc	LR+	LR−
Tongue with furrows	85%	58%	2.0	0.3
Sunken eyes	62%	82%	3.4	0.5
Confusion	57%	73%	2.1	0.6
Upper/lower extremity weakness	43%	82%	2.3	0.7
Speech not clear or expressive	56%	82%	3.1	0.5
Capillary refill time >normal	34%	95%	6.9	0.7

APPROACH—"for patients with suspected acute blood loss, severe postural dizziness (preventing upright vitals measurements) or postural pulse increment are predictive. Postural hypotension has no incremental value. For patients with suspected hypovolemia not due to blood loss, severe postural dizziness, postural pulse increment, or dry axilla can be helpful. Moist mucous membranes and tongue without furrows argue against it. Capillary refill time and poor skin turgor have no proven diagnostic value"

JAMA 1999 281:11

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, type/cross-match, PTT, INR, AST, ALT, ALP, bilirubin, albumin, fecal occult blood
- **IMAGING**—CXR, AXR
- **GASTROSCOPY**

PROGNOSTIC ISSUES

RISK STRATIFICATION FOR PEPTIC ULCER DISEASE

- **CLINICAL ROCKALL SCORING**—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
- **COMPLETE ROCKALL SCORING**—in addition to clinical Rockall score, add the following based on endoscopic findings: no lesion observed, Mallory–Weiss tear=0; peptic 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= clinical Rockall score 0 or complete Rockall score ≤2

RISK OF ULCER RE-BLEED

- **HIGH-RISK FEATURES**—active spurting/oozing during endoscopy (90% chance), non-bleeding visible vessel (50% chance), adherent clot (25–30% chance). If none of above factors and clinically not severe bleed, very low chance of rebleed and may consider discharging shortly after. Other factors include size and location of ulcer
- **LOW-RISK FEATURES**—flat spot (10% chance), clean ulcer base (3–5% chance)

MANAGEMENT

ACUTE—**ABC**, O_2, **IV hydration** (two large-bore IV). **Transfusion** (especially if hematocrit <30%, platelets $<50\times10^9$). NPO, consider NG tube. **Hold**

MANAGEMENT (CONT'D)

antihypertensive and diuretic therapy. If prolonged PT/PTT, ***vitamin K*** 10 mg PO/IV (small risk of anaphylaxis with IV administration) and/or ***FFP*** 2–4 U IV if rapid reversal required. If on heparin, ***protamine*** infusion (1 mg antagonizes 100 U of heparin—beware of excessive protamine which can cause paradoxical coagulopathy). If suspect varices, ***octreotide*** 50 μg IV bolus, then 25–50 μg/hour. If suspect ulcer, ***pantoprazole*** 80 mg IV bolus, then 8 mg/h until endoscopy. If cirrhosis and acute variceal hemorrhage, **transfuse** 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** for gastroscopy and consider ***erythromycin*** 250 mg IV 30–90 min before endoscopy for clot lavage

TREAT UNDERLYING CAUSE—**avoid** ASA, NSAIDs. **Peptic ulcer** (endoscopic hemostasis with thermal coagulation/fibrin sealant/endoclips plus 1:10,000 ratio epinephrine injection. After endoscopy, start *pantoprazole* 80 mg IV bolus if not given already, then 8 mg/h ×72 h [if high-risk lesion], switch to 40 mg PO BID ×1 month then daily). **Varices** (endoscopy within 12 h with ligation/band/glue/sclerotherapy → balloon tamponade → TIPPS → portacaval/distal splenorenal shunt, or liver transplant. Continue octreotide for 3–5 days. Repeat endoscopy every 2 weeks until varices obliterated, then at 1–3 months and again every 6–12 months afterward. Consider non-selective β-blocker such as *nadalol* 40 mg PO daily. **Mallory–Weiss tear** (*omeprazole* 20 mg PO daily). ***H. pylori*** (see DYSPEPSIA p. 113 for treatment). **Intractable or recurrent bleed** (consult surgery. See TREATMENT ISSUES below)

TREATMENT ISSUES

CRITERIA FOR SURGICAL CONSULT FOR ULCER BLEED—hemodynamic instability despite

TREATMENT ISSUES (CONT'D)

resuscitation (>3 U PRBC), shock, recurrent hemorrhage after two endoscopic attempts, continued slow bleed requiring >3 U PRBC/day), high-risk endoscopic lesion

COMPLICATIONS OF ENDOSCOPY—perforations, bleeding, sedation-related respiratory failure

DISCHARGE DECISIONS FOR PATIENTS' PEPTIC ULCER DISEASE—patients with low-risk of re-bleed

TREATMENT ISSUES (CONT'D)

(complete 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, while patients with high-risk features should be admitted and monitored closely

Lower GI Bleed

DIFFERENTIAL DIAGNOSIS

UPPER GI SOURCE WITH BRISK BLEEDING (10%)

INFECTIOUS—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, *E. coli* (EHEC, EIEC), *C. 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's diverticulum

CLINICAL FEATURES

HISTORY—volume of bleed, melena, abdominal pain, past medical history (IBD, cancer, diverticulosis), medication history (anticoagulants, NSAIDs)

PHYSICAL—acute bleeding, sinus tachycardia, supine hypotension (SBP <95 mmHg), postural pulse increase >30/min or dizziness, anemia (conjunctival, facial or palmar pallor), abdominal tenderness. Perform a rectal examination and test for fecal occult blood

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, type/X-match, PTT, INR, AST, ALT, ALP, bilirubin, albumin
- **MICROBIOLOGY**—stool C&S, fecal occult blood
- **ENDOSCOPY**—colonoscopy, gastroscopy

SPECIAL

- **IMAGING**—for obscure bleed, consider ^{99}Tc RBC scan (detects 0.1 mL/min), angiography

INVESTIGATIONS (CONT'D)

(detects 0.5 mL/min), capsule endoscopy, push enteroscopy, double balloon enteroscopy, and/or Meckel's scan

DIAGNOSTIC ISSUES

OCCULT BLEED—no obvious melena or bright red blood per rectum (BRBPR), but possible bleed as fecal occult blood positive

OBSCURE BLEED—obvious bleeding but source cannot be found

OVERALL APPROACH—gastroscopy and/or colonoscopy (start with the end with the most likely source of bleed, then scope the other end if no yield) → if negative, repeat panendoscopy → if negative, small bowel followthrough → if negative, consider angiography, RBC scan, capsule, push or double balloon endoscopy, or laparotomy

MANAGEMENT

ACUTE—**ABC**, O_2, **IV hydration** (two large-bore IVs). **Transfusion** (especially if hematocrit <30%, platelets $<50\times10^9$/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/or ***FFP*** 2–4 U IV or prothrombin complex concentrate (PCC) if rapid reversal required. If on unfractionated heparin, ***protamine*** infusion (1 mg antagonizes 100 U of heparin). **Consult GI** for endoscopy

TREAT UNDERLYING CAUSE

Inflammatory Bowel Disease Exacerbation

DIFFERENTIAL DIAGNOSIS

See differential diagnosis for
ACUTE ABDOMINAL PAIN (p. 115)
LOWER GI BLEED (p. 120) and
CHRONIC DIARRHEA (p. 124)

PATHOPHYSIOLOGY

TYPES

- **CROHN'S**—**mild to moderate** (relatively asymptomatic, tolerating oral diet), **moderate to severe** (failed treatment for mild disease, symptomatic),

PATHOPHYSIOLOGY (CONT'D)

severe to fulminant (failed steroid treatment, very symptomatic)

- **ULCERATIVE COLITIS**—**ulcerative proctitis** (limited to rectum), **distal colitis/protosigmoiditis** (extending up to mid-sigmoid colon), **left-sided colitis** (extending up to splenic flexure), **extensive colitis** (extending up to but not including cecum), **pancolitis** (extending up to cecum)

CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN CROHN'S DISEASE AND ULCERATIVE COLITIS

	Crohn's disease	Ulcerative colitis
Degree of involvement	Segmental Rectal sparing	Continuous
Symptoms	Abd pain Diarrhea Anorexia Perianal disease	Bloody diarrhea Tenesmus Fever
Serology	*Saccharomyces cerevisiae* IgG antibody (sens 77%, spec 92%, PPV 82%)	P-ANCA (sens 70%, spc 88%, PPV 75%)
Pathology	Transmural granuloma	Mucosal inflammation No granuloma
Complications	Obstruction Strictures Fistulas Fissures Abscesses Colorectal cancer	Toxic megacolon (1–2%) Colorectal cancer (1%/year after 10 years)

CLINICAL FEATURES (CONT'D)

EXTRAINTESTINAL MANIFESTATIONS—fever, clubbing, uveitis, iritis, anemia, jaundice (primary sclerosing cholangitis), aphthous ulcers (Crohn's only), arthritis (spondylitis; type I arthropathy: pauciarticular and related to IBD activity; type II arthropathy: polyarticular and unrelated to IBD activity), erythema nodosum, pyoderma gangrenosum, DVT, amyloidosis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, ESR, CRP, Fe, TIBC, ferritin, % sat, AST, ALT, ALP, bilirubin, albumin, Ca, Mg, PO_4, vitamin B12, folate
- **MICROBIOLOGY**—stool C&S, fecal occult blood, stool for *C. difficile* toxin assay
- **IMAGING**—AXR
- **ENDOSCOPY**—flexible sigmoidoscopy, colonoscopy

MANAGEMENT

SUPPORTIVE THERAPY

- **DIET AND NUTRITION**—if mild, low-fiber diet, elemental diet; if severe, TPN and bowel rest
- **ANTIDIARRHEAL AGENTS**—contraindicated in severe exacerbation and toxic megacolon

ANTIINFLAMMATORY AGENTS

- **5ASA SUPPOSITORIES**—if localized disease. *Mesalamine* 1 g PR qhs, glucocorticoid enema/suppositories daily-BID

MANAGEMENT (CONT'D)

- **SYSTEMIC 5ASA**—for induction and maintenance (*sulfasalazine* induction 0.5 g PO BID, then titrate to 0.5–1.5 g PO QID, maintenance 1 g PO BID–QID; *mesalamine* 800–1600 mg PO TID maintenance 400–800 mg PO TID; *olsalazine*)
- **GLUCOCORTICOIDS**—for flares (*methylprednisolone* 30 mg IV BID, *prednisone* 50 mg PO daily, reduce by 5 mg/week)
- **IMMUNOSUPPRESSIVE AGENTS**—*azathioprine* 50 mg PO daily, increase by 25 mg daily every 2 weeks to a max of 2–3 mg/kg/day as tolerated, *methotrexate* 25 mg IM weekly
- **ANTIBIOTICS**—*metronidazole* 500 mg PO TID, *ciprofloxacin* 500 mg PO BID
- **BIOLOGICAL AGENTS**—*infliximab* IV infusions of 5 mg/kg at 0, 2, 6 weeks. Dosing regimens differ for adalimumab and certolizumab. Drug coverage for anti-TNF therapy differs between Canadian provinces

SURGERY

Related Topics
Clostridium difficile Colitis (p. 122)
Inflammatory Arthritis (p. 282)

TREATMENT ISSUES

CROHN'S COLITIS

- **STEPWISE TREATMENT**—oral 5ASA or sulfasalazine for 3–4 weeks. If failed, add metronidazole and ciprofloxacin. If failed, add oral steroids for 4 weeks. If failed, consider immunosuppressive therapy. Consider metronidazole and ciprofloxacin for treatment of perianal fistula

ULCERATIVE COLITIS

- **ULCERATIVE PROCTITIS**—5ASA suppositories or enemas for 2–4 weeks for active treatment. If failed, add steroid foams. Consider oral 5ASA if patient cannot tolerate suppositories. Maintenance therapy may be required
- **DISTAL COLITIS/PROTOSIGMOIDITIS AND LEFT-SIDED COLITIS**—similar treatment to ulcerative proctitis, push to maximal dose if necessary. If failed, add budesonide enemas. If failed, add oral prednisone. Maintenance therapy is recommended
- **EXTENSIVE AND PANCOLITIS** (mild-moderate)—oral 5ASA or sulfasalazine, plus topical 5ASA or steroid enemas. Add oral prednisone if failed or severe symptoms. Maintenance therapy is required
- **EXTENSIVE AND PANCOLITIS** (severe)—hospitalize with bowel rest, hydration, nutrition, parenteral steroids, and adjunctive rectal and oral therapy. Consider adding metronidazole, ciprofloxacin, and cyclosporine. May need surgical consult

TREATMENT ISSUES (CONT'D)

TOXIC MEGACOLON

- **PATHOPHYSIOLOGY**—a potential complication of inflammatory bowel disease, infectious colitis (*C. difficile*, other inflammatory organisms), ischemic colitis, and obstructive colon cancer
- **CLINICAL FEATURES**—the combination of abdominal distension and diarrhea (may be bloody, improvement of diarrhea may actually suggest onset of megacolon) should prompt investigations for toxic megacolon. Patient usually toxic with fever, hypotension, delirium, and abdominal pain
- **DIAGNOSIS**—**dilated colon on X-ray** (usually transverse or right colon, >6 cm), plus **three of the following** (fever $>38^{\circ}$C [100.4°F], tachycardia >120/min, leukocytosis $>10.5\times10^{9}$/L, anemia), plus **one of the following** (dehydration, delirium electrolyte disturbances, hypotension)
- **TREATMENTS**—supportive therapy (NPO, IV fluids, hold all 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 aggressively with metronidazole or vancomycin. Patients with toxic megacolon who do not respond to therapy within 72h should be considered for colectomy. ICU admission for monitoring. Serial blood tests and AXR daily to assess progress

Acute Diarrhea

NEJM 2004 350:1

DIFFERENTIAL DIAGNOSIS

INFLAMMATORY/INVASIVE (fever, bloody, tenesmus)

- **INVASIVE INFECTIONS**—*Salmonella*, *Shigella*, *Campylobacter*, *Yersinia*, EHEC, EIEC, *Vibrio parahaemolyticus*, *Clostridium difficile*, *Entamoeba*
- **INFLAMMATORY**—ulcerative colitis, Crohn's
- **ISCHEMIC COLITIS**
- **RADIATION COLITIS**

NON-INFLAMMATORY

- **NON-INVASIVE INFECTIONS**—**bacterial** (*Vibrio cholera*, *Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*, *C. difficile*, ETEC, EPEC), **viral** (Rotavirus, norovirus, CMV), **parasites** (*Giardia*, *Cryptosporidium*, *Amoeba*)
- **MEDICATIONS**—antibiotics, laxatives, chemotherapy

PATHOPHYSIOLOGY

DEFINITION OF DIARRHEA—3 bowel movements/day or at least 200 g of stool/day. Acute diarrhea is defined as <2 weeks, whereas chronic diarrhea is defined as ≥2 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–Barre syndrome
- ***YERSINIA***—mesenteric adenitis, erythema nodosum, polyarthritis, reactive arthritis, bacteremia

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)

PATHOPHYSIOLOGY (CONT'D)

- **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 contact, 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 and test for fecal occult blood. Inspect stool sample if available

SALMONELLA* AND *CAMPYLOBACTER—although they are classified as inflammatory, patients usually only develop fever and severe diarrhea and not bloody diarrhea

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, lactate
- **MICROBIOLOGY**—stool C&S (sens 1.5–5.6%), O&P, C. diff toxin A+B, viral culture

SPECIAL

- **FECAL TESTING**—fecal leukocytes (inflammatory, sens 73%, spc 84%), fecal lactoferrin (inflammatory, sens 92%, spc 79%), Giardia toxin, fecal occult blood
- **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). ***Vibrio cholera*** (tetracycline). ***Isospora* and *Cyclospora*** (*trimethoprim–sulfamethoxazole* 160/800 PO BID ×7–10 days). ***C. difficile, Giardia,* and *Entamoeba*** (*metronidazole* 500 mg TID ×10 days)

Related Topic
Acute Abdominal Pain (p. 115)

SPECIFIC ENTITIES

ANTIBIOTICS-ASSOCIATED DIARRHEA AND PSEUDOMEMBRANOUS COLITIS

- **PATHOPHYSIOLOGY**—organisms include *C. difficile* (particularly with clindamycin, cephalosporins, penicillins) and non-*C. difficile* organisms (*Salmonella*, *C. perfringens*, *S. aureus*, *Candida*). 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. Note emergence of virulent *C. difficile* strain NAP-1/027 characterized by increased secretion of toxins A/B, binary toxin production 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. In patients with severe *C. difficile* infection, significant leukocytosis, pseudomembranous colitis, toxic megacolon (see p. 120), acute renal failure, and hypotension may develop
- **DIAGNOSIS**—*C. difficile* toxin A/B, colonoscopy (pseudomembranous colitis). *C. difficile* toxin levels are usually unnecessary immediately after treatment completion as up to one-third of patients have positive assays despite successful treatment
- **TREATMENTS**—**IV hydration**. **Discontinue** implicated antibiotics. **Avoid** use of antiperistaltic agents (opiates, loperamide). ***C. difficile* treatment** (*metronidazole* 250 mg PO QID ×10–14 days or *vancomycin* 125–500 mg PO QID ×10–14 days). For severe cases, consider oral vancomycin as first-line agent. If significant ileus or toxic megacolon, give vancomycin via NG or enema and *add* metronidazole 500 mg IV QID. 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**, consider retreatment with 14-day course and minimize use of other antibiotics. For further recurrences, consider tapering doses of *vancomycin* 125 mg PO QID ×1 week, then BID ×1 week, then daily ×1 week, then every other day ×1 week, then every 3 days ×2 weeks. Alternatives include *vancomycin* 125 mg PO QID and *rifampin* 600 mg BID ×7 days, or *Saccharomyces boulardii* 250 mg PO QID in combination with metronidazole or vancomycin

Chronic Diarrhea

NEJM 1995 332:11

DIFFERENTIAL DIAGNOSIS

★MISO★

MOTILITY—hyperthyroidism, diabetic neuropathy, bacterial overgrowth, irritable bowel syndrome (IBS), scleroderma

INFLAMMATORY

- **INFECTIONS**—*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *E. coli* (EHEC, EIEC), *C. difficile*, Amoeba
- **INFLAMMATORY**—ulcerative colitis, Crohn's, 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, calcitoninoma, gastrinoma, somatostatinoma
- **MEDICATIONS**—senna, dulcolax
- **OTHERS**—bile salt enteropathy, fatty acid induced, collagenous colitis, lymphocytic colitis

OSMOTIC

- **MALDIGESTION/MALABSORPTION**—pancreatic insufficiency, celiac disease, lactose intolerance, short bowel syndrome, enteric fistula
- **MEDICATIONS**—antacids, antibiotics, Mg citrate, Mg hydroxide, lactulose, sorbitol (i.e. "chewing gum diarrhea"), colchicine

Related Topics
Inflammatory Bowel Disease (p. 120)
Irritable Bowel Syndrome (p. 126)

CLINICAL FEATURES

HISTORY—characterize diarrhea (duration, frequency, volume, blood, floating), infectious contact, 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 and test for fecal occult blood

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, albumin, TSH, antitransglutaminase antibody, endomysial antibody
- **MICROBIOLOGY**—stool C&S, O&P, C. diff toxin A+B, Giardia toxin

SPECIAL

- **FECAL TESTING**—fecal leukocytes, fecal fat, fecal lytes, fecal occult blood, stool for phenothalin (laxative abuse), α-1 antitrypsin colonoscopy

INVESTIGATIONS (CONT'D)

- **IMAGING**—SBFT, CT abd
- **ENDOSCOPY**—upper and lower, for biopsy

INVESTIGATION ISSUES

DISTINGUISHING FEATURES

- **INFLAMMATORY**—bloody stool, fecal leukocytes
- **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—$280-2\times$(stool Na+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

SPECIFIC ENTITIES

CELIAC DISEASE

- **PATHOPHYSIOLOGY**—sensitivity to gluten in **B**arley, **R**ye, **O**at, **W**heat **★BROW★**→ T-cell-mediated immune reaction to gliadin → intestinal epithelial cell death → villous atrophy, crypt hyperplasia → malabsorption in small bowel. More common in females (2–3:1). Associated with type 1 diabetes, dermatitis herpetiformis (p. 361), IgA deficiency, liver dysfunction, and small bowel lymphoma (especially if no response to celiac diet)
- **CLINICAL FEATURES**—isolated weight loss, iron-deficiency anemia in the absence of gastrointestinal blood loss, nutritional deficiency, osteoporosis and sometimes osteomalacia (Looser zones on radiography), diarrhea (sometimes)
- **DIAGNOSIS**—antitransglutaminase IgA (sens 94%, spc 99%), antiendomysial IgA, antigliadin IgG (celiac patients with IgA deficiency may not be antitransglutaminase positive). Small bowel biopsy is helpful for diagnosis (intraepithelial lymphocytosis, crypt hyperplasia, villous atrophy, and good response to gluten-free diet). Once diagnosed, a bone density scan is recommended
- **TREATMENTS**—gluten-free diet lifelong. Steroids. If symptoms persist despite special diet, consider workup for enteropathy-associated lymphoma

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, HCO_3; 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's disease, or pseudo-obstruction 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. 397)
Celiac Disease (p. 124)
Vitamin B12 Deficiency (p. 405)

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, 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"

JAMA 1994 271:1

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, fasting lipid profile, Ca, Mg, PO_4, albumin, pre-albumin, carotene, Fe, ferritin, antitransglutaminase antibody, vitamin B12, RBC folate
- **IMAGING**—U/S abd

SPECIAL

- **COLONOSCOPY**—for Crohn's

INVESTIGATIONS (CONT'D)

- **GASTROSCOPY**—for Celiac disease
- **ERCP/MRCP**—if suspect chronic pancreatitis
- **STOOL FAT**—>6 g/day suggests steatorrhea
- **D-XYLOSE TEST**—if suspect malabsorption
- **BREATH TEST**—for carbohydrate malabsorption and lactose intolerance, including H_2, $^{14}CO_2$, or $^{13}CO_2$
- **ANTIINTRINSIC FACTOR ANTIBODY**—for vitamin B12 deficiency (has replaced historical Schilling test)

MANAGEMENT

SYMPTOM CONTROL—dietician 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

SPECIFIC ENTITIES (CONT'D)

- **VITAMIN E DEFICIENCY**—skeletal myopathy, spinocerebellar ataxia, pigmented retinopathy, and hemolysis

WATER-SOLUBLE VITAMIN DEFICIENCY

- **VITAMIN B1 (THIAMINE) DEFICIENCY**—Wernicke syndrome, Korsakoff syndrome, Leigh's syndrome (subacute necrotizing encephalomyopathy)
- **VITAMIN B3 (NIACIN, NICOTINIC ACID) DEFICIENCY ★DDDD★**—**D**ermatitis (photosensitive, pigmented, pellagra), **D**iarrhea, **D**ementia, **D**eath
- **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

Constipation NEJM 2003 349:14

DIFFERENTIAL DIAGNOSIS

★DUODENUM★

DIET—low fiber, dehydration

ψSYCHIATRY—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's, multiple sclerosis, stroke, autonomic neuropathy (cachexia–anorexia syndrome)

UNKNOWN

MISCELLANEOUS—irritable bowel syndrome (IBS), amyloidosis, scleroderma, immobility

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, TSH, Ca, Mg
- **IMAGING**—AXR

DIAGNOSTIC ISSUES

CONSTIPATION SCORE—based on flat abdominal X-ray. Divide into four quadrants (ascending, transverse, descending, and rectosigmoid colon). Rate amount of stool in each quadrant from 0–3. A total score >6/12 suggests constipation

MANAGEMENT

LIFESTYLE CHANGES—wheat **bran**, high-bran cereals, ***psyllium/Metamucil*** 2–3 teaspoon/day, **exercise**, **hydration** (8–10 glasses/day)

SYMPTOM CONTROL—**laxatives** (in order of increasing potency: *docusate* 100–240 mg daily-QID, *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, *PEG/Golytely* 4 L PRN). **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

SPECIFIC ENTITIES

IRRITABLE BOWEL SYNDROME (IBS)

- **PATHOPHYSIOLOGY**—heightened response to noxious visceral stimuli, such as balloon distenstion of the rectum and sigmoid colon
- **CLINICAL FEATURES**—Rome criteria define IBS as >3 months of abdominal pain relieved with defecation, associated with a change in the frequency or consistency of stool, plus two of the following

SPECIFIC ENTITIES (CONT'D)

for >25% of days: disturbed defecation (>3 bowel movements/day or <3 bowel movements/-week), altered stool formation, altered stool passage (straining, urgency, or feeling of incomplete evacuation), passage of mucus, bloating, or feeling of abdominal distenstion

RATIONAL CLINICAL EXAMINATION SERIES: WILL THE HISTORY AND PHYSICAL EXAMINATION HELP ESTABLISH THAT IRRITABLE BOWEL SYNDROME IS CAUSING THIS PATIENT'S LOWER GASTROINTESTINAL TRACT SYMPTOMS?

MANNING CRITERIA—abdominal pain relieved by defecation, more frequent stools with onset of pain, looser stools with onset of pain, passage of mucus per rectum, feeling of incomplete emptying, patient-reported visible abdominal distension

ROME I CRITERIA—abdominal pain or discomfort relieved with defecation or associated with a change in stool frequency or consistency for ≥3 months, plus ≥2 of the following on at least 25% of occasions or days: (1) altered stool frequency, (2) altered stool form, (3) altered stool passage, (4) passage of mucus per rectum, (5) bloating or distension

KRUIS MODEL—a computer model based on a number of signs and symptoms to rule in and rule out IBD. Symptoms include (1) abdominal pain, flatulence, or bowel irregularity for >2 years; (2) description of abdominal pain as "burning, cutting, very strong, terrible, feeling of pressure, dull, boring, or not so bad"; and (3) alternating constipation and diarrhea. Signs include (1) abnormal physical findings and/or history pathognomonic for any diagnosis other than IBS, (2) ESR >10 mm/h, (3) leukocytosis $>10\times10^9$/L, (4) hemoglobin <120 g/L [<12 g/dL] for females or <140 g/L [<14 g/dL] for males, (5) impression by the physician that the patient's history suggests blood in the stool

	Sens	Spc	LR+	LR−
Symptoms				
Lower abd pain	90%	32%	1.3	0.29
Passage of mucus	45%	65%	1.2	0.88
Feeling of incomplete evacuation	74%	45%	1.3	0.62
Looser stools at onset of pain	59%	73%	2.1	0.59
More frequent stools at onset of pain	53%	72%	1.9	0.67
Pain relieved by defecation	60%	66%	1.8	0.62
Patient reported visible abdominal distension	39%	77%	1.7	0.79
Diagnostic criteria				
Manning criteria	78%	72%	2.9	0.29
Rome I criteria	71%	85%	4.8	0.34
Kruis system	77%	89%	8.6	0.26

APPROACH—"absence of abdominal pain reduced the likelihood of IBS. Overall, individual symptoms have limited accuracy for diagnosing IBS in patients referred with lower GI symptoms. The accuracy of the Manning criteria, Rome I criteria and Kruis scoring system were only modest"

JAMA 2008 300:15

Related Topics
Acute Abdominal Pain (p. 115)
Constipation in the Palliative Setting (p. 396)
Nausea and Vomiting (p. 111)
Opioid Use (p. 391)

SPECIFIC ENTITIES (CONT'D)

- **ASSOCIATIONS**—patients with IBS are more likely to have functional dyspepsia, urinary symptoms, dysmenorrhea, dyspareunia, sexual dysfunction, a history of physical or sexual abuse, and fibromyalgia

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—IBS is a diagnosis of exclusion. Consider flexible sigmoidoscopy/colonoscopy, evaluation for celiac sprue (p. 124), and stool cultures to rule out other diseases
- **TREATMENTS**—reassurance, stress reduction, fiber supplementation. Consider fibers, osmotic laxatives for constipation, *loperamide* 2–4 mg daily and *alosetron* 0.5–1 mg PO BID ×12 weeks (5HT3 antagonist) for diarrhea, and antispasmodics (hyoscyamine), TCAs (*amitriptyline* 10–75 mg qhs), *desipramine* 50–150 mg PO daily, and SSRIs for abdominal pain. Cognitive behavioral therapy may also be useful

NEJM 2008 358:16

Acute Liver Failure

DIFFERENTIAL DIAGNOSIS

HEPATOCELLULAR INJURY PATTERN (↑↑ AST/ALT ± ↑ 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, halogen anesthetics, glyburide, propylthiouracil, Amanita mushroom, heavy metals, anabolic steroids, cocaine, ecstasy, phencyclidine
- **VASCULAR**—ischemic ("shock liver"), Budd–Chiari, congestive, venoocclusive disease (BMT, chemotherapy, OCP)
- **NEOPLASTIC**—hepatoma
- **AUTOIMMUNE**—autoimmune hepatitis
- **HEREDITARY**—Wilson's, hemochromatosis, α1-antitrypsin deficiency, glycogen storage disease
- **PREGNANCY**—acute fatty liver of pregnancy, HELLP
- **OTHERS**—liver surgery, Reye's syndrome with viral illness, and ASA use
- **NON-HEPATIC**—celiac sprue, adrenal insufficiency, myopathy, strenuous exercise

CHOLESTATIC PATTERN (↑↑ ALP/bilirubin ± ↑ 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 (↑↑ ALP with ↑ GGT ± ↑ bili/AST/ALT)

- **INFECTIOUS**—TB, histoplasmosis, abscess (bacterial, amoebic)
- **NEOPLASM**—hepatoma, lymphoma
- **GRANULOMATOUS DISEASE**—sarcoidosis, TB, fungal
- **OTHERS**—amyloidosis

ISOLATED HYPERBILIRUBINEMIA (↑↑ bilirubin only)—see JAUNDICE (p. 138)

PATHOPHYSIOLOGY

DEFINITIONS

- **ABNORMAL LIVER ENZYMES**—defined as ±2 standard deviations, so 5% of the population would have abnormal liver enzymes by definition
- **ACUTE (FULMINANT) LIVER FAILURE**—development of jaundice, coagulopathy, and encephalopathy within 8 weeks of onset of hepatocellular injury; subclassified into hyperacute (day 0–7), acute (day 8–28) and subacute (day >28)
- **CHRONIC HEPATITIS**—↑ ALT >6 months

Related Topics
Acetaminophen Overdose (p. 102)
Alcohol-Related Issues (p. 105)
Hemochromatosis (p. 420)
Hepatitis B (p. 130)
Hepatitis C (p. 131)
Hepatoma (p. 205)
Liver Diseases in Pregnancy (p. 411)
Wilson's Disease (p. 132)

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 **L**iver), ALP (liver, gut, bone, placenta), GGT, 5'NT, LDH (bone, muscle, liver, lungs)

COMPLICATIONS OF HEPATIC FAILURE

★SCREAM★

- **S**epsis
- **C**oagulopathy
- **R**enal failure
- **E**ncephalopathy
- **A**scites
- **M**etabolic changes (hypoglycemia, electrolyte abnormalities, acidosis)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HAV IgM, HAV IgG, HBsAg, HBsAb, HBcIgM, HBcIgG, lactate
- **IMAGING**—U/S abd, CT abd

SPECIAL

- **LABS**—EBV, CMV, HSV, ANA, antismooth muscle antibody (ASMA), antimitochondrial antibody (AMA), quantitative immunoglobulin, ferritin, Fe,

INVESTIGATIONS (CONT'D)

TIBC, % sat, ceruloplasmin, α1-antitrypsin, AFP, antitransglutaminase antibody, lipase, amylase, LDH, haptoglobin, acetaminophen, CK, TSH

- **ERCP/MRCP**
- **GASTROSCOPY**
- **LIVER BIOPSY**

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 abdominal U/S with dopplers, viral serologies, ANA, ASMA, quantitative Ig, ceruloplasmin, iron studies, antitransglutaminase antibody, and possibly liver biopsy

↑ **ALP/BILI**—ask about pain, symptoms of infiltrative disease, or IBD. To confirm liver involvement, perform bilirubin fractionation, GGT, 5′NT, abdominal U/S, AMA, and quantitative Ig. Consider MRCP/ERCP and liver biopsy

MONITORING—INR and bilirubin are much more useful to monitor liver function compared to transaminases

SURVIVAL IN ACUTE HEPATIC FAILURE—35% in hyperacute, 7% in acute, and 14% subacute

MANAGEMENT OF ACUTE LIVER FAILURE

SYMPTOM CONTROL

- **ACUTE**—ABC, O_2, IV hydration
- **ELEVATED INTRACRANIAL PRESSURE**—for cerebral edema, consider prophylactic phenytoin, raise head of bed, hyperventilate, dexamethasone, mannitol, avoid excessive fluids
- **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**—protein intake up to 1 g/kg/day. *Lactulose* 30 g PO QID PRN titrate to 2–4 bowel movements/day
- **ACIDOSIS**—D10W with 1–2 amp $NaHCO_3$ at 150–250 mL/h IV. Give with caution as risk of cerebral edema with increased fluid
- **HYPOGLYCEMIA**—D10W, tube feed, TPN
- **DETOXIFICATION**—*N-acetylcysteine* 150 mg/kg IV (~60 mL) in 200 mL D5W over 1 h, then 50 mg/kg (~20 mL) in 500 mL D5W over 4 h, then 100 mg/kg (~40 mL) in 1L D5W over 16 h. Alternatively, *N-acetylcysteine* 140 mg/kg PO/NG, followed by 70 mg/kg q4h for 17 doses. May continue *N*-acetylcysteine until INR normalized

MANAGEMENT OF ACUTE LIVER FAILURE (CONT'D)

PREVENTION—**hepatitis B vaccine** (0, 1, 6 months), **HBIG** (post-exposure), hepatitis A vaccine (see p. 270)

TREAT UNDERLYING CAUSE—**hepatitis B** (if acute liver failure from HBV, provide supportive care only without active HBV treatment). **Hepatitis C** (pegylated interferon ± ribavirin). **Alcoholic hepatitis** (abstinence, nutrition, *prednisolone* 40 mg PO ×28days but avoid if pancreatitis, GI bleed, renal failure, or active infection; *pentoxifylline* 400 mg PO TID ×28 days, *S-adenosylmethionine* 1200 mg PO daily ×2 years). **Autoimmune hepatitis** (steroid). **Wilson's disease** (D-penicillamine)

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, and degree of urgency
- **KING'S COLLEGE CRITERIA FOR TYLENOL OVERDOSE ACUTE HEPATIC FAILURE** (rule of **3**'s)—either arterial pH <**7.3** or grade **III** or IV encephalopathy, plus Cr >**300** μmol/L [>**3.3** mg/dL], plus INR >**6**
- **KING'S COLLEGE CRITERIA FOR NON-TYLENOL ACUTE HEPATIC FAILURE**—INR >3 or any 3 of following: age <10 or >40, non-A non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions, duration of jaundice before onset of encephalopathy >7 days, INR >1.5, bilirubin >308 μmol/L [179 mg/dL]
- **CONTRAINDICATIONS**—malignancy (except hepatocellular carcinoma), irreversible cardiopulmonary comorbidities, neuropsychiatric comorbidities, sepsis, substance abuse, non-compliance, HIV

SPECIFIC ENTITIES

AST/ALT THOUSAND 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**—fatty liver, alcoholic hepatitis, micronodular cirrhosis
- **DIAGNOSIS**—AST:ALT = 2:1 (low ALT activity 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 ↑
- **TREATMENTS**—abstinence, nutrition, *prednisolone* 40 mg PO ×28 days, *pentoxifylline* 400 mg PO TID ×4 weeks, *S-adenosylmethionine* 1200 mg PO daily ×2 years

SPECIFIC ENTITIES (CONT'D)

NON-ALCOHOLIC STEATOHEPATITIS (NASH)

- **ASSOCIATIONS**—obesity, hyperlipidemia, diabetes, Cushing's, TPN, high-protein diets for weight loss, amiodarone, tamoxifen

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—liver biopsy
- **TREATMENTS**—weight loss, metformin (experimental)

Hepatitis B

NEJM 2004 350:11; NEJM 2008 359:14

PATHOPHYSIOLOGY

NATURAL HISTORY—acute hepatitis → chronic disease develops in >90% of neonates, in 10% if 12 years old, and in <1% 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% with compensated cirrhosis progress to hepatocellular carcinoma. Lifetime risk of hepatocellular carcinoma/death in patients with chronic hepatitis is 40% for ♂ and 15% for ♀

ACUTE HEPATITIS B—may range from subclinical/anicteric hepatitis (70%) to icteric hepatitis (30%) and even fulminant hepatic failure (0.5–1%). Symptoms may include fever, anorexia, rash, nausea, jaundice, RUQ tenderness, arthralgia, and arthritis. ↑↑ ALT and AST

CHRONIC HEPATITIS B

- **REPLICATIVE PHASE WITH IMMUNE TOLERANCE** (only if vertical transmission)—HBeAg positive, asymptomatic as lack of immune response in children. May last 10–30 years
- **REPLICATIVE PHASE WITH IMMUNE CLEARANCE**—HBeAg positive with seroconversion to HBeAb, may be symptomatic with increased liver enzymes due to immune response against HBV
- **NON-REPLICATIVE PHASE**—HBeAb positive, low level of viral replication. Usually normal liver enzymes
- **SUSPECT PROGRESSION TO CIRRHOSIS**—if hypersplenism or impaired synthetic function (↑ INR, ↑ bilirubin, hypoalbuminemia)

GENOTYPES—there are currently eight different genotypes (A to H)

RISK FACTORS—vertical transmission, endemic areas, transfusions, dialysis, healthcare workers, IDU, high-risk sex/homosexuals, body piercing, tattoos, organ transplantation

Related Topics
Acute Liver Failure (p. 128)
Chronic Liver Failure (p. 132)
HBV/HIV Co-infection (p. 261)
Hepatitis C (p. 131)
Hepatoma (p. 205)

CLINICAL FEATURES

HISTORY—symptoms of liver failure (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. 132), weight

EXTRAHEPATIC MANIFESTATIONS OF HBV—polyarteritis nodosa, membranous nephropathy, membranoproliferative glomerulonephritis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HBV serology (HBsAb, HBsAg, HBcIgM, HBcIgG to determine infection/immune status, HBeAg, HBeAb, HBV DNA to see if active replication), HAV serology, HCV serology, HDV serology, iron, TIBC, HIV serology
- **IMAGING**—U/S abd

SPECIAL

- **LIVER BIOPSY**

DIAGNOSTIC ISSUES

HEPATITIS B SEROLOGY

- **HBsAg**—hepatitis B surface antigen. Positive if active infection
- **HBcIgM**—IgM antibody against hepatitis B core antigen. Suggestive of early infection (indicates the window period) or reactivation
- **HBsAb**—antibody against hepatitis B surface antigen. Positive if immunized (through past infection or vaccination)
- **HBcIgG**—IgG antibody against hepatitis B core antigen. Suggestive of hepatitis B exposure
- **HBeAg**—hepatitis B envelope protein. HBeAg positivity suggests high viral replication with high infectivity. However, HBeAg negativity without HBeAb positivity suggests chronic HBV infection with pre-core mutants/promoter mutations, with a more aggressive phenotype than HBeAg+ HBV, more treatment failures, and progressive hepatic

DIAGNOSTIC ISSUES (CONT'D)

injury. HBeAg negative infection is associated with fluctuating ALT and lower levels of HBV DNA. By definition, HBeAg seroconversion cannot occur

- **HBEAB**—antibody against hepatitis B envelope protein. Suggests low/no viral replication, usually with low infectivity

DIAGNOSTIC ISSUES (CONT'D)

- **HBV DNA**—direct determination of hepatitis B virus DNA. HBV DNA level reflects viral replication activity and is associated with the risk of cirrhosis and hepatoma. HBV DNA determination is important in both HBeAg+ and HBeAg– individuals to determine need for antiviral therapy

	HBsAg	HBcIgM	HBsAb	HBcIgG	HBeAg	HBeAb
Acute infection						
Early	+	–	–	–	+	–
Window	–	+	–	–	+	–
Late	–	+/–	+	–	+	–
Immunity						
Vaccinated	–	–	+	–	–	–
Cured	–	–	+/–	+	–	+
Chronic infection						
Infectious/active	+	–	–	+	+	–
Pre-core mutant	+	–	–	+	–	–
Low replicative	+	–	–	+	–	+

MANAGEMENT

LIFESTYLE CHANGES—avoid alcohol use, sexual education, HBV vaccination

TREAT UNDERLYING CAUSE—interferon, pegylated interferon, lamivudine, adefovir, entecavir, telbivudine, tenofovir

VACCINATION—household and sexual contacts

TREATMENT ISSUES

TREATMENT DECISION FOR CHRONIC HEPATITIS B INFECTIONS

- **HBEAG POSITIVE PATIENTS**—no spontaneous seroconversion after 6 months with recurrent flares,

TREATMENT ISSUES (CONT'D)

significant fibrosis or inflammation, or polyarteritis nodosa with persistently high HBV DNA level, cirrhosis regardless of HBV DNA level

- **HBEAG NEGATIVE PATIENTS (PRE-CORE OR CORE PROMOTER MUTATIONS)**—high HBV DNA level

Please see **NEJM 2008 359:14** and **Can J Gastroenterol 2007 21 Supp C** at www.hepatology.ca for consensus statement on management of hepatitis B

Hepatitis C NEJM 2001 345:1

PATHOPHYSIOLOGY

NATURAL HISTORY—acute infection → 55–85% of total will develop chronic infection → 50% of total will develop chronic hepatitis → 5–20% of total will develop cirrhosis → 3–5%/year of acute decompensation, also 1–5%/year of developing hepatocellular carcinoma (after 10–30 years)

RISK FACTORS FOR TRANSMISSION

- **HIGH**—IDU, transfusions, immigration from endemic regions
- **LOW**—perinatal transmission, transfusion before 1992, body piercing, long-term dialysis, occupational exposure, intranasal drug use, multiple sexual partners

CLINICAL FEATURES

HISTORY—symptoms of liver failure (jaundice, bleeding, infections, ascites, confusion), weight change, risk factors of hepatitis (sexual activity, IDU, tattoos, piercing, healthcare worker, transfusions, dialysis), past medical history (alcohol, HBV, HIV), medication history

PHYSICAL—liver examination, stigmata of chronic liver disease (see p. 132), weight. Also examine for extrahepatic manifestations of HCV

Related Topics
Acute Liver Failure (p. 128)
Chronic Liver Failure (p. 132)
HCV/HIV Co-infection (p. 261)
Hepatitis B (p. 130)
Hepatoma (p. 205)

CLINICAL FEATURES (CONT'D)

EXTRAHEPATIC MANIFESTATIONS OF HCV

- **HEENT**—uveitis, corneal ulcer, sialadenitis
- **RENAL**—nephritic syndrome (MPGN II), nephrotic syndrome (membranous)
- **HEMATOLOGIC**—aplastic anemia, lymphoma, cryoglobulinemia, ITP
- **VASCULAR**—necrotizing vasculitis, polyarteritis nodosa
- **RHEUMATOLOGIC**—arthralgias, arthritis, myalgia, sicca
- **NEUROLOGIC**—weakness, peripheral neuropathy
- **ENDOCRINE**—diabetes, antithyroid antibodies
- **DERMATOLOGIC**—psoriasis (20%), pruritus, Raynaud's, porphyria cutaneous tarda, lichen planus, cutaneous necrotizing vasculitis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, anti-HCV IgM and total (sens 92–97%), HCV RNA PCR (qualitative, quantitative), genotyping, βhCG (before treatment), HAV serology, HBV serology, HDV serology, iron, TIBC, HIV serology
- **IMAGING**—U/S abd

SPECIAL

- **LIVER BIOPSY**—not mandatory before starting treatments

PROGNOSTIC ISSUES

GOOD PREDICTIVE FACTORS—age <40, female, weight <75 kg [165 lbs], low titer, genotype 2/3, mild fibrosis

POOR PROGNOSTIC FACTORS—age of infection >40, male, high BMI, alcohol, HIV co-infection

PROGNOSTIC ISSUES (CONT'D)

UNCERTAIN PROGNOSTIC FACTORS—genotype, viral load, route of transmission

MANAGEMENT

TREAT UNDERLYING CAUSE—pegylated interferon and ribavirin ×48–72 weeks if genotype 1 or 4 (response rate ~50%) or ×12–48 weeks if genotype 2 or 3 (response rate ~80%), orthotopic liver transplant

TREATMENT ISSUES

TREATMENT DECISION—complex decision depending on patient's wishes, risk of progression, chance of response (genotypes II and III better), and any contraindications to treatment

- **GOOD CANDIDATES**—chronic hepatitis with significant fibrosis, compensated cirrhosis, stable CBC and Cr, good adherence. Elevated ALT is no longer considered a decision factor
- **SPECIAL CIRCUMSTANCES** (regimen modification required and should be done under expert guidance)—acute HCV, HIV/HCV, HBV/HCV previous treatment failures, liver transplant, renal failure, current drug or alcohol use
- **ABSOLUTE CONTRAINDICATION**—decompensated cirrhosis

Please see **Can J Gastroenterol 2007 21 Supp C** at www.hepatology.ca for consensus statement on management of hepatitis C

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, schistosomiasis, toxoplasmosis

STEATOHEPATITIS—alcohol, non-alcoholic steatohepatitis (NASH)

MEDICATIONS—acetaminophen/paracetamol (chronic use, controversial)

AUTOIMMUNE—autoimmune hepatitis

DIFFERENTIAL DIAGNOSIS (CONT'D)

NEOPLASM—hepatoma, cholangiocarcinoma

METABOLIC—hemochromatosis, Wilson's, α1-antitrypsin deficiency, glycogen storage disease

BILIARY CIRRHOSIS—primary biliary cirrhosis, primary sclerosing cholangitis, secondary biliary cirrhosis (stones, strictures)

PATHOPHYSIOLOGY OF CHRONIC LIVER DISEASE

CHILD–PUGH CLASSIFICATION OF LIVER CIRRHOSIS

	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]	34–52 μM [2–3 mg/dL]	1.7–2.3
3	3–4	Mod	<28 g/L [<2.8 g/dL]	>52 μM [>3 mg/dL]	>2.3

PATHOPHYSIOLOGY OF CHRONIC LIVER DISEASE (CONT'D)

The Child–Pugh score is calculated as either encephalopathy plus ascites plus INR, or albumin plus bilirubin plus INR. Patients with score >7 or any clinical signs of decompensation (variceal bleeding, ascites, encephalopathy) should be considered for liver transplantation. Alternative calculation is a total score of all five parameters, grade A=5–6, grade B=7–9, grade C=10–15

MODEL FOR END-STAGE LIVER DISEASE (MELD) SCORE—originally designed to predict survival in patients with portal hypertension undergoing elective TIPS procedure, now used as a tool for organ allocation in patients with chronic liver disease. The MELD score ranges from 6 to 40, with higher values indicating a worse prognosis

- **ORIGINAL MELD** = $9.57 \times \log_e$(Cr in mg/dL) + $3.78 \times \log_e$(total bilirubin in mg/dL) + $11.2 \times \log_e$(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 × MELD × (140 – Na)] + 140

For web-based calculator, please see http://www.unos.org/resources/MeldPeldcalculator.asp?index=98 or http://www.mayoclinic.org/meld/

CLINICAL FEATURES

HISTORY—symptoms of liver failure (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/paracetamol, other hepatotoxins)

PHYSICAL

- **STIGMATA OF CHRONIC LIVER DISEASE**—leukonychia, clubbing, Dupuytren's 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
- **CLUES TO ETIOLOGY**—obesity (fatty liver), excoriations (PBC), tattoos/needle tracks (hepatitis), bronze skin (hemochromatosis), Kayser–Fleischer rings (Wilson's disease)

DISTINGUISHING LIVER FROM RIGHT KIDNEY

1. The liver has no palpable upper border and extends more laterally and medially

CLINICAL FEATURES (CONT'D)

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 resonant 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

RATIONAL CLINICAL EXAMINATION SERIES: PHYSICAL EXAMINATION OF THE LIVER

INSPECTION—bulging mass over right costal margin (low sens)

PALPATION—move fingers 2 cm [0.79 in.] up at each exhalation. Palpable liver suggests hepatomegaly (LR+ 2.5, LR− 0.45)

PERCUSSION—locate upper border along midclavicular line. Locate lower border with palpation, scratch test, or percussion. Liver span >12 cm (>4.7 in.) suggests hepatomegaly

AUSCULTATION—friction rubs (tumors, infection), venous hums (portal hypertension), arterial bruit (tumors, alcohol hepatitis)

APPROACH—"if clinical suspicion low, start with palpation. If positive, percuss liver span. If negative, hepatomegaly is unlikely. If clinical suspicion is high, palpate and percuss. Overall, negative findings cannot rule out abnormal liver, and positive findings cannot rule in liver disease"

JAMA 1994 271:23

RIEDEL'S LOBE—an extension of the right lobe of the liver down below the costal margin along the anterior axillary line. It is often mistaken for a pathological enlargement of the liver or gallbladder. It is a normal anatomical variant

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HBsAg, HBsAb, HBcIgM, HBcIgG, HCV serology
- **IMAGING**—U/S abd, CT abd

INVESTIGATIONS (CONT'D)

SPECIAL

- **LABS**—ANA, antismooth muscle antibody, AMA, ferritin, ceruloplasmin, α1-antitrypsin, AFP, anti-transglutaminase
- **GASTROSCOPY**—to check for varices
- **LIVER BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE—consideration for liver transplantation

SYMPTOM CONTROL—for variceal bleed prophylaxis, consider band ligation, and non-selective β-blocker if moderate/large varices or Child–Pugh B/C (*propranolol* 10 mg QID or *nadolol* 40–80 mg daily) to target heart rate of 55–60/min. Perform initial screen for esophageal varices with endoscopy → repeat endoscopy in 3 years if no varices; repeat in 2 years if small varices; repeat more often if moderate/large varices. For active variceal bleed after failed endoscopic therapy, consider TIPS. See UPPER GI BLEED (p. 118), HEPATIC ENCEPHALOPATHY (p. 135), and ASCITES (p. 136) for details

HEPATOMA SCREENING—for all patients with cirrhosis, and those with HBV and hepatocellular carcinoma risk factors, consider AFP and abdominal U/S every 6–12 months for surveillance

SPECIFIC ENTITIES

CAUSES OF HEPATOMEGALY

- **PSEUDOHEPATOMEGALY**—obstructive lung disease (emphysema), subdiaphragmatic collection
- **CONGESTIVE**—right heart failure, constrictive pericarditis, tricuspid regurgitation, IVC obstruction, hepatic vein obstruction
- **INFILTRATION**—malignancy, amyloidosis, hemochromatosis, fatty liver
- **REACTIVE**—hepatitis

WILSON'S DISEASE

- **ETIOLOGY**—copper excretion defect
- **DIAGNOSIS**—Kayser–Fleischer ring, serum ceruloplasmin, 24-h urine for copper
- **TREATMENTS**—**dietary restriction** (avoid shellfish, organs, chocolate, nuts, and mushrooms), **chelating agent** (D-penicillamine or trientine), and zinc. For severe liver failure, consider orthotopic liver transplantation

AUTOIMMUNE HEPATITIS

- **SUBTYPES**—**I** (classic, female predominance, extrahepatic disease, ANA >1/160, antismooth muscle antibody >1/40, ↑ IgG, steroid responsive), **II** (anti-liver-kidney-microsomal antibody, less steroid responsive), **III** (anti-SLA)
- **DIAGNOSIS**—quantitative immunoglobulins (↑ IgG), ANA, antismooth muscle antibody, anti-LKM antibody, liver biopsy

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—steroids, azathioprine, or MMF. For fulminant hepatitis or cirrhosis, consider liver transplantation

HEPATIC HYDROTHORAX

- **PATHOPHYSIOLOGY**—low oncotic pressure, congenital diaphragmatic defect, ascitic fluid move to pleural space due to pressure gradient → transudative pleural effusion → decreased lung volumes → V/Q mismatch → hypoxemia
- **DIAGNOSIS**—diagnostic thoracentesis. U/S abd to assess liver and ascites. CT chest and abd to rule out other lesions. Intraperitoneal injection of ^{99}mTc-labeled serum albumin may be helpful to confirm diagnosis
- **TREATMENTS**—O_2, therapeutic thoracentesis, salt restriction, diuretics, TIPSS. Chest tube is a last resort and only with small pigtail catheter

HEPATOPULMONARY SYNDROME

- **PATHOPHYSIOLOGY**—portal hypertension → ↓ metabolism of vasodilating substance, or ↓ production of vasoconstricting substance → pulmonary capillary dilatation → diffusion–perfusion imbalance → hypoxemia, dyspnea on exertion and/or at rest, orthodeoxia and platypnea, cynosis, clubbing and spider nevi
- **DIAGNOSIS**—contrast echocardiogram/bubble study (presence of microbubbles in the left atrium 3–6 cardiac cycles after intravenous injection of normal saline suggests dilated pulmonary capillaries), lung perfusion scan, pulmonary angiogram (if severe hypoxemia)
- **TREATMENTS**—O_2, liver transplant

NEJM 2007 358:22

PORTOPULMONARY HYPERTENSION

- **PATHOPHYSIOLOGY**—portal hypertension → unknown substance reaches pulmonary vasculature causing vasoconstriction → findings similar to primary pulmonary hypertension
- **DIAGNOSIS**—echocardiogram, right heart catheterization
- **TREATMENTS**—O_2, diuretics, sildenafil, prostaglandins, calcium channel blockers, liver transplant

HEPATORENAL SYNDROME

- **PATHOPHYSIOLOGY**—liver failure → dilated systemic circulation → ↑ renin–aldosterone system with ↑ cardiac output but not enough to counter splanchnic vasodilatation → pre-renal failure. Type I is more serious, defined as >50% reduction of CrCl to ≤20 mL/min in ≤2 weeks or >2× increase in creatinine to >220 μmol/L [>2.2 mg/dL]. Patients are usually oligouric or anuric. Type II includes patients not meeting criteria for type I and is characterized by ascites resistant to diuretics

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—diagnosis of exclusion (especially important to rule out ATN and pre-renal causes). Check for infection and GI bleed
- **TREATMENTS**—stop diuretics, fluid (usually no response), albumin, vasoconstrictors (midodrine, octreotide, norepinephrine), TIPS, renal replacement therapy, liver transplant

FLOOD SYNDROME (SPONTANEOUS UMBILICAL HERNIA RUPTURE)

- **PATHOPHYSIOLOGY**—liver failure → portal hypertension → ascites → umbilical hernia (up to 20%) → spontaneous rupture (rare)

SPECIFIC ENTITIES (CONT'D)

- **PROGNOSIS**—50% mortality with supportive care, 10–20% mortality with urgent surgical repair

Related Topics
Acute Hepatic Failure (p. 128)
Ascites (p. 136)
Encephalopathy (p. 135)
Hemochromatosis (p. 420)
Hepatitis B (p. 130)
Hepatitis C (p. 131)
Jaundice (p. 138)

Hepatic Encephalopathy

NEJM 1997 337:7

DIFFERENTIAL DIAGNOSIS

DRUGS

- **ALCOHOL**—acute intoxication, withdrawal, Wernicke–Korsakoff
- **PSYCHOACTIVE**—benzodiazepines, cocaine, heroine, ecstasy
- **OTHERS**—salicylates

INFECTIOUS—pneumonia, UTI, meningitis, encephalitis, abscess, spontaneous bacterial peritonitis

METABOLIC

- **ORGAN FAILURE**—hepatic, azotemia, hypothyroidism, hypoxemia, CO_2 narcosis
- **ELECTROLYTES**—ketoacidosis, hyponatremia, hypomagnesemia, hypercalcemia, glucose (hypo, hyper)

STRUCTURAL

- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral
- **STROKE**—basilar
- **TUMOR**
- **EPILEPSY**

NEUROPSYCHIATRIC

PATHOPHYSIOLOGY

GRADING OF HEPATIC ENCEPHALOPATHY

- **1**— reversed sleep cycle, mild confusion, tremor, incoordination
- **2**— lethargy or irritability, disoriented to time, asterixis, ataxia
- **3**— somnolence or agitation, disoriented to place, asterixis, hyperreflexia, positive Babinski
- **4**— coma, decerebrate

PRECIPITANTS OF HEPATIC ENCEPHALOPATHY

- ↑ **NH_4 PRODUCTION**—↑ protein intake, constipation, GI bleed, transfusion, infection (spontaneous bacterial peritonitis), azotemia, hypokalemia

PATHOPHYSIOLOGY (CONT'D)

- ↑ **DIFFUSION ACROSS BLOOD–BRAIN BARRIER**—alkalosis
- ↓ **METABOLISM**—dehydration, hypotension, hypoxemia, anemia, portosystemic shunt, hepatoma, progressive liver damage

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)

PHYSICAL—vitals, signs of chronic liver disease, rectal examination (if suspect GI bleed), neurological examination, check for asterixis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, TSH, AST, ALT, ALP, bilirubin, INR, PTT, NH_4, Ca, Mg, PO_4, osmolality, CK, troponin (as part of delirium workup), urinalysis
- **MICROBIOLOGY**—blood C&S, urine C&S, sputum Gram stain/C&S
- **IMAGING**—U/S abd, CT abd
- **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**—consider sedation (*haloperidol* 1–2 mg PO/IV/SC q6h and q1h PRN) and ventilation, *mannitol* 1 g/kg 20% solution, acetylcysteine, epoprostenol
- **TREAT UNDERLYING CAUSE**—liver transplant

CHRONIC HEPATIC ENCEPHALOPATHY

- **SYMPTOM CONTROL**—protein restriction no longer routinely recommended. ***Lactulose*** 30 g PO BID–QID PRN titrate to 2–4 bowel movements/day or 300 mL lactulose mixed with 700 mL H_2O PR if NPO (also lactitol and lactose). ***Neomycin*** 500–2000 mg PO q8h or ***metronidazole*** 800 mg PO daily (alternatives to lactulose or use in combination). **Others** (*H. pylori* treatment, ornithine aspartate, branched amino acids)
- **TREAT UNDERLYING CAUSE**—liver transplant

Related Topic
Delirium (p. 380)

Ascites NEJM 2004 350:16

DIFFERENTIAL DIAGNOSIS

↑ HYDROSTATIC PRESSURE

- **CARDIAC**—right heart failure, tricuspid regurgitation, constrictive pericarditis
- **HEPATIC**—**pre-sinusoidal** (portal vein thrombosis, schistosomiasis), **sinusoidal** (cirrhosis), **post-sinusoidal** (Budd–Chiari, veno-occlusive)

↓ **ONCOTIC PRESSURE**—malnutrition, liver disease, nephrotic, protein-losing enteropathy

DIFFERENTIAL DIAGNOSIS (CONT'D)

↑ 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%	4.16	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%	2.04	0.73
Alcoholism	60%	58%	1.44	0.69
Hx of carcinoma	13%	85%	0.91	1.01
Physical				
Bulging flanks	81%	59%	2.0	0.3
Flank dullness	84%	59%	2.0	0.3
Shifting dullness	77%	72%	2.7	0.3
Fluid wave	62%	90%	6.0	0.4

APPROACH—"most useful findings for ruling out ascites are negative history of ankle swelling, ↑ abdominal girth, and negative for bulging flanks, flank dullness, or shifting dullness. Most powerful findings for making diagnosis of ascites are positive fluid wave, shifting dullness, or peripheral edema. Puddle sign and auscultatory percussion not recommended"

JAMA 1992 267:19

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, amylase, lipase, TSH, urinalysis
- **IMAGING**—U/S abd, CT abd

INVESTIGATIONS (CONT'D)

- **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 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 non-albumin 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/μL	9.1	0.25
Ascitic fluid WBC >500 cells/μL	5.9	0.21
Ascitic fluid WBC >250 cells/μL	0.9	1.1
Ascitic fluid PMN >500 cells/μL	10.6	0.16
Ascitic fluid PMN >250 cells/μL	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 ≤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 ≥0.10	11.3	0.12

FEATURES SUGGESTIVE OF PORTAL HYPERTENSION

	LR+	LR−
Serum ascites albumin gradient (SAAG)		
Serum-ascites albumin gradient ≥11 g/L	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/μL), PMN count (>250 cells/μL) 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])"

JAMA 2008 299:10

DIAGNOSTIC ISSUES (CONT'D)

PARACENTESIS PROCEDURE—NEJM 2006 355:e21

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** (*furosemide* 40–160 mg PO daily and *spironolactone* 100–400 mg PO daily, stepwise increase). **Paracentesis**. **Albumin** (if >5 L, then replace with albumin. In general, give 100 mL of 25% for every 3 L of ascites removed over 5 L), TIPS, liver transplant

TREAT UNDERLYING CAUSE—stop alcohol consumption

SPECIFIC ENTITIES

DIFFERENTIAL DIAGNOSIS OF ANASARCA—renal (nephritic syndrome), cardiac (HF, tricuspid regurgitation, constrictive pericarditis), liver (cirrhosis), thyroid (hypothyroidism), malignancy (venous/lymphatic obstruction)

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

- **PATHOPHYSIOLOGY**—overgrowth of bacteria in bowel (usually *E. coli*) → transverse bowel wall → infect ascites. Usually in patients with cirrhosis and large volume ascites. 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/μL, 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
- **TREATMENTS**—*cefotaxime* 1–2 g IV q8h ×5–10 day, *albumin* 1.5 g/kg IV within 6 h of detection, then 1 g/kg IV on day 3 (reduces mortality

SPECIFIC ENTITIES (CONT'D)

and incidence of hepato-renal syndrome). **Secondary prophylaxis** include *ciprofloxacin* 750 mg PO weekly or *trimethoprim–sulfamethoxazole* DS 1 tab PO daily

Jaundice

DIFFERENTIAL DIAGNOSIS OF JAUNDICE/HYPERBILIRUBINEMIA

PRE-HEPATIC (hemolysis)

- **RBC MEMBRANE**—spherocytosis, elliptocytosis
- **RBC ENZYMES**—G6PD, pyruvate kinase deficiency
- **RBC HEMOGLOBIN**—sickle cell
- **BLOOD**—toxins, drugs (fludarabine), infections (malaria), immune
- **VASCULAR**—abnormal valve, vasculitis, HUS/TTP/DIC, HELLP, severe hypertension
- **INEFFECTIVE ERYTHROPOIESIS**—megaloblastic anemia

HEPATIC

- ↓ **UPTAKE**—Gilbert's, drugs (rifampin, contrast)
- ↓ **CONJUGATION**—Gilbert's, 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, ulcerative colitis, hereditary disorders), medications

PHYSICAL—signs of chronic liver disease, liver and spleen examination

JAUNDICE—becomes clinically evident at levels of bilirubin >70 μmol/L [>41 mg/dL]

DARK URINE—suggests conjugated hyperbilirubinemia

PALE STOOL/PRURITUS—suggests cholestasis (bile cannot be secreted into the biliary system)

CLINICAL FEATURES (CONT'D)

PAIN—painful jaundice suggests acute obstruction (by stones, masses); investigate with U/S abd ERCP/MRCP/EUS. Painless jaundice suggests pancreatic cancer, infiltration, PSC, PBC, and drugs; investigate with biopsy

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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, antismooth muscle antibody (ASMA), anti-mitochondrial antibody (AMA), ferritin, ceruloplasmin, α1-antitrypsin, AFP, LDH, haptoglobin, peripheral smear, reticulocyte counts
- **IMAGING**—U/S, CT abd

SPECIAL

- **ENDOSCOPIC U/S**
- **MRCP**
- **ERCP**
- **LIVER BIOPSY**

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

PRIMARY BILIARY CIRRHOSIS (PBC)

- **PATHOPHYSIOLOGY**—autoimmune destruction of intrahepatic bile ducts → cholestasis → inflammation and necrosis → cirrhosis
- **CLINICAL FEATURES**—pruritus, fatigue, RUQ pain, xanthelasmas, sicca syndrome, hyperlipidemia. With disease progression, symptoms of liver failure may be seen
- **DIAGNOSIS**—antimitochondrial antibody (sens 95%), ANA (40%), ↑ bilirubin, ↑ ALP, ↓ C4, ↑ IgM, hyperlipidemia (the cholesterol, rather than TG, is what classically becomes elevated). Liver biopsy can be helpful for staging but is not essential for diagnosis
- **TREATMENTS**—*ursodeoxycholic acid* 250 mg PO daily, increase dose every 3–4 days to a target dose of 13–15 mg/kg/day. Ursodeoxycholic acid has been shown to improve liver enzymes, slow disease progression (for stages I and II), delay time to transplant but does not treat pruritus. For pruritus, consider cholestyramine, rifampin, and naltrexone. Consider

SPECIFIC ENTITIES (CONT'D)

treating hyperlipidemia (despite hypercholesterolemia, risk of atherosclerotic death not increased). Prevent osteoporosis with calcium and vitamin D. Also provide supplement with fat-soluble vitamins (KADE) which are not well absorbed in cholestasis. Consider liver transplant if rising bilirubin, liver decompensation, refractory pruritus, or severe bone disease

NEJM 2007 357:15

SPECIFIC ENTITIES (CONT'D)

PRIMARY SCLEROSING CHOLANGITIS (PSC)

- **PATHOPHYSIOLOGY**—cholangitis → fibrosis with intra-and extrahepatic duct strictures → cirrhosis; 75% associated with ulcerative colitis, 10% with cholangiocarcinoma
- **DIAGNOSIS**—ERCP (beading, strictures), biopsy
- **TREATMENTS**—liver transplant

Acute Pancreatitis NEJM 1994 330:17

CAUSES

★BAD HITS★
BILIARY STONES
ALCOHOL
DRUGS—thiazides, furosemide, sulfonamide, tetracycline, calcium, estrogen, vinca alkaloids, antiretrovirals (didanosine, pentamidine)
HYPER—hypercalcemia, hyperlipidemia (V, I, IV)
INFECTIOUS—*E. coli*, HIV, CMV, mumps, Ascariasis
IDIOPATHIC
INHERITED—familial
TRAUMA—blunt
SURGERY—ERCP, sphincter of Oddi dysfunction

PATHOPHYSIOLOGY

COMPLICATIONS OF ACUTE PANCREATITIS
★SCAR★
Sepsis
Calcium (hypocalcemia)
Abdominal (necrotizing pancreatitis ± hemorrhage, pancreatic pseudocyst ± hemorrhage [10–20%], pancreatic abscess, splenic vein thrombosis, fistula, cholangitis
Respiratory failure 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, volume status, abdominal examination, Cullen's sign (periumbilical ecchymoses suggestive of hemoperitoneum), Grey Turner's sign (ecchymoses of the flanks suggestive of retroperitoneal hemorrhage), Fox's sign (ecchymoses parallel and inferior to inguinal ligament along upper thighs suggesting retroperitoneal hemorrhage), Bryant's sign (blue scrotum suggesting retroperitoneal hemorrhage)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, LDH, lipase, amylase, Ca, albumin, fasting lipid profile
- **IMAGING**—U/S abd, CT abd (+ contrast for necrotic pancreatitis)
- **ERCP**—both diagnostic and therapeutic

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'S CRITERIA

- **ON ADMISSION**—age >55, WBC >16×10^9/L, glucose >11.1 mmol/L [>200 mg/dL], AST >250 U/L, LDH >350 U/L
- **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, O_2, **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 (for theoretical concern of morphine-causing sphincter of Oddi spasm, some consider using Demerol instead). Antiemetics (*dimenhydrinate* 50 mg 2IM/IV q4h, *metoclopramide* 10 mg IV q4h). Consider ***imipenem*** 500 mg IV q6h if CT abd showed necrosis in pancreas
NUTRITION SUPPORT—enteral or parenteral
TREAT UNDERLYING CAUSE—**gallstone pancreatitis** (ERCP and biliary sphincterotomy within 72 h, cholecystectomy). **Necrotizing pancreatitis** (ICU admission, surgical debridement)

SPECIFIC ENTITIES

ASCENDING CHOLANGITIS

- **PATHOPHYSIOLOGY**—biliary calculi (choledocholithiasis), post-ERCP, tumors, primary sclerosing cholangitis, or benign stricture → biliary obstruction and stasis → bacterial colonization and infection (*E. coli*, *Klebsiella, Enterobacter*, *Enterococcus*, anaerobes) → liver failure, sepsis
- **CLINICAL FEATURES**—Charcot's triad consists of fever, right upper quadrant pain, and jaundice. Reynold's pentad is associated with the addition of hypotension and confusion

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—↑ bilirubin, ALP, and potentially AST and ALT. Blood cultures essential. U/S abd to check for common bile duct dilatation and stones, ERCP, MRCP
- **TREATMENTS**—**antibiotics** (*imipenem* 500 mg IV q6h, ampicillin plus gentamicin). **Facilitate biliary drainage** (ERCP with sphincterotomy, stone extraction, stent insertion, percutaneous drainage, surgical decompression)

Notes

Notes

6
HEMATOLOGY
Section Editor: Dr. Michael Kroll

Polycythemia

DIFFERENTIAL DIAGNOSIS

SPURIOUS—stress (Geisböck's syndrome), decrease intravascular volume
PRIMARY—polycythemia rubra 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's syndrome

PATHOPHYSIOLOGY

DEFINITION OF POLYCYTHEMIA—hematocrit >0.6 in ♂, hematocrit >0.5 in ♀

Related Topics
Hypoxemia (p. 92)
Myeloproliferative Disorders (p. 165)

CLINICAL FEATURES

HISTORY—hyperviscosity (headache, blurred vision, epistaxis), dyspnea, epigastric pain, 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**—CBCD, lytes, urea, Cr, LAP, vitamin B12, RBC mass (total blood volume × Hct, to rule out spurious causes), carboxyhemoglobin level, cortisol level, peripheral blood smear
- **IMAGING**—CXR

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
- **EPO LEVEL**—low in PRV, high if secondary causes
- **HYPOXIA WORKUP**—oximetry, ABG, CO-hemoglobin
- **SOLID TUMOR WORKUP**—CT abd, MRI head (if tumors)
- **BONE MARROW BIOPSY**—rule out myelofibrosis and CML

DIAGNOSTIC ISSUES

CRITERIA FOR POLYCYTHEMIA RUBRA VERA (PRV)
- **ABSOLUTE**—↑ RBC mass, no secondary cause (normal PaO_2, EPO not elevated)
- **MAJOR**—splenomegaly, JAKV617F
- **MINOR**—WBC $>12\times10^3/\mu L$, platelet $>400\times10^3/\mu L$,
- LAP >100U/L and vitamin B12 >650pmol/L [>880 pg/mL]
- **DIAGNOSIS**—need absolute criteria plus one major or two minor criteria for the diagnosis of polycythemia rubra vera. See myeloproliferative disorders (p. 165) for more details

MANAGEMENT

TREAT UNDERLYING CAUSE—**relative** (hydration), **CO hemoglobinemia** (smoking cessation. See p. 418), **sleep apnea** (CPAP. See p. 17), **polycythemia vera** (cytoreduction with hydroxyurea is preferable to phlebotomy to keep hematocrit <0.45 in ♂ and <0.42 in ♀, *ASA* 81 mg PO daily prevents thrombosis—but watch out for bleeding)

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_6,

Microcytic Anemia

NEJM 2005 352:10

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 → ↑ INFγ, TNFα, 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 chlorosis, atrophic glossitis, lymphadenopathy (anemia of chronic disease), rectal examination for occult blood and pelvic examination for blood loss

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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 deficieny and anemia of chronic disease

INVESTIGATIONS (CONT'D)

- **LIVER BIOPSY**
- **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/↓

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
- **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

- **<30 ng/ml**—iron deficiency anemia (PPV 92–98%)
- **30–100 ng/ml**—combination of anemia of chronic disease and true iron deficiency if (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** 2 U PRBC IV over 2 h
TREAT UNDERLYING CAUSE—**iron deficiency** (*iron gluconate* 300 mg PO TID, *iron sulfate* 325 mg PO TID, *sodium ferric gluconate* complex in sucrose 125 mg IV, *ferumoxytol* 510 mg IV). It may take up to 6 weeks to correct anemia and 6 months to replete iron stores

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, myeloproliferative disorders, lymphoma, metastasis, infections (esp. TB)
- **DECREASED EPO**—renal failure
- **ANEMIA OF CHRONIC DISEASE**

SEQUESTRATION—splenomegaly

↑ DESTRUCTION

- **IMMUNE**—autoimmune hemolytic anemia (warm agglutinins, cold agglutinins)
- **NON-IMMUNE**
  - **RBC MEMBRANE**—spherocytosis
  - **RBC ENZYMES**—G6PD, pyruvate kinase deficiency
  - **RBC HEMOGLOBIN**—sickle cell anemia
  - **MICROANGIOPATHIC**—DIC, HUS/TTP, prosthetic valve, hypertensive crisis
  - **BLOOD**—toxins, infections (malaria), immune

MIXED PICTURE—combined microcytic and macrocytic anemia (e.g. malnutrition 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 (NSAIDs, ASA, chemotherapy, antibiotics, antiepileptics), family history (thalassemia)

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**—CBCD, 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 (if suspect GI bleed)

INVESTIGATIONS (CONT'D)

SPECIAL

- **URINE TESTS**—urinalysis (hemoglobinuria)
- **BONE MARROW 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 suggests immune rather than non-immune 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 RBC incubated with patient's serum. It is mainly used to detect low concentrations of antibodies in a patient's serum prior to blood transfusion

RETICULOCYTE PRODUCTION INDEX (RPI, corrected reticulocyte count)—more accurate 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 patients on active chemotherapy

SPECIFIC ENTITIES

AUTOIMMUNE HEMOLYTIC ANEMIA: WARM AGGLUTININS—IgG

- CAUSES—**neoplasia** (CLL, especially with fludarabine, pentostatin, cladribine), **autoimmune** (SLE), **infections** (viral), **drugs** (penicillins, fludarabine, methyldopa)
- CLINICAL FEATURES—anemia, jaundice, splenomegaly, anemia, 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 effectiveness of antibodies (IVIG, splenectomy). **Immunosuppression** (*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, Waldenstrom's macroglobulinemia, adenocarcinoma), **infections** (mycoplasma pneumonia, infectious mononucleosis, CMV, VZV)
- CLINICAL FEATURES—anemia, agglutination, jaundice, splenomegaly. Anemia, smear (spherocytosis), ↑ reticulocytes, ↑ bilirubin, ↑ LDH, ↓ haptoglobin, direct Coombs test (IgG–, C3+), cold agglutinin screen
- TREATMENTS—**symptom control** (avoidance of cold). **Chemotherapy** (cyclophosphamide, chlorambucil). **Biological agents** (rituximab, INFα). 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. 105)
Chronic Liver Disease (p. 132)
Myelodysplastic Syndrome (p. 166)
Vitamin B12 Deficiency (p. 405)

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)

CLINICAL FEATURES (CONT'D)

PHYSICAL—look for signs of hypothyroidism, vitamin B12 deficiency and liver disease. Vitals (bradycardia, hypoventilation, hypotension), leukonychia, clubbing, Dupuytren's contractures, palmar erythema, asterixis, cool and dry skin, vitiligo, hair thinning, alopecia areata, periorbital edema, scleral icterus, conjunctival pallor, altered mental status, anemia, 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), peripheral neuropathy

INVESTIGATIONS

BASIC

- LABS—CBCD, peripheral smear, reticulocyte count, vitamin B12, RBC folate, TSH, AST, ALT, ALP, bilirubin, INR, PTT

SPECIAL

- SCHILLING'S TEST for poor vitamin B12 absorption from intrinsic factor deficiency
- BONE MARROW BIOPSY

MANAGEMENT

SYMPTOM CONTROL—transfusion 2 U PRBC IV over 2 h in everyone except those with pernicious

MANAGEMENT (CONT'D)

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

MANAGEMENT (CONT'D)

TREAT UNDERLYING CAUSE—**folate deficiency** (*folate* 0.4 mg PO/SC/IM daily ×4–5 d). **Vitamin B12 deficiency** (*vitamin B12* 1000 μg SC/IM daily ×5–10 days, then 1000 μg SC/IM qweek ×4 weeks, then every month). **Hypothyroidism** (*L-thyroxine* start 12.5–50 μg PO daily, adjust every 2 weeks)

Sickle Cell Disease

PATHOPHYSIOLOGY

β-CHAIN MUTATION—leads to formation of hemoglobin S ($\alpha 2\beta S2$) → 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

★ ABCDEFGH 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 (venoocclusion 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 sequestration crisis, iron overload (transfusions)

PULMONARY—restrictive lung disease (chronic interstitial fibrosis), obstructive lung disease, hypoxemia, pulmonary hypertension, fat embolism

CLINICAL FEATURES (CONT'D)

ANEMIA—remember that sickle cell disease is associated with both acute and chronic anemia

INFECTIONS—sepsis (particularly asplenic patients), meningitis, pneumonia, osteomyelitis

NEUROLOGIC—ischemic stroke, intracerebral hemorrhage, septic emboli, spinal cord infarction or compression, vestibular dysfunction, sensory hearing loss, cognitive failure

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, haptoglobin, smear (sickled red cells, polychromasia from reticulocytosis, Howell–Jolly bodies from hyposplenia), 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, C. diff toxin A/B

MANAGEMENT

ACUTE—ABC, O_2, IV

- **VASOOCCLUSIVE PAIN CRISIS**—fluids, pain control (morphine, ketorolac)
- **APLASTIC CRISIS**—transfusions. Avoid GCSF
- **SEQUESTRATION CRISIS**—younger patients
- **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*, *Niesseria 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

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 pre-prescribed 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**

Neutropenia

DIFFERENTIAL DIAGNOSIS

★PANIC★
POST-INFECTIOUS—sepsis
AUTOIMMUNE—drug induced, SLE
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. 236)

PATHOPHYSIOLOGY

DEFINITION OF NEUTROPENIA—neutrophils $< 1.5 \times 10^3/\mu L$

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, peripheral smear, PTT, INR, AST, ALT, ALP

INVESTIGATIONS (CONT'D)

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°C [>100.4°F]) in a neutropenic patient is considered an emergency, as overwhelming sepsis can develop quickly. Patients with febrile neutropenia (see p. 236 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 being in contact with people with active infections

SPECIFIC ENTITIES

ETHNIC NEUTROPENIA—neutrophil counts in blacks are generally lower. Neutrophil count may be down to $1.5 \times 10^3/\mu L$ and still be considered normal

Eosinophilia

DIFFERENTIAL DIAGNOSIS

★PAIN★
PRIMARILY ORGAN-SPECIFIC DISORDERS

- **PULMONARY**—interstitial lung disease, AIDS-related pneumonia, idiopathic eosinophilic pneumonia, drug-induced lung disease

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **GASTROINTESTINAL**—eosinophilic gastroenteritis, eosinophilic esophagitis, primary biliary cirrhosis, primary sclerosing cholangitits

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **GENITOURINARY**—acute interstitial nephritis, acute post-streptococcal glomerulonephritis, eosinophilic cystitis, eosinophilic prostatitis
- **RHEUMATOLOGIC**—eosinophilia–myalgia syndrome and idiopathic eosinophilic synovitis, Churg–Strauss syndrome
- **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's lymphoma, non-Hodgkin's 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/μL

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**—CBCD, 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 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
- **CAUSES**—**infectious** (Loeffler's 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** (Churg–Strauss, allergic bronchopulmonary aspergillosis)

Thrombocytosis

NEJM 2004 350:12

DIFFERENTIAL DIAGNOSIS

PRIMARY (clonal thrombocytosis)—essential thrombocythemia, chronic myelogenous leukemia, polycythemia rubra 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 >450×10^3/μL

Related Topic
Myeloproliferative Disorders (p. 165)

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
Splenomegaly	Y (40%)	N
Peripheral smear	Giant platelets	Normal platelets
Platelet function	Abnormal	Normal
BM megakaryocytes	↑, giant	↑, normal

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, PTT, INR, Fe, ferritin, TIBC, % sat, ESR (secondary cause), CRP (secondary cause)

SPECIAL

- **BONE MARROW BIOPSY**

DIAGNOSTIC ISSUES

IMPORTANT PEARL—remember that essential thrombocythemia 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 >450×10^3/μL, use ***ASA*** 81 mg PO daily (low dose) plus **hydroxyurea** (or **anagrelide)** targeting normalization of the platelet count. When the platelets are >1500×10^3/μL, **plateletpheresis** must be started for active ischemia and can be considered for use in asymptomatic 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)
DILUTIONAL—PRBC transfusion (at least 15–20 units), pregnancy
↓ **PRODUCTION**
- **INFILTRATIVE**—leukemia, MDS, bone marrow metastasis
- **INFECTIONS**—HIV, rubella, mumps, varicella, parvovirus, HCV, EBV
- **APLASIA**—aplastic anemia, Fanconi anemia
- **TOXINS**—chemotherapy, radiation, alcohol
- **B12/FOLATE DEFICIENCY**

HYPERSPLENISM—congestive, reactive, infiltrative (see SPLENOMEGALY p. 164)
↑ **DESTRUCTION**
- **IMMUNE THROMBOCYTOPENIC PURPURA**—primary, secondary (lymphoma, CLL, HIV, SLE, Evans syndrome)
- **ALLOIMMUNE**—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, EBV, CMV
- **MEDICATIONS**—heparin, GPIIb/IIIa inhibitors, quinine, quinidine, valproic acid, thiazides, sulfonamides, rifampin, indomethacin, vancomycin, linezolid

PATHOPHYSIOLOGY

DEFINITION—platelets $< 150\times10^3/\mu L$. 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

BLEEDING RISK IN UNDER-PRODUCTION THROMBOCYTOPENIA

Platelet count ($\times10^3/\mu L$)	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 intracranial bleed (fundoscopy), petechiae, and purpura. Check for lymphadenopathy and hepatosplenomegaly

INVESTIGATIONS

BASIC
- **LABS**—CBCD, 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)
- **SCHISTOCYTES/FRAGMENTS**—microangiopathic hemolytic anemia (DIC, TTP)

BONE MARROW BIOPSY
- **DECREASED MEGAKARYOCYTES**—underproduction
- **INCREASED MEGAKARYOCYTES**—destruction/sequestration/MDS

MANAGEMENT

SYMPTOM CONTROL—in under-production thrombocytopenia, **transfuse** 5 U platelets if platelets $<50\times10^3/\mu L$ and severe bleeding, platelets $<10\times10^3/\mu L$ in afebrile non-bleeding patient, $<20\times10^3/\mu L$ in febrile non-bleeding patient, and prior to certain procedures (expect platelet rise of ~5/unit). 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 may return to normal in 14–21 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 and schistocytes. Causes include DIC, HELLP, TTP, HUS, malignancy, malignant hypertension, artificial heart valve, insertion of foreign bodies, and medications

SPECIFIC ENTITIES (CONT'D)

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

- **PATHOPHYSIOLOGY**—damage to endothelium → release of tissue factor → massive activation of coagulation cascade → intravascular coagulation and depletion of clotting factors
- **CAUSES**—trauma, shock, sepsis (*Escherichia coli*, *N. meningitidis*, malaria), neoplasm (lung, prostate, pancreatic), obstetrical (abruptio placentae, pre-eclampsia, amniotic fluid embolus)
- **CLINICAL FEATURES**—microangiopathic hemolytic anemia, thrombocytopenia, bleeding, thrombosis, ischemia. ↑ INR, ↑ PTT, ↓ fibrinogen (although it can be normal or even elevated), ↓ factor VIII (in contrast to liver diseases, which have normal factor VIII). Schistocytes on peripheral smear
- **TREATMENTS**—**treat underlying cause and complications** (hypoxia, dehydration, acidosis, acute renal failure). **Replete coagulation factors if bleeding** (FFP 2 U, cryoprecipitate 10 U). **Anticoagulation if thrombosis** (consider IV heparin)

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

- **PATHOPHYSIOLOGY**—↓ ADAMTS13 activity → failure to degrade unusually large multimers of vWF → agglutination of platelets → arteriolar thrombi → systemic but CNS predominates
- **CAUSES**—idiopathic, vasculitis, malignancy, drug induced, pregnancy (second term)
- **CLINICAL FEATURES**—microangiopathic hemolytic anemia (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 splenectomy if not resolving. Avoid platelet transfusion, ASA and antimotility agents

NEJM 2006 354:18

HEMOLYTIC UREMIC SYNDROME (HUS)

- **PATHOPHYSIOLOGY**—exposure to Shiga toxin or defect in plasma factor H → arteriolar thrombi → predominantly renal involvement
- **CAUSES**—*E. coli* O157:H7
- **CLINICAL FEATURES**—microangiopathic hemolytic anemia (100%), thrombocytopenia (90%), renal dysfunction (90%). Schistocytes on peripheral smear
- **TREATMENTS**—supportive care only. Does not respond to plasma exchange

Related Topics
Anticoagulation Therapy (p. 160)
Antiphospholipid Antibody Syndrome (p. 156)
Thrombocytopenia in Pregnancy (p. 414)

SPECIFIC ENTITIES (CONT'D)

HEPARIN-INDUCED THROMBOCYTOPENIA AND THROMBOSIS (HITT)

- **PATHOPHYSIOLOGY**—**type I** (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. It is usually more severe (platelet drop >50%) and has great clinical significance. The pathogenesis is as follows: heparin complexes with PF4 (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**. If patient has indication for anticoagulation (acute thrombosis, atrial fibrillation), consider **danaparoid, lepirudin, argatroban**. Since the risk of thrombosis due to HITT approaches 50%, one should also consider primary prophylaxis with these agents until platelets return to normal. If both HITT and DVT, avoid warfarin until platelets $>150\times10^3/\mu L$ 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)

IDIOPATHIC/IMMUNE THROMBOCYTOPENIC PURPURA (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 if patient symptomatic and/or platelets $<20\times10^3/\mu L$. The goal of treatment is to support platelet counts until spontaneous remission occurs
  - **FIRST LINE**—***prednisone*** 1–2 mg/kg PO daily until platelet count returns to normal. Platelet recovery occurs within 3 weeks in 2/3 of patients. If platelet count did not increase after 4 weeks of treatment, consider splenectomy
  - **URGENT SUPPORT**—given to patients with active bleeding or extremely low platelets before steroid effect takes place. ***IVIG*** 1 g/kg IV daily ×1–2 days, which may increase the platelet count within days and lasts for a few weeks. ***Methylprednisolone*** 1 g IV daily ×3 days. **Platelet transfusions** may also provide temporary support for actively bleeding patients
  - **SECOND LINE**—**splenectomy**, with platelet recovery within 2 weeks in 2/3 of patients. See p. 147 for details on counseling of patients undergoing splenectomy

SPECIFIC ENTITIES (CONT'D)

- **THIRD LINE**—for patients with chronic refractory ITP (platelets $< 50\times10^3/\mu L$ after 3 months) who failed or refused splenectomy, consider observation if no bleeding and platelets $>20\times10^3/\mu L$. Otherwise, treat with romiplostim or eltrombopag
- **OTHER OPTIONS**—rituximab, chemotherapy (CVP), danazol. HAART for HIV-associated ITP

NEJM 2002 346:13

SPECIFIC ENTITIES (CONT'D)

DRUG-INDUCED IMMUNE THROMBOCYTOPENIA—patients usually present with severe thrombocytopenia (platelets $< 20\times10^3/\mu L$). 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

NEJM 2007 357:6

EVANS SYNDROME—ITP and autoimmune hemolytic anemia

Pancytopenia

DIFFERENTIAL DIAGNOSIS

★**PANIC**★

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA (PNH)—↑ complement-mediated red cell lysis

APLASTIC ANEMIA

- **IDIOPATHIC** (50%)
- **INFECTIONS**—EBV, CMV, parvovirus, hepatitis
- **FANCONI'S 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**—CBCD, 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 used for screening, followed by Ham acid hemolysis test for diagnosis. Currently flow cytometry is used to measure the expression of the complement regulatory proteins CD55 and CD59, which are deficient on all blood cells among persons with PNH

INVESTIGATIONS (CONT'D)

DIAGNOSTIC ISSUES

PRE-MEDS FOR BONE MARROW BIOPSY—*morphine* 2.5–5 mg IV, *lorazepam* 1 mg SL, Elma cream

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

APLASTIC ANEMIA

- **PATHOPHYSIOLOGY**—precipitants (e.g. *Parvovirus*, drugs) → T-cell subsets produce local concentrations of INFγ → ↑ Fas on CD34+ cells (maturing stem cells) → apoptosis → severe pancytopenia and hypocellular marrow. Complications include paroxysmal nocturnal hemoglobinuria, acute leukemia, and MDS
- **TREATMENTS**—antithymocyte globulin, cyclosporine, allogeneic stem cell transplant (if age < 50)

FANCONI'S 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

Bleeding Diathesis

DIFFERENTIAL DIAGNOSIS

★**PVC**★ **p**latelets, **v**essels, **c**oagulopathy

EXTRINSIC PATHWAY (isolated PT ↑)

- **FACTOR DEFICIENCY OR INHIBITOR**—VIIr

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **VITAMIN K DEFICIENCY**—malnutrition, pancreatic insufficiency, recent antibiotic use, warfarin use (early stage)

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **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
- **SEVERE VITAMIN K DEFICIENCY**—malnutrition, pancreatic insufficiency, recent antibiotic use, long term warfarin use
- **SEVERE LIVER DISEASE**
- **SEVERE DIC**

PLATELET DYSFUNCTION (normal PT and PTT, platelet $>90\times10^3/\mu L$, bleeding time ↑)

- **INHERITED**—Bernard–Soulier syndrome, Glanzmann's thrombasthenia, storage pool disease
- **ACQUIRED**—renal failure, liver failure, myeloproliferative disorders, paraproteinemias, autoantibodies, DIC, acquired storage pool disease

VESSELS—collagen vascular disease, scurvy

NOTE: INR=international normalized ratio, helps to standardize interpretation of PT

PATHOPHYSIOLOGY

HEMOSTASIS

- **PRIMARY HEMOSTASIS**—endothelium, platelets
- **SECONDARY HEMOSTASIS**—clotting factors, clotting cascade

PLATELET ACTIVATION PATHWAY

1. Collagen binds to GPIa/IIa 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 cross-linked by factor XIII and platelet–fibrin via GPIIb/IIIa

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

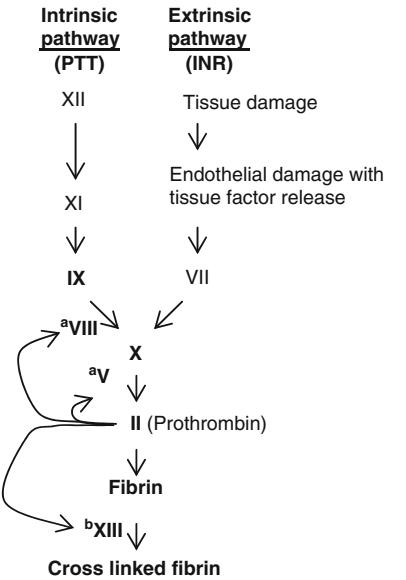
PATHOPHYSIOLOGY (CONT'D)

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, Z
- **SYNTHESIZED IN ENDOTHELIAL CELLS AND MEGAKARYOCYTES**—vWF

COAGULATION PATHWAY



[a]Non-enzymatic cofactors; [b]Factor XIII is called "fibrin-stabilizing factor" because it covalently cross-links fibrin polymers and strengthens the clot

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 bleed

CLINICAL FEATURES (CONT'D)

- **COAGULATION FACTORS**—joints/muscles (hemarthroses, muscle hematomas, large/palpable ecchymosis), delayed bleed

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, AST, ALT, ALP, bilirubin, albumin, 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 (hemophilia) vs. inhibitors
- **HEMOPHILIA WORKUP**—factor VII, factors VIII, IX, XI, factors X, V, II, I
- **ANTIPHOSPHOLIPID ANTIBODY SYNDROME WORKUP**—lupus anticoagulant, anticardiolipin antibody, Russell's viper venom time
- **VON WILLEBRAND DISEASE WORKUP**—von Willebrand factor (vWF) antigen levels, factor VIII level, ristocetin cofactor activity, ristocetin-induced platelet aggregation
- **PLATELET DISORDER WORKUP**—bleeding time
- **MYELOMA WORKUP**—serum protein electrophoresis

MANAGEMENT

ACUTE—ABC, O_2, 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** heparin, LMWH, warfarin. **Vitamin K deficiency** (*vitamin K* 10 mg PO/SC 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

	Inheritance	Pathophysiology
I	Autosomal dominant	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	Autosomal recessive	Complete absence of vWF

SPECIFIC ENTITIES (CONT'D)

- **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 support 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)

	vWFantigen 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	↓↓

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—*DDAVP* 0.3 μg/kg by IV infusion or 300 μg one spray each nasal for all type I and most type II patients. vWF concentrates containing all vWF multimers may be used for type III and for bleeding or surgical management of type II/I

SPECIFIC ENTITIES (CONT'D)

BERNARD–SOULIER SYNDROME—mutation of GPIb/IX (platelet receptor for vWF)
GLANZMANN'S THROMBASTHENIA—mutation of GPIIb/IIIa (platelet receptor for fibrinogen)
STORAGE POOL DISEASE—defect in releasing platelet granules (especially ADP)

Hypercoagulable States

DIFFERENTIAL DIAGNOSIS

ANTICOAGULATION FACTORS

- **DEFICIENCY**—protein S, protein C, antithrombin III, plasminogen. Secondary causes of clotting factor deficiencies include HITT, DIC, TTP, HUS, PNH, APA, and nephrotic syndrome (reduced protein S and protein C)
- **ALTERATION**—factor V Leiden, prothrombin G20210A
- **EXCESS**—fibrinogen, hyperhomocysteinemia

VASCULAR DAMAGE—**vasculitis**, **sepsis**, **trauma**, **surgery**, **cancer** (Trousseau's syndrome, lymphoproliferative disease)

STASIS—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
- **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**—homocysteinemia, dysfibrinogenemia, plasminogen activator deficiency
- **PLATELET DEFECTS**—myeloproliferative disorders, HITT, PNH
- **HYPERVISCOSITY**—polycythemia rubra vera, Waldenstrom's macroglobulinemia, cryoglobulinemia, sickle cell disease
- **OTHERS**—antiphospholipid antibody syndrome, vasculitis, paradoxical embolism
- **BIOPROSTHETIC HEART VALVE**—low-level anticoagulation (INR 2–3) in first 3 months following valve replacement

NEJM 2002 346:10

FACTOR V LEIDEN—mutation that resists cleavage by activated protein C. Most common hereditary form of thrombophilia (3–4% general population)

THROMBOPHILIC MUTATIONS—antithrombin III, homozygous factor V Leiden >protein S, protein C > heterozygous factor V Leiden in terms of risk of clots

INVESTIGATIONS

BASIC

- **LABS**—CBCD, PT, INR, activated protein C resistance, factor V Leiden, prothrombin G20210A, anticardiolipin antibody, lupus anticoagulant, homocysteine, protein C, protein S, antithrombin III, fibrinogen, urinalysis
- **IMAGING**—CXR

SPECIAL

- **PREGNANCY TEST**—if female <50

Related Topics
Anticoagulation Therapy (p. 160)
DVT (p. 158)
Pulmonary Embolism (p. 8)

DIAGNOSTIC ISSUES

WARFARIN AND PROTEIN C—draw protein C and S prior to warfarin therapy as it reduces protein C before those of all other vitamin K-dependent factors

MANAGEMENT

ACUTE—ABC, O_2 to keep sat >94%, IV, consider thrombolysis

ANTICOAGULATION—**heparin** (*unfractionated heparin* 5000U IV bolus, then 1000U/h and adjust to 1.5–2.5× normal PTT) or **LMWH** (*enoxaparin* 1 mg/kg SC BID or 1.5 mg/kg SC daily). Start ***warfarin*** 5 mg PO daily within 72 h and continue heparin/LMWH until INR is between 2 and 3 for two consecutive days

IVC FILTER—if anticoagulation contraindicated

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 administering heparin along with warfarin

PRIMARY PROPHYLAXIS OF THROMBOEMBOLISM IN HOSPITALIZED MEDICAL PATIENTS

- **INDICATIONS**—patients on the medical service >40-year old have limited mobility for $\geq$3 days, and have at least 1 of following risk factors
  - **CONDITIONS**—acute infectious disease, congestive heart failure, acute myocardial infarction, acute respiratory disease, stroke, rheumatic disease, inflammatory bowel disease, cancer
  - **CLINICAL CHARACTERISTIC**—previous venous thromboembolism, older age (especially >75),

TREATMENT ISSUES (CONT'D)

recent surgery or trauma, immobility or paresis, BMI >30 kg/m^2, central venous catheterization, 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* 5000 U SC q8h, *enoxaparin* 40 mg SC daily, *dalteparin* 5000 U SC daily, or *fondaparinux* 2.5 mg SC daily. For patients at high risk for bleeding, consider non-pharmacologic measures such as graduated compression stockings and pneumatic compression devices

NEJM 2007 365:14

RISK REDUCTION BY ANTICOAGULATION

- **ACUTE VTE EPISODE**—without anticoagulation, the risk for recurrent DVT is 50% and for PE is 50%. Warfarin ↓ risk to 8–10% by 1 month and 4–5% by 3 months
- **VTE WITH LONG-TERM RISK FACTORS**—recurrent DVT risk 15%/year. Warfarin ↓ risk to 3%
- **VTE IN PATIENTS WITH CANCER**—risk of recurrence at 6 months 17% with warfarin and 9% with *dalteparin* 200 IU/kg for 3 weeks, followed by 150 IU/kg for at least 6 months
- **AF WITH PREVIOUS STROKE**—recurrent stroke risk 12%/year. ASA ↓ risk to 10%/year. Warfarin ↓ risk to 4%/year
- **AF WITH OTHER RISK FACTORS**—recurrent stroke 8%/year. ASA ↓ risk to 4%/year. Warfarin ↓ risk to 2%/year
- **LONE AF**—recurrent stroke risk 1–2%/year. ASA or warfarin ↓ risk to < 1%/year

MECHANICAL HEART VALVE—recurrent arterial embolic risk 4%/year. ASA ↓ risk to 2%. Warfarin ↓ risk to 0.7–1%/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-β2GP1 (β2-glycoprotein 1) antibody → may lead to hypercoagulable state and may rarely inhibit coagulation
- **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 antibodies (IgG or IgM at moderate or high levels on ≥2 occasions at least 6 weeks apart) or the presence of a lupus anticoagulant (≥2 occasions at least 6 weeks apart). Diagnosis requires at least one clinical and one laboratory criteria (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 warfarin anticoagulation targeting an INR of 2–3. See p. 414 for management of APS in pregnancy

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 hemoglobulinuria, chronic renal failure due to iron deposits. Also ↑ platelet activation due to complements, tissue damage with ↑ tissue factor, ↓ fibrinolysis → ↑ thrombosis
- **CLINICAL FEATURES**—hemolysis, thrombosis (hepatic vein, portal vein, splenic vein, renal vein), marrow aplasia, MDS, leukemia, infections, esophageal spasm, sexual dysfunction
- **DIAGNOSIS**—flow cytometry, historically, Ham's test (RBC sensitivity to acidity)
- **TREATMENTS**—steroids, allogeneic stem cell transplant

Deep Vein Thrombosis

NEJM 2004 351:3

DIFFERENTIAL DIAGNOSIS OF UNILATERAL LEG SWELLING/DEEP VEIN THROMBOSIS

VASCULAR—DVT, venous insufficiency, superficial thrombophlebitis (chronic)

LYMPHATIC—lymphedema (chronic)

DRUGS—drug-induced edema (calcium channel blockers)

OTHER—cellulitis, necrotizing fasciitis, knee injury, calf muscle tear, Baker cyst rupture

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, ~25% extend into proximal veins within a week

COMPLICATIONS—clot extension, pulmonary embolism, recurrent thrombosis, post-thrombotic syndrome, chronic pulmonary hypertension

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, PTT, INR, D-dimer, fibrinogen, AST, ALT, ALP, bili
- **IMAGING**—CXR, compression U/S (sens 95%, spc 95%), impedance plethysmography

INVESTIGATIONS (CONT'D)

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; check antiphospholipid antibodies if the VTE was unprovoked
- **PREGNANCY TEST**—in female <50
- **VENOGRAM**—gold standard

DIAGNOSTIC ISSUES

COMPRESSION U/S—high sensitivity (95%) and specificity (95%) for DVT. U/S of calf veins is not routinely performed because of lower sensitivity (70%). Rather, U/S of thigh (deep veins) is usually repeated in 1 week after a normal test to detect the possible extension of DVT from calf into proximal veins

Related Topics
Anticoagulation Therapy (p. 160)
Hypercoagulable States (p. 156)
Pulmonary Embolism (p. 8)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE DEEP VEIN THROMBOSIS?

WELL'S 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 WELL'S 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

- **LOW RISK** (0 or less points)— <5% chance of DVT. If D-dimer negative, can exclude DVT
- **MODERATE RISK** (1–2 points)—17% chance of DVT. Workup may or may not be needed
- **HIGH RISK** (3 or greater points)—53% chance of DVT. D-dimer testing not useful. Proceed to compression U/S 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 <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"

JAMA 2006 295:2

DISGNOSTIC ISSUES (CONT'D)

THROMBOPHILIA WORKUP—should be done if suspect a hereditary cause of thromboembolic disease. Alarm features include age < 45, unprovoked situation, family history (1 or more first degree relative), or

DIAGNOSTIC ISSUES (CONT'D)

clot in unusual location (upper extremities, mesenteric vessels, brain)

MALIGNANCY WORKUP—debatable when this should be done. Basic screening includes physical exam, CXR, U/S abd, mammogram, PSA

DIAGNOSTIC ISSUES (CONT'D)

PROTEIN S AND PROTEIN C DEFICIENCY WHILE ANTICOAGULATED—when anticoagulated, usually levels decrease by similar proportion. If significant decrease of one compared to the other, may suggest a deficiency

MANAGEMENT

ANTICOAGULATION—**heparin** (*unfractionated heparin* 5000U IV bolus, then 1000U/h, and adjust to 1.5–2.5× normal PTT) or **LMWH** (*enoxaparin* 1 mg/kg SC BID or 1.5 mg/kg SC daily). For long-term anticoagulation, continue **LMWH** in cancer patients or start ***warfarin*** 5 mg PO daily within 72 hours and continue heparin/LMWH until INR is between 2 and 3 for two consecutive days

IVC FILTER—if anticoagulation contraindicated

THROMBOLYSIS—may have a role in hemodynamically unstable pulmonary embolism or massive iliofemoral thrombosis

TREATMENT ISSUES

ANTICOAGULATION DURATION

- **AT LEAST 6 MONTHS**—first DVT with reversible or time-limited risk factor removed (i.e. if DVT in second term of pregnancy, stop therapy 3 months post-partum)
- **AT LEAST 1 YEAR**—first DVT and idiopathic

TREATMENT ISSUES (CONT'D)

- **LIKELY LIFELONG**—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 10 days, active bleeding, severe bleeding diathesis, or platelet $< 20\times10^3/\mu L$
- **RELATIVE**—mild–moderate bleeding diathesis or thrombocytopenia ($20–100\times10^3/\mu L$), 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. Extension to deep vein system rarely occurs through perforating veins and is most likely when the proximal greater saphenous vein or saphenous–femoral junction is involved

Notes

Approach to Anticoagulation Therapies

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	*Warfarin* 5 mg PO daily ×3 days, then adjust based on INR	**Complications**—bleeding (may be reversed with vitamin K), coumadin-induced skin necrosis **Monitor**—INR
Unfractionated heparin	**Indirect thrombin and factor Xa inhibitor (non-selective)**. 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 clot, *unfractionated heparin* 5000 U IV bolus, then 1000 U/h, and adjust to 1.5–2.5× normal PTT For DVT prophylaxis, *unfractionated heparin* 5000U SC 2 h before surgery, then 5000U SC BID	**Complications**—bleeding (may be reversed by protamine 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: *Enoxaparin* *Dalteparin* *Tinzaparin*	**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 *both* 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 clots, *enoxaparin* 1 mg/kg SC BID or 1.5 mg/kg SC daily, *dalteparin* 200 U/kg SC daily, *tinzaparin* 175 U/kg SC daily For DVT prophylaxis, *enoxaparin* 40 mg SC daily ×7–14 days starting 12 h pre-op, *dalteparin* 2500U SC 1 h pre-op, then 2500 U SC 6 h after, then 5000 U SC daily ×5–14 days	**Complications**—bleeding (may be reversed partially with *protamine sulfate* 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
Heparinoids: *Danaparoid (organon)*	**Indirect factor Xa inhibitors (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 More selective factor Xa inhibitor than LMWH, with a ratio of antifactor Xa to AT activity of 28:1 compared to 3:1 with LMWH. aPTT not useful for monitoring	HITT Acute DVT	For HITT, *danaparoid* 2000 anti-factor Xa U IV bolus, then 150–200 U/h, titrate to plasma anti-Xa level of 0.5–0.8 U/mL	**Complications**—bleeding **Monitor**—anti-factor Xa activity. Particularly important in renal failure 10% cross-reactivity between danaparoid and the antibody responsible for HITT, but clinical significance is uncertain

Approach to Anticoagulation Therapies (cont'd)

Class/Drugs	Mechanism	Indications	Usual dose	Complications/ monitoring
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, *fondaparinux* 2.5 mg SC daily (start 6–8 h after surgical hemostasis) For acute clots, *fondaparinux* 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 For UA/NSTEMI, *fondaparinux* 2.5 mg SC daily $\times$8 days or until discharge For STEMI, *fondaparinux* 2.5 mg IV $\times$1 then 2.5 mg SC daily $\times$8 days or until discharge	**Complications**—bleeding; avoid in spinal surgery **Monitor**—antifactor Xa activity
Rivaroxaban	**Direct factor Xa inhibitors (highly selective)**. Similar to fondaparinux, but specifically inhibits factor Xa by binding to its active site without interacting with AT	DVT prophylaxis (phase II)		**Complications**—bleeding **Monitor**—antifactor Xa activity
Direct thrombin inhibitors: *Dabigatran* *Desirudin* *Lepirudin* *Argatroban* *Ximelagatran*	**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 $\pm$ exosite I) are not masked by fibrin. Does not depend on AT for action and thus unaffected by AT deficiency	HITT (lepirudin, argatroban) ACS (hirudin, argatroban) DVT prophylaxis (hirudin, dabigatran)	For HITT, *lepirudin* 0.1–0.4 mg/kg IV bolus, then 0.1–0.15 mg/kg/h; *argatroban* 2 μg/kg/min infusion	**Complications**—bleeding **Monitor**—aPTT

CONTRAINDICATIONS TO WARFARIN THERAPY

ABSOLUTE—neurosurgery, ocular surgery or intracranial bleeding within the past 10 days, active bleeding, severe bleeding diathesis, or platelet $<20\times10^3/\mu L$

RELATIVE—mild to moderate bleeding diathesis or thrombocytopenia ($20–100\times10^3/\mu L$), brain metastases, recent major trauma, major abdominal surgery $<$2 days, GI or GU bleeding $<$2 weeks, endocarditis, severe hypertension (>200/120 mmHg)

Related Topics
DVT (p. 158)
Hypercoagulable States (p. 156)
Pulmonary Embolism (p. 8)

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 and 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 prothromin complex concentrate in selected cases

INR >9—if no significant bleeding, hold warfarin and administer *vitamin K1* 5–10 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 prothrombin complex concentrate or recombinant factor VIIa, depending on volume status and urgency. If life-threatening bleeding, hold warfarin therapy and administer recombinant factor VIIa, FFP, and *vitamin K1* 10 mg by slow IV infusion. Monitor INR and repeat as necessary. May also consider prothromin complex concentrate in selected cases

CORRECTION OF SUPRATHERAPEUTIC INR DUE TO WARFARIN USE (CONT'D)

Transfusion Reactions

COMPLICATIONS OF TRANSFUSIONS

Adverse Effect	Pathophysiology	Onset and Symptoms	Treatments
ABO incompatibility	Recipient Ab against donor RBC major antigen, 1/40,000	Immediate. Fever, ↓ BP, CP, lumbar pain, hemoglobinuria, and bleed	Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis
Acute hemolytic reaction	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
Febrile reaction	Recipient Ab against donor WBC PRBC, 1/300; or platelets (5U), 1/10	End of transfusion. Fever, chills	Antihistamine (*diphenhydramine* 50 mg IV ×1 dose), acetaminophen
Anaphylaxis	Recipient Ab against donor IgA, 1/40,000	Immediate. ↓ BP, bronchospasm, no fever	Stop transfusion, epinephrine, corticosteroids
Urticaria	Recipient IgE against donor antigens, 1/100 plasma-containing products	Acute. Pruritic rash	Antihistamine (*diphenhydramine* 50 mg IV ×1 dose)
Post-transfusion purpura (PTP)	Recipient Ab against donor platelet	7–10 days after. Consumptive thrombocytopenia and purpura	Steroids, plasmapheresis
Transfusion-associated circulatory overload (TACO)	Hypervolemia 1/700	Acute/delay. Pulmonary edema	Epinephrine, corticosteroids
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
Air embolism		Acute. SOB, ↓ BP	Supportive measures
TRALI	Donor Ab against recipient WBC, 1/5000 plasma-containing products	Acute. Hypoxemic, pulmonary edema	Supportive measures
GVHD	Donor lymphocytes against recipient tissue	Delay. Rash, hepatitis, diarrhea	
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—CBCD, peripheral smear, urea, Cr, 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)—prevention 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 (kills all leukocytes and prevents transfusion-associated GVHD)—stem cell transplant recipients (prevents GVHD), recipients of directed donor transfusions from blood relatives, Hodgkin's 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

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
ANISOCHROMIA—two cell populations circulating simultaneously. One population is microcytic and hypochromic and the other is normocytic and normochromic. Causes include treated iron deficiency anemia, post-transfusion of a hypochromic patient, sideroblastic anemia

RBC INTRACELLULAR INCLUSIONS

BASOPHILIC STIPPLING—β-thalassemia, lead, or arsenic poisoning
HEINZ BODIES—G6PD deficiency, alpha thalassemia
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, extramedullary erythropoiesis
HOWELL–JOLLY BODIES—asplenia, megaloblastic hematopoiesis
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—myelophthisis, myelofibrosis with myeloid metaplasia (MMM), severe iron deficiency, thalassemia major. Disappear after splenectomy
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

Splenomegaly

DIFFERENTIAL DIAGNOSIS

CONGESTIVE—right heart failure, constrictive pericarditis, tricuspid regurgitation, IVC obstruction, hepatic/splenic vein obstruction, cirrhosis with portal hypertension

INFILTRATIVE

- **MALIGNANCY**—lymphoma (Hodgkin's, non-Hodgkin's, hairy cell leukemia), leukemia (CLL, CML), myeloproliferative disorders (PRV, CML, ET, MF), splenic tumor, metastasis
- **AMYLOIDOSIS**
- **SARCOIDOSIS**

REACTIVE

- **INFECTIONS**—**bacterial** (endocarditis, sepsis, TB, MAC), **viral** (mononucleosis, hepatitis), **fungal** (*Histoplasma*), **parasitic** (malaria, *Leishmania*, trypanosomiasis)
- **INFLAMMATORY**—rheumatoid arthritis (Felty's syndrome), SLE, Still's disease

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **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
4. Spleen is not usually ballotable unless gross ascites are 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 cm^3, 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 10^{th} rib and points anteriorly toward, the left colic flexure

	Sens	Spc
Inspection		
Bulging mass over left costal margin	Low	–
Percussion		
Castell's method (percuss lowest intercostal space in the left anterior axillary line during both expiration and full inspiration; dullness suggests splenomegaly	82%	83%
Nixon's method (right lateral decubitus position; percuss from lower level of pulmonary resonance in posterior axillary line downward obliquely to lower midanterior costal margin; $>$8 cm suggests splenomegaly)	59%	94%
Traube's space (percuss space 6^{th} rib superiorly, mid-axillary line laterally and costal margin inferiorly; dullness suggests splenomegaly	62%	72%
Palpation		
Two-handed palpation with patient in right lateral decubitus position	71%	90%
One-handed palpation with patient supine	–	–

APPROACH—"given the low sensitivity of the clinical examination, routine examination for splenomegaly cannot definitively rule in or rule out splenomegaly in normal, asymptomatic patients where the prevalence is $<$ 10% and additional imaging tests will be required. Rather, the examination for splenomegaly is most useful to rule in the diagnosis of splenomegaly among patients in whom there is a clinical suspicion of at least 10%. The examination should always start with percussion. If no dullness is detected on percussion, there is no need to palpate as the results of palpation will not effectively rule in or rule out splenic enlargement. If the possibility of missing splenic enlargement remains an important clinical concern, then ultrasound or scintigraphy is indicated. In the presence of percussion dullness, palpation should follow. If both tests are positive, the diagnosis of splenomegaly is established (providing the clinical suspicion of splenomegaly was at least 10% before examination). If palpation is negative, diagnostic imaging will be required to confidently rule in or rule out splenomegaly"

JAMA 1993 270:18

INVESTIGATIONS

BASIC

- **LABS**—CBCD, peripheral smear, AST, ALT, ALP, bili
- **MICROBIOLOGY**—blood C&S
- **IMAGING**—U/S abd

SPECIAL

- **CT ABD**—weight = 0.43×Length×Width ×Thickness
- **SCINTIGRAPHY**
- **MALIGNANCY WORKUP**—bone marrow biopsy, lymph node biopsy, laparoscopy/laparotomy

MANAGEMENT

TREAT UNDERLYING CAUSE

SPLENECTOMY—see p. 147 for more details

SPECIFIC ENTITIES

CAUSES OF MASSIVE SPLENOMEGALY—lymphoma, hairy cell leukemia, CML, myelofibrosis, malaria, MAC in HIV, thalassemia major, sarcoidosis, Gaucher's disease

Myeloproliferative Disorders NEJM 2007 357:3

DIFFERENTIAL DIAGNOSIS

ESSENTIAL THROMBOCYTOSIS (ET)
POLYCYTHEMIA RUBRA VERA (PRV)
CHRONIC MYELOGENOUS LEUKEMIA (CML)
MYELOFIBROSIS (MF)
OTHERS—chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), chronic neutrophilic leukemia, systemic mastocytosis

PATHOPHYSIOLOGY

MYELOPROLIFERATIVE DISORDERS—associated with increased red blood cells (especially PRV), white blood cells (especially CML), and/or platelets (especially ET). MPS should not be confused with myelodysplastic syndrome (MDS), which is assoicated with a decreased production of blood cells. Both MPS and MDS can eventually lead to AML

POLYCYTHEMIA RUBRA VERA—see POLYCYTHEMIA (p. 143)

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

- **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 $<100\times10^3/\mu L$
- **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 $>1.0\times10^3/\mu L$ for at least 6 months), anemia, thrombocytopenia, and splenomegaly

PATHOPHYSIOLOGY (CONT'D)

ESSENTIAL THROMBOCYTOSIS—see THROMBOCYTOSIS (p. 150)

MYELOFIBROSIS—↑ fibroblasts, marked ↑ spleen, teardrop RBC, nucleated RBC, large platelets

> **Related Topics**
> Polycythemia (p. 143)
> Thrombocytosis (p. 150)

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**—CBCD, peripheral smear, reticulocyte count, uric acid
- **BONE MARROW BIOPSY**—not useful for PRV. Consider cytogenetic studies of blood/bone marrow (FISH) or quantitative PCR to look for Ph chromosome

SPECIAL

- **GENETIC TESTING**—JAK2 mutation (sensitivity ~100% for PRV and highly specific for other myeloproliferative disorders), bcr–abl testing (CML)
- **LEUKOCYTE ALKALINE PHOSPHATASE** (LAP)—↑ in PRV, MF, ET, and leukemoid reactions; can be ↓ in CML and CMML
- **VITAMIN B12**—↑ in CML due to granulocyte transcobalamin I levels
- **EPO**—↓ in PRV

DIAGNOSTIC AND PROGNOSTIC ISSUES

LEUKOCYTE ALKALINE PHOSPHATASE—elevated in PRV, MF, and ET, but decreased in CML and CMML

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

POLYCYTHEMIA RUBRA VERA—median survival 10–15 years, ~1/100 transforms to CML, MF, AML

CHRONIC MYELOGENOUS LEUKEMIA—median survival 3–4 years, ~1/2 transforms to AML

ESSENTIAL THROMBOCYTOSIS—median survival 10–15 years, ~1/1000 transforms to AML

MYELOFIBROSIS—median survival 5 years, ~1/10 transforms to AML

MANAGEMENT

POLYCYTHEMIA RUBRA VERA—phlebotomy 1–2/week, aspirin, hydroxyurea

CHRONIC MYELOGENOUS LEUKEMIA

- **CHRONIC PHASE**—*imatinib mesylate* 400–800 mg PO daily with cytogenetic response rate 63%, dasatinib and nilotinib may be used for imatinibresistant disease. Allogeneic stem cell transplant is associated with 60–70% cure rate
- **ACCELERATED PHASE**—*imatinib mesylate* 600–800 mg PO daily. Allogeneic stem cell transplant is associated with 30–45% cure rate
- **BLAST CRISIS**—*imatinib mesylate* 800 mg PO daily, plasmapheresis. Allogeneic stem cell transplant is associated with 10–15% cure rate
- **IMATINIB-RESISTANT CML**—dasitinib, nilotinib, and stem cell transplantation

ESSENTIAL THROMBOCYTOSIS—aspirin, anagrelide (↓ platelet via stabilizing membrane), hydroxyurea, alkylating agents, ^{32}P

MYELOFIBROSIS—splenectomy, interferon α, thalidomide

TREATMENT ISSUES

RESPONSE CRITERIA FOR CML

- **HEMATOLOGICAL RESPONSE**
  - **COMPLETE RESPONSE**—WBC $<10\times10^3/\mu L$ with no immature granulocytes and $<5\%$ basophils, platelet $<450\times10^3/\mu L$, and non-palpable spleen

TREATMENT ISSUES (CONT'D)

  - **PARTIAL RESPONSE**—persistence of immature cells in peripheral blood, platelets $>450\times10^3/\mu L$ but $<50\%$ of pre-treatment levels, or persistent splenomegaly but $<50\%$ of pre-treatment size
- **CYTOGENIC RESPONSE** (FISH detection of the Philadelphia chromosome)
  - **COMPLETE**—0% Ph+ cells
  - **PARTIAL**—1–35% Ph+ cells
  - **MAJOR**—complete and partial cytogenetic response
  - **MINOR**—36–65% Ph+ cells
  - **MINIMAL**—66–95% Ph+ cells
- **MOLECULAR RESPONSE** (bcr–abl transcript detection by RT-PCR)
  - **COMPLETE**—negative
  - **MAJOR**—bcr–abl to control gene ratio <0.1 (3 log decrease in bcr–abl transcript in peripheral blood)

DEFINITION OF TREATMENT FAILURE FOR CML PATIENTS ON IMATINIB THERAPY

Months	Suboptimal	Failure
3	< CHR	No HR
6	< PCGR	< CHR, no CGR
12	< CCGR	< PCGR
18	< MMR	< CCGR
Anytime	ACA, loss of MMR	Loss of CHR or CCGR

where HR=hematologic response, CHR=complete hematologic response, CGR=cytogenetic response, PCGR=partial cytogenetic response, CCGR=complete cytogenetic response, MMR=major molecular response, ACA=additional chromosomal abnormality

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, overexpression or amplification of bcr–abl

Acute Myelogenous Leukemia

NEJM 1999 341:14

HEMATOLOGIC MALIGNANCIES OVERVIEW

MYELO—bone marrow. Myeloproliferative disorders (PRV, 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

HEMATOLOGIC MALIGNANCIES OVERVIEW (CONT'D)

LYMPHOID—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. More aggressive course

HEMATOLOGIC MALIGNANCIES OVERVIEW (CONT'D)

- **CHRONIC LEUKEMIA**—involves mature differentiated cells. More indolent course

LYMPHOMA—malignancy of lymphoid origin and presents more in lymphoid organs

- **HODGKIN'S LYMPHOMA**—B cell (Reed–Sternberg cell)
- **NON-HODGKIN'S 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

RISK FACTORS FOR AML

- **FAMILY HISTORY**—family history (3×), Down's, Klinefelter, Fanconi syndrome, Bloom's, ataxia telangiectasia, neurofibromatosis
- **ENVIRONMENTAL**—previous chemotherapy (alkylating agents [melphalan, cyclophosphamide, chlorambucil, temozolomide], topoisomerase II inhibitors [anthracyclines, etoposide]), radiation, benzene
- **DISEASES**—MDS, MPS (PRV, CML, ET, MF), PNH, aplastic anemia

DISTINGUISHING FEATURES BETWEEN TREATMENT-INDUCED 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	Worse	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 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**—CBCD, smear (Auer rods), lytes, urea, Cr, Ca, PO_4, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen

INVESTIGATIONS (CONT'D)

- **BONE MARROW BIOPSY (>20% BLASTS) WITH CYTOGENETIC ANALYSIS**

SPECIAL

- **IMAGING**—MUGA scan
- **LUMBAR PUNCTURE**—CSF for cytology (risk of CNS involvement greatest with high circulating blasts, elevated LDH, and monocytic variants of AML)
- **HLA TESTING**—to assist in obtaining HLA-matched platelets if needed during treatment and to find HLA-matched allogeneic bone marrow

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIAGNOSTIC CRITERIA—>20% blasts in bone marrow

HISTOLOGIC TYPE

- **FAB M0**—AML, minimally differentiated
- **FAB M1**—AML, without maturation (19%)
- **FAB M2**—AML, with maturation (32%)
- **FAB M3**—acute promyelocytic leukemia (PML), with both hypergranular and variant microgranular subtypes (M3v)
- **FAB M4**—acute myelomonocytic leukemia (AMML), including the variant AMML with abnormal eosinophils (M4EO) (17%)
- **FAB M5**—acute monoblastic leukemia, including poorly differentiated (M5a) and differentiated (M5b)
- **FAB M6**—acute erythroleukemia
- **FAB M7**—acute megakaryoblastic leukemia

PROGNOSTIC FACTORS

- **GOOD RISK** (70% 5-year survival, 33% relapse)—favorable karyotypes t(8;21), t(15;17), inv(16)/t(16;16)/del(16q), FAB M3
- **INTERMEDIATE RISK** (48% 5 year survival, 50% relapse)—neither good nor bad; normal cytogenetics or trisomy 8
- **POOR RISK** (15% 5-year survival, 78% relapse)—adverse karyotypes include monosomy chromosome 5 or chromosome 7, del(5q), abn(3q26), t(6;9), 11q23 aberrations except for t(9;11), or multiple chromosomal changes, resistant disease after first course of chemotherapy (>15% blasts)
- **ADDITIONAL POOR PROGNOSTIC FACTORS**—age >60, Karnofsky score <60%, CD34+, MDR1+, FLT3 mutation, prior MDS, MPS, chemotherapy, radiation, trisomy 8, t(6;9), LDH >2.9× UNL

MANAGEMENT

AGE <60

- **INDUCTION CHEMOTHERAPY**—IDAC (also known as the 7+3 regimen, cytarabine ×7 days + one of daunorubicin/idarubicin/mitoxantrone ×3 days), HDAC (same except higher dose of cytarabine q12h ×12 doses leads to longer disease free survival) or NOVE (mitoxantrone plus etoposide)

MANAGEMENT (CONT'D)

- **CONSOLIDATION TREATMENT**
  - **COMPLETE REMISSION POST-INDUCTION**
    - **GOOD RISK**—chemotherapy IDAC or HDAC ×3
    - **INTERMEDIATE RISK**—sibling-donor allogeneic stem cell transplant (SCT) if available; otherwise, consolidation chemotherapy
    - **POOR RISK**—allogeneic SCT if matched donor available; otherwise, consolidation chemotherapy
  - **LACK OF COMPLETE REMISSION POST-INDUCTION**—repeat induction or give cyclophosphamide plus etoposide. Proceed to consolidation as in poor risk disease if complete remission. Otherwise, palliation only
- **RELAPSE**—allogeneic SCT if matched donor available (preferred); otherwise, salvage chemotherapy with cytarabine/carboplatin, clinical trials, or palliation

AGE >60—individualized treatment. If unable to tolerate aggressive therapy, consider IDAC with attenuated doses or palliation with hydroxyurea cytoreduction

Related Topics
Febrile Neutropenia (p. 236)
Tumor Lysis Syndrome (p. 228)

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. After induction, the remission rate in younger patients (<55 years) is 70–85%, but only 40–50% in older patients

ALLOGENEIC SCT—if HLA matched, may opt for consolidation chemotherapy while waiting for match donor. Allogeneic SCT has resulted in cure rates of 50–60% for recipients in 1st remission

SPECIFIC ENTITIES

MYELODYSPLASTIC SYNDROME (MDS)—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, refractory 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

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—peripheral blood smear (RBC with abnormal morphologic features, dysgranulopoiesis with Pelger-Huët deformity, nuclear atypia and hypogranulation, relative monocytosis), bone marrow biopsy

INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MYELODYSPLASTIC SYNDROMES

Score	0	0.5	1	1.5	2
% blasts in BM	<5	5–10	–	11–20	21–30
Karyotype	Good	Med.	Poor	–	–
Cytopenia	0/1	2/3	–	–	–

For karyotype, good = –y, del(5q), del(20q); medium = neither good nor poor; poor = chromosome 7 or complex abnormalities

Risk group	Score	Median survival
Low	0	5.7 years
Intermediate 1	0.5–1.0	3.5 years
Intermediate 2	1.5–2.0	1.2 years
High	≥2.5	0.4 year

- **TREATMENTS**—transfusions, EPO, treat infections early, 5-azacytidine, lenalidomide, decitabine, allogeneic stem cell transplant (IPSS ≥1.5)

ACUTE PROMYELOCYTIC LEUKEMIA (M3, APL, PML)

- **PATHOPHYSIOLOGY**—associated with t(15;17)(q22;q21), which results in fusion of PML gene and retinoic acid receptor α gene. This gene product plays a key role in leukemogenesis. Other combinations include t(11;17) with fusion of PLZF gene, t(5;17) with fusion of NPM gene, or t(11;17) with fusion of NuMA gene. Note that all except PLZF-RARA are susceptible to retinoic acid treatment
- **CLINICAL FEATURES**—similar to AML. DIC commonly occurs in PML and should be monitored closely
- **TREATMENTS**—**induction** with all-*trans*-retinoic acid plus idarubicin, then **consolidation** with anthracycline and cytarabine, and then **maintenance** with all-*trans*-retinoic acid for 1 year. Retinoic acid exerts its effect via (1) degradation of PML-RAR protein, (2) transformation of PML-RAR from transcription repressor to activator, and (3) differentiation. Retinoic acid syndrome may occur with fever, respiratory distress, interstitial pulmonary infiltrates, pleural and pericardial effusion, episodic hypotension, acute renal failure, and weight gain. Arsenic trioxide can be used for **recurrent disease** but is associated with QT prolongation and sudden death

Acute Lymphoblastic Leukemia

NEJM 2006 354:2

PATHOPHYSIOLOGY

HISTOLOGIC TYPE

- **FAB L1**—small, uniform lymphoblasts with indistinct nucleoli
- **FAB L2**—larger, pleomorphic lymphoblasts with low nucleus to cytoplasm ratio and clear nucleoli
- **FAB L3**—large, pleomorphic lymphoblasts with basophilic cytoplasm, large nucleoli, vacuoles

WHO CLASSIFICATION

- **PRECURSOR B CELL** (L1, L2)
  - **PRO-B ALL**—resembles an early stage of B cell
  - **PRE-B-CELL ALL**—intracytoplasmic immunoglobulin
  - **B-CELL ALL**—express surface immunoglobulin
- **PRECURSOR T CELL** (L1, L2)
- **BURKITT-LIKE ALL** (L3)

RISK FACTORS FOR ALL—old age, previous chemotherapy or radiation, Down's syndrome

CLINICAL FEATURES

PANCYTOPENIA—weakness, fatigue, infections, gingival bleed, ecchymosis, petechiae, epistaxis, menorrhagia

ORGAN INVOLVEMENT—lymphadenopathy, hepatomegaly, splenomegaly, bone pain, cranial nerve palsies, headaches

NOTE: precursor B lymphoblastic lymphoma is associated with lymphadenopathy/extranodal involvement and $< 25\%$ blasts, while precursor T LBL is associated mediastinal mass and $< 25\%$ blasts

DISTINGUISHING FEATURES BETWEEN AML AND ALL

	AML	Precursor ALL
Blasts	Larger	Small
Auer rods	+	–
TdT	–	+
MPO	+	–

INVESTIGATIONS

BASIC

- **LABS**—CBCD, smear, lytes, urea, Cr, Ca, PO_4, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen, flow cytometry of peripheral blood (immunophenotyping)
- **BONE MARROW BIOPSY**—>25% blast, flow cytometry for immunophenotyping, cytogenetic analysis (detection of BCR–ABL fusion and chromosomal abnormalities with pulsed-field gel electrophoresis and/or RT-PCR)
- **LUMBAR PUNCTURE**—CSF for cytology
- **TISSUE BIOPSY**—lymph node, skin, mediastinal mass

INVESTIGATIONS (CONT'D)

SPECIAL

- **IMAGING**—MUGA scan
- **HLA TESTING**—to assist in obtaining HLA-matched platelets if needed during treatment and to find HLA-matched allogeneic bone marrow

PROGNOSTIC ISSUES

PROGNOSTIC FACTORS—while childhood ALL is curable in 85% of cases, adult ALL has a worse prognosis, with a 5-year survival of 35%. Factors associated with poorer survival include the following:

- **CLINICAL**—lack of response to induction therapy (most important), old age, leukocyte count, CNS involvement
- **CYTOGENETICS**—BCR–ABL fusion or t(9;22) (also known as the Philadelphia chromosome, in 20–50% of adults), MLL–AF4 fusion or t(4;11) (in 5–6% of adults), t(8;14), t(1;19), hypodiploidy (< 45 chromosomes/cell), del(7), trisomy
- **FAVORABLE PROGNOSIS**—hyperdiploidy, del(9), TEL-AML1 fusion or t(12;21) (in 10% of adults)

RISK CATEGORIES

- **HIGH RISK**—any of age >60, t(9;22) or bcr–abl, t(4;11), t(1;19); WBC $>30\times10^3/\mu L$ in B-ALL or $>100\times10^3/\mu L$ in T-ALL or pro-B ALL
- **STANDARD RISK**—none of high-risk features

RISK FACTORS FOR CNS RELAPSE—high-risk genetic features, T-ALL, large tumor burden, CSF positivity

MANAGEMENT

REMISSION INDUCTION THERAPY—combination chemotherapy with prednisone, vincristine, an anthracycline $\pm$ asparaginase, and cyclophosphamide. Complete response 80–90%. Management of specific subgroups include

- **PH+ ALL**—add imatinib
- **B-CELL ALL**—treat as aggressive non-Hodgkin's lymphoma
- **T-CELL ALL**—treat with cyclophosphamide-containing regimens

CNS PROPHYLAXIS—to start after remission with intrathecal methotrexate with high-dose systemic methotrexate. Consider cranial radiation for patients at high risk of CNS relapse

INTENSIFICATION/CONSOLIDATION THERAPY

- **STANDARD RISK**—consolidation chemotherapy with various combinations of cyclophosphamide, 6-mercaptopurine, cytarabine, vincristine, and doxorubicin

MANAGEMENT (CONT'D)

- **HIGH RISK**—allogeneic SCT if HLA-matched donor available and eligible for transplant; otherwise, consolidation chemotherapy

MAINTENANCE THERAPY—POMP (6-mercaptopurine daily, methotrexate weekly, vincristine and prednisone monthly) or dexamethasone for 2–3 years, except for patients who received allogeneic SCT

TREATMENT ISSUES

SURVIVORSHIP ISSUES—risk of secondary malignancies, neurologic sequelae, cardiotoxicity, infertility, depression, anxiety, and fatigue

Related Topics
Febrile Neutropenia (p. 236)
Tumor Lysis Syndrome (p. 228)

Chronic Lymphocytic Leukemia

NEJM 2005 352:8

DIFFERENTIAL DIAGNOSIS OF LYMPHOCYTOSIS

NEOPLASTIC

- **CHRONIC LYMPHOCYTIC LEUKEMIA** (CLL, most common cause)
- **PROLYMPHOCYTIC LEUKEMIA**
- **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, hepatitis, toxoplasmosis

PATHOPHYSIOLOGY

WHO CLASSIFICATION—CLL is identical to small lymphocytic lymphoma (SLL, mature B-cell non-Hodgkin's 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's transformation) 3–10%, Hodgkin's 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**—CBCD, smear (smudge cells), lytes, urea, Cr, Ca, PO_4, 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**
- **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 $>5\times10^3/\mu L$, with ≥1 B-cell marker (CD19, CD20, CD23) and CD5; >55% atypical cells
- **BONE MARROW**—a normocellular to hypercellular marrow with >30% lymphocytes. Interstitial/nodular pattern (70%) has a better prognosis than diffuse/extensive pattern (30%)
- **IMMUNOPHENOTYPE**—CD5+, CD19+, CD20+, CD23+, CD43+, CD10–, SIg+
- **NOTE**—for patients with lymphocyte count $5–10\times10^3/\mu L$, 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 $\times10^3$/mL). Median survival 19 months

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

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 (<$100\times10^3/\mu L$). 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, P2X7 receptor, p53 mutation, gene 1513A/A genotype, 17p deletion, 11q deletion, trisomy 12

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

AGE <65 AND OTHERWISE HEALTHY (potentially curative)—consider high-dose chemotherapy + allogeneic stem cell transplant

AGE >65 OR COMORBIDITIES (palliative)—first-line regimens include **FR** (fludarabine, rituximab) **or FCR** (fludarabine, cyclophosphamide, rituximab). Second-line therapy includes mainly **alkylating agents** (chlorambucil, cyclophosphamide, CVP). **Alemtuzumab** (anti-CD52 antibody) is useful for fludarabine-refractory disease (i.e. lack of CR/PR, or response but <6 months).

Indications for treatment include symptoms (weakness, painful lymphadenopathy, B symptoms, symptomatic splenomegaly), anemia (Hb <110 g/L [<11 g/dL]), thrombocytopenia (platelets <$100\times10^3/\mu L$), autoimmune hemolytic anemia/thrombocytopenia that failed steroids, progressive disease (increasing lymphocytosis with doubling time <6 months ± rapidly enlarging lymph nodes, spleen, and liver). If evidence of Richter's transformation, treat as aggressive lymphoma with CHOPR

NOTE—while traditionally SLL has been managed as a low-grade non-Hodgkin's lymphoma, it is identical to CLL and should be treated as such

TREATMENT ISSUES

NCI WORKING GROUP DIAGNOSTIC CRITERIA FOR TREATMENT RESPONSE

- **COMPLETE RESPONSE**—normal physical examination and no symptoms. Lymphocytes ≤4 $\times10^3/\mu L$, neutrophils ≥$1.5\times10^3/\mu L$, platelets >$100\times10^3/\mu L$, Hb >110 g/L [>11 g/dL], and bone marrow lymphocytes < 30% with no nodules. Duration of at least 2 months
- **PARTIAL RESPONSE**—nodes/liver/spleen ≥50% decrease PLUS one of neutrophils ≥$1.5\times10^3/\mu L$, platelets >$100\times10^3/\mu L$, or Hb >110 g/L [>11 g/dL] or 50% improvement. Duration of at least 2 months
- **STABLE DISEASE**—between PR and PD
- **PROGRESSIVE DISEASE**—any one of nodes/liver/spleen ≥50% increase or new lesions, lymphocytes ≥50% increase, or Richter's syndrome

SPECIFIC ENTITIES

HAIRY CELL LEUKEMIA

- **PATHOPHYSIOLOGY**—rare indolent non-Hodgkin's lymphoma with mononuclear cells displaying cytoplasmic projections giving a hairy appearance. Secretes fibronectin, cytokines, and TNF-causing bone marrow fibrosis
- **CLINICAL FEATURES**—splenomegaly (90%), cytopenia (fatigue, recurrent infections, thrombocytopenia), and leukocytosis. Lymphadenopathy is uncommon
- **TREATMENTS**—treat only if symptomatic (cytopenia, splenomegaly, B symptoms). Cladribine (2Cda) is first-line treatment and may be repeated. Other treatments include pentostatin, interferon, splenectomy, rituximab, and BL22 (CD22 antibodies)

Hodgkin's Lymphoma

PATHOPHYSIOLOGY

HISTOLOGIC TYPE

- **CLASSICAL HODGKIN'S 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

PATHOPHYSIOLOGY (CONT'D)

- **NODULAR SCLEROSIS** (70%)—more common in females, above diaphragm involvement (mediastinal mass). Three grades include lymphocyte predominant (G1), mixed (G2), and syncytial (G3)

PATHOPHYSIOLOGY (CONT'D)

- **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'S LYMPHOMA** (5%)—males, upper neck involvement. Characterized by popcorn cells. Slow progression, excellent prognosis. CD20 positive

RISK FACTORS

- **FAMILY HISTORY**
- **ENVIRONMENTAL**—wood workers, farmers, meat workers
- **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**

DISTINGUISHING FEATURES BETWEEN MALIGNANT AND NON-MALIGNANT LYMPHADENOPATHY

	Malignancy	Benign
Size	Larger, grows	Smaller
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's 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. II-2)
- **III** Involvement on both sides of diaphragm. III-1 indicates involvement of the spleen or splenic hilar, celiac, or portal nodes. Stage III-2 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's 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**—CBCD, 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 $<4\times10^3/\mu L$, platelets $<125\times10^3/\mu L$
- **ENT EXAMINATION**—stage IA or IIA with upper cervical lymph node involvement
- **MRI SPINE**—if suspect spinal cord compression
- **MUGA SCAN**—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'S 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 $>15\times10^3/\mu L$, lymphocyte $<0.6\times10^3/\mu L$, 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

LIMITED STAGE (stage IA, IIA, and IB in some institutions, 30%)—ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) x2 cycles. PET scan afterward, if complete remission, 2 more cycles; otherwise, give involved field radiation. If stage IA low bulk high neck (above hyoid) or epitrochlear nodular lymphocyte-predominant disease, involved field radiation only

ADVANCED STAGE (70%)—ABVD $\times6$ cycles. Reassess with CT and/or PET scan. If residual disease, consider involved field irradiation. Alternative regimens include BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) combined with involved field radiotherapy or Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, prednisone) combined with involved field radiotherapy

MANAGEMENT (CONT'D)

REFRACTORY OR RELAPSED DISEASE—high-dose chemotherapy with CBV (cyclophosphamide, BCNU, etoposide) or BEAM (BCNU, etoposide, cytarabine, melphalan) and irradiation plus autologous stem cell transplant. Overall, 40–50% of refractory disease and 60–70% of first relapse can be cured

TREATMENT ISSUES

INDICATIONS FOR AUTOLOGOUS STEM CELL TRANSPLANT—progression during first-line chemotherapy, relapse <1 year after completion of chemotherapy, relapse with B symptoms or extranodal sites. Patients with relapse >1 year or only in previously unirradiated lymph nodes may or may not require transplant

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)

Non-Hodgkin's 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's, non-Hodgkin's
- **LEUKEMIA**
- **METASTATIC CANCER**
- **LYMPHOPROLIFERATIVE**—Castleman's disease, angioimmunoblastic lymphadenopathy, autoimmune lymphoproliferative disease

INFLAMMATORY—RA, SLE, dermatomyositis, Still's disease, Churg–Strauss syndrome

INFILTRATIVE—sarcoidosis, amyloidosis, histiocytosis, chronic granulomatous disease

DIFFERENTIAL DIAGNOSIS OF LYMPHADENOPATHY (CONT'D)

OTHERS—**medications** (phenytoin), **endocrine** (hypothyroidism, Addison's 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 (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

PATHOPHYSIOLOGY (CONT'D)

- **HAIRY CELL LEUKEMIA** (HCL)
- **LYMPHOPLASMACYTIC LYMPHOMA** (LPL, 2–3%)—previously Waldenstrom's 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 bcl2 translocations)
- **LEUKEMIC B-CELL LYMPHOMAS**
  - **BURKITT'S LYMPHOMA** (BL)
  - **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**—angioimmunoblastic (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's lymphoma is 50× higher in Africa than in the USA)
- **DISEASES**—infections (HIV, EBV, HHV8, HCV, HTLV, *Helicobacter pylori*), inflammatory disorders (RA, SLE, Sjogren's syndrome, mixed cryoglobulinemia, inflammatory bowel disease), inherited immune defects

PATHOPHYSIOLOGY (CONT'D)

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'S LYMPHOMA**—t(8;14), t(2;8), or t(8;22) in 100%, c-myc

INFECTIONS AND LYMPHOMA

- **EBV**—Hodgkin's lymphoma, Burkitt lymphoma, post-transplant lymphoproliferative disorders, primary CNS lymphoma
- **HCV**—splenic marginal zone lymphoma
- **HHV8**—Castleman disease, primary effusion lymphoma
- **HIV**—primary CNS lymphoma
- **HTLV**—adult T-cell leukemia/lymphoma
- ***BORRELIA BURGDORFERI***—cutaneous marginal zone lymphoma
- ***CAMPYLOBACTER JEJUNI***—small bowel marginal zone lymphoma
- ***CHLAMYDIA PSITACCI***—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's 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, 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)

DESIGNATIONS

- **E**—single extralymphatic site (i.e. involvement outside of lymph nodes, spleen, thymus, and Waldeyer's 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**—CBCD, peripheral smear, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, PO_4, 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**
- **BONE MARROW BIOPSY WITH SURFACE MARKERS**

SPECIAL

- **MRI SPINE**—if suspect spinal cord compression
- **MUGA SCAN**—evaluate cardiac function prior to anthracycline therapy for patients with significant cardiac risk factors

DIAGNOSTIC AND PROGNOSTIC ISSUES

IMMUNOPHENOTYPE OF SELECTED LYMPHOMAS

	CLL	MCL	FL	MZL
CD20	+	+	+	+
CD5	+	+	−	−
CD23	+	−	−	−
CD43	+	+	−	+
CD10	−	−	+	−

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's ring)

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **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. 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

INDOLENT LYMPHOMAS

- **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%), CVPR ×8 cycles (cyclophosphamide, vincristine, prednisone, and rituximab), followed by maintenance rituximab for 2 years if PR/CR (15% relapse with maintenance rituximab compared to 35% for CVPR alone or 70% for CVP alone). Second-line agents include fludarabine, cyclophosphamide, rituximab, I^{131}-tositumomab, and Y^{90}-ibritumomab. Stem cell transplant in fit individuals

AGGRESSIVE LYMPHOMAS

- **LIMITED STAGE** (IA or IIA, 30%)—CHOPR (cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab) ×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%)—**CHOPR** ×6. PET scan afterwards, if local residual disease, give involved field radiation; if diffuse residual disease, consider **salvage therapy** (see below). For patients with bone marrow/peripheral blood involvement, **intrathecal chemotherapy** may be considered as 5–20% chance of leptomeningeal disease otherwise
- **SALVAGE**—**GDPR** (gemcitabine, dexamethasone, cisplatin, rituximab) or **RICE** (rituximab, ifosfamide, carboplatin, etoposide), followed by **autologous stem cell transplant**

HIGHLY AGGRESSIVE LYMPHOMAS

- **BURKITT'S LYMPHOMA**—expedited staging (within 1–2 days). For **low-risk disease** (stage I or II, nonbulky <5 cm, no bone marrow/blood/CNS

MANAGEMENT (CONT'D)

disease and normal LDH), give CODOX-MR (cyclophosphamide, doxorubicin, vincristine, methotrexate, rituximab) ×1 then restage. If CR/PR, give IVAC-R (ifosfamide, etoposide, cytarabine) ×1 then CODOX-MR ×1; otherwise, give IVAC-R ×1 then proceed to stem cell transplant. For **high-risk disease**, give CODOX-MR ×1, IVAC-R ×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). Cure rate ~60%

- 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)

TREATMENT ISSUES

INTERNATIONAL WORKSHOP CRITERIA FOR TREATMENT RESPONSE FOR HODGKIN'S AND NON-HODGKIN'S LYMPHOMA

COMPLETE REMISSION (CR)—disappearance of all evidence of disease

- **Nodal masses:** if FDG-avid or PET positive prior to therapy, mass of any size permitted if PET negative. If variably FDG-avid or PET negative, regression to normal size on CT required
- **Liver and spleen:** not palpable, nodules disappeared
- **Bone marrow:** infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative

PARTIAL REMISSION (PR)—regression of measurable disease and no new sites

- **Nodal masses:** ≥50% decrease in sum of the product of the diameter (SPD) of up to 6 largest dominant masses; no increase in size of other nodes. If FDG-avid or PET positive prior to therapy, one or more PET positive at previously involved site; or if variably FDG-avid or PET negative, regression on CT ≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter)
- **Liver and spleen:** no increase in size

TREATMENT ISSUES (CONT'D)

- **Bone marrow:** irrelevant if positive prior to therapy; cell type should be specified

STABLE DISEASE (SD)—failure to attain CR/PR or PD

- **Nodal masses:** if FDG-avid or PET positive prior to therapy, PET positive at prior sites of disease and no new sites on CT or PET. If variably FDG-avid or PET negative, no change in size of previous lesions on CT

RELAPSED DISEASE (RD) **OR PROGRESSIVE DISEASE** (PD)—any new lesion or increase by ≥50% of previously involved sites from nadir

- **Nodal masses:** appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy
- **Liver and spleen:** >50% increase from nadir in the SPD of any previous lesions
- **Bone marrow:** new or recurrent involvement

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SPECIFIC ENTITIES

EYE LYMPHOMA

- PATHOPHYSIOLOGY—periorbital involvement (mostly MALT type) or intraocular involvement (usually DLBCL with more indolent course)
- TREATMENTS—for periorbital MALT, involved field radiation if localized disease or CVP if widespread disease. For intraocular disease, steroids, and involved field radiation. High-dose methotrexate may be useful

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
- TREATMENTS—high-dose corticosteroid with high-dose methotrexate is preferred. Whole brain radiation represents an alternative. Prognosis is 60% 2-year survival and 30% 5-year survival

LEPTOMENINGEAL MENINGITIS

- RISK FACTORS—aggressive lymphomas (lymphoblastic lymphoma, DLBCL, Burkitt's lymphoma, MCL), extranodal sites involvement (bone marrow, testicular, paranasal, retroperitoneal lymph nodes), any of the five IPI prognostic factors

SPECIFIC ENTITIES (CONT'D)

- **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

LOCALIZED PARANASAL SINUS LYMPHOMA

- **PATHOPHYSIOLOGY**—usually DLBCL type. May involve CNS if invade through the base of skull
- **CLINICAL FEATURES**—local pain, rhinorrhea, nasal or upper airway obstruction, facial swelling, epistaxis, diplopia, visual loss
- **TREATMENTS**—CHOPR$\times$3 + involved field radiation + intrathecal chemotherapy$\times$6

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
- **ASSOCIATIONS**—*H. pylori*-associated chronic gastritis, celiac disease, crohn's disease, gastrointestinal nodular lymphoid hyperplasia
- **DIAGNOSIS**—for gastric MALT, need to determine presence of *H. pylori* by biopsy (gastroscopy) $\pm$ 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. Considered lymphoma if $<$ 5% blasts in bone marrow; otherwise, considered leukemia
- **CLINICAL FEATURES**—usually mediastinal mass in young males

SPECIFIC ENTITIES (CONT'D)

BURKITT'S LYMPHOMA

- **PATHOPHYSIOLOGY**—t(8;14) 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 U/S
- **TREATMENTS**—unilateral orchiectomy + CHOPR + 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's 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 malignant 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. 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. Sezary syndrome is a 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

SPECIFIC ENTITIES (CONT'D)

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, IFNα, 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, alternating with GDP for 6 cycles for advanced stage disease. Consider allogeneic stem cell transplant

CASTLEMAN'S DISEASE

- **PATHOPHYSIOLOGY**—lymphoid proliferation associated with POEMS syndrome, lymphomas (Hodgkin's, non-Hodgkin's), and Kaposi's sarcoma. HIV and HHV8 common in multicentric subtype
- **CLINICAL FEATURES**—unicentric (isolated lymphadenopathy, benign, HHV8 negative). Multicentric (fever, night sweats, fatigue, lymphadenopathy, pulmonary infiltrates, frequently HHV8 and HIV positive)
- **TREATMENTS**—unicentric (resection with high chance of cure, radiation, rituximab). Multicentric (steroid, antivirals, anti-IL-6, CHOP, rituximab. Survival 8–14 months)

Multiple Myeloma

NEJM 1997 336:23
NEJM 2004 351:18

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%)

WALDENSTROM'S 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

EPIDEMIOLOGY

- **INCIDENCE**—1%
- **MORTALITY**—1%

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

CLINICAL FEATURES (CONT'D)

- **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 meninges, cord compression, or radiculopathy from vertebral osteolytic lesions ± plasmacytoma
- **RENAL FAILURE**
  - **PRE-RENAL**—N&V, renal vein thrombosis, Ca-induced vasospasm
  - **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**—CBCD, peripheral smear, lytes, urea, Cr, Ca, β2 microglobulin, serum viscosity, quantitative immunoglobulin, albumin, serum protein electrophoresis (reciprocal depression), urinary

INVESTIGATIONS (CONT'D)

protein electrophoresis, 24 h urinary collection for Bence Jones protein

- **IMAGING**—skeletal survey
- **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; nonsecretatory myeloma (3%) requires bone marrow biopsy for diagnosis

Related Topics
Amyloidosis (p. 420)
Renal Failure (p. 68)

DIAGNOSTIC AND PROGNOSTIC ISSUES

INTERNATIONAL MYELOMA WORKING GROUP CRITERIA

- **MULTIPLE MYELOMA**
  - **BONE MARROW PLASMA CELLS/PLASMACYTOMA**—no percent specified, but usually >10%
  - **M-PROTEIN**—in serum and/or urine, no concentration specified, but >30 g/L [>3 g/dL] in serum if overt myeloma
  - **TISSUE IMPAIRMENT**—★**CRAB**★ increased **c**alcium (>2.75 mmol/L [>11 mg/dL]), **r**enal insufficiency (Cr >173 μmol/L [>1.9 mg/dL]), **a**nemia (Hb < 100 g/L [< 10 g/dL] or drop by 20 g/L [2 g/dL]), **b**one lesions (lytic lesions, fractures). Other features include hyperviscosity, amyloidosis, or recurrent infections (>2 episodes in 12 months)
- **SMOLDERING MULTIPLE MYELOMA** (SMM)
  - **BONE MARROW PLASMA CELLS**—>10%
  - **M-PROTEIN**—>30 g/L [>3 g/dL] (but not necessary if bone marrow plasma cells>10%)
  - **TISSUE IMPAIRMENT**—no symptoms
- **MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE** (MGUS)
  - **BONE MARROW PLASMA CELLS**— < 10% (bone marrow biopsy is not required for suspected MGUS if M-protein ≤15 g/L [≤1.5 g/dL], IgG subtype, and patient asymptomatic)
  - **M-PROTEIN**— < 30 g/L[<3g/dL]
  - **TISSUE IMPAIRMENT**—no symptoms
  - **COURSE**—occurs in 2% of population over age 50 and 3% over age 70. Rate of transformation to malignant plasma cell disorder (multiple myeloma, Waldenstrom's macroglobulinemia, primary amyloidosis, B-cell lymphoma, or chronic lymphocytic leukemia) is about 1% per year

NEJM 2006 355:26

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
- **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
- **SERUM M PROTEIN LEVEL**—the higher the level, the higher the likelihood of multiple myeloma. Some define 35 g/L [3.5 g/dL] for IgG and 20 g/L [2 g/dL] for IgA as cutoff, others define 30 g/L [3 g/dL] regardless of Ig subtype as cutoff

DURIE–SALMON STAGING FOR MULTIPLE MYELOMA

- **STAGE I** (low tumor burden, $<0.6\times10^{12}/m^2$)—all of Hb >100 g/L [>10 g/dL], $Ca^{2+}\leq2.6$ 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, $0.6–1.2\times10^{12}/m^2$)—between stages I and III. Median survival ~30 months
- **STAGE III** (high tumor burden, $>1.2\times10^{12}/m^2$)—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 μmol/L [< 1.9 mg/dL]) and B (renal failure with Cr >175 μmol/L [>1.9 mg/dL])

PROGNOSTIC FACTORS FOR MULTIPLE MYELOMA—β2 microglobulin, albumin, platelet, creatinine, and age. The international staging system for multiple myeloma is particularly useful

- **STAGE I**—β2 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**—β2 microglobulin ≥5.5 mg/L. Median survival 29 months

JCO 2005 23:15

MANAGEMENT

MULTIPLE MYELOMA

- **AGE <65 AND OTHERWISE HEALTHY** (curative)—**induction chemotherapy** with thalidomide plus dexamethasone (first choice), lenalidomide plus dexamethasone, pulse dexamethasone, or VAD (vincristine, doxorubicin, dexamethasone) ×3–4 months. If good response, then proceed to **high-dose melphalan followed by autologous stem cell transplant.** This regimen prolongs survival by 12 months, but is not curative. Consider **tandem transplantation** if less than a good partial response (i.e. ≤90% reduction of monoclonal protein)
- **AGE >65 OR COMORBIDITIES** (palliative)—**MP** (melphalan + prednisone) ± thalidomide. Addition of interferon to MP provides small benefit. If bony disease, add **bisphosphonate** (alendronate, zoledronate). Second-line options include **thalidomide** (response ~30%) + **dexamethasone**, **lenalidomide** + **dexamethasone**, **bortezomib** (response ~30%), **dexamethasone** alone, and infusional VAD
- **SUPPORTIVE MEASURES**—**hydration** (>3 l/day), **hypercalcemia** (hydration, *prednisone* 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 great caution given the increased risk of thromboembolism and death), **hyperviscosity syndrome** (Ostwald viscosimeter >5, plasmapheresis), **anticoagulation** (if on thalidomide/lenalidomide and chemotherapy)

MANAGEMENT (CONT'D)

SMM—no treatment. Follow clinically
MGUS—no treatment. Follow clinically

TREATMENT ISSUES

INDICATIONS FOR TREATING MULTIPLE MYELOMA—>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. 420 for more details. Workup include abdominal fat biopsy, abd U/S, and echocardiogram

POEMS SYNDROME—osteosclerotic myeloma with **P**olyneuropathy, **O**rganomegaly, **E**ndocrine (diabetes, hypothyroidism, parathyroid hypogonadism, HPA), **M**onoclonal protein, **S**kin 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's phenomenon, or purpuric eruptions on exposure to the cold

Febrile Neutropenia

See FEBRILE NEUTROPENIA (p. 236)

Hematopoietic Stem Cell Transplant

CMAJ 2004 170:10
NEJM 2006 354:17

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)

TERMINOLOGIES (CONT'D)

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

TERMINOLOGIES (CONT'D)

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** (unlimited supply of donors, although limited amount of cord blood. More tolerant for mismatches in allogeneic transplant)

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's lymphoma (60–70% cure if relapse, 40–50% cure if refractory disease), multiple myeloma, 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 graft vs. host disease, 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—need to ensure good match of the following loci: 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

ALLOGENEIC TRANSPLANTATION (CONT'D)

- **HEMATOLOGIC**—pancytopenia, febrile neutropenia
- **EARLY NON-HEMATOLOGIC**—alopecia, N&V, oropharyngeal mucositis, diarrhea, sinusoidal obstruction syndrome (previously known as hepatic veno-occlusive disease with tender hepatomegaly, jaundicem and ascites), seizures, parotitis, pericarditis, cardiomyopathy, interstitial pneumonitis, hemorrhagic cystitis, rash
- **LATE NON-HEMATOLOGIC**—hypothyroidism, sterility or premature menopause, growth impairment, 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
- **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 $>0.5\times10^{3}/\mu L$, with platelet and RBC engraftment following. GCSF 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 PCP, 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

IMMUNORECONSTITUTION—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. Graft vs. host disease (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-GRAFTMENT** (<30 days)—HSV, Gram-negative bacteria, Gram-positive *Streptococcus*, fungal, central line infections (*S. epidermis*)
- **EARLY INFECTIONS** (30–100 days)—CMV, some fungal, PCP, central line infections (*S. epidermis*)
- **LATE INFECTIONS** (>100 days)—VZV, encapsulated bacteria, PCP, 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. 166)
Chemotherapy-Induced Diarrhea (p. 231)
Non-Hodgkin's Lymphoma (p. 173)
Febrile Neutropenia (p. 236)
Fungal Infections (p. 265)
Multiple Myeloma (p. 178)
Oral Mucositis (p. 230)
Sepsis (p. 99)
Tumor Lysis Syndrome (p. 228)

Notes

Notes

7
ONCOLOGY

Section Editor: Dr. Sharlene Gill

Lung Cancer

NEJM 2004 350:4

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **SMALL CELL** (SCLC, 15%)—smokers, central lesions, early metastasis compared to NSCLC
- **NON-SMALL CELL** (NSCLC, 85%)
  - **ADENOCARCINOMA** (50–60%)—women, non-smokers, peripheral lesions. Bronchoalveolar (BAC) subtype may originate distal to grossly recognizable bronchi. BAC tends to be well differentiated, grows along intact alveolar spetra, and has a propensity for aerogenous and lymphatic spread. May present as diffuse infiltration on chest X-ray
  - **SQUAMOUS** (25%)—smokers, central, cavitary lesions
  - **LARGE CELL** (15%)—peripheral lesions with prominent necrosis, slightly worse prognosis than squamous and adenocarcinoma
- **CARCINOID** (2%)—neuroendocrine origin. May cause airway obstruction, ectopic Cushing's, and carcinoid syndrome
- **CYSTIC ADENOID CARCINOMA**—locally invasive but may also metastasize
- **CARCINOSARCOMA**—localized lesion usually

RISK FACTORS

- **SMOKING**—30× increased risk compared to non-smokers. 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 1A1 and 2A6) and inactivating enzymes (glutathionone *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 (salty suggests bronchoalveolar), hemoptysis, dyspnea, chest pain, wheezing, dysphagia, brachial plexus, hoarseness, Horner's syndrome, superior vena cava syndrome

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's	✓			
Neurological syndromes[a]	✓			
Hypercalcemia		✓	✓	
Clubbing or hypertrophic osteoarthropathy		✓	✓	
Hypercoagulable state	✓	✓	✓	✓
Gynecomastia				✓

[a]Neurological syndromes associated with SCLC include dementia, cerebellar degeneration, limbic encephalopathy, optic neuritis and retinopathy, paraneoplastic sensory neuropathy (anti-Hu antibodies), and Eaton–Lambert syndrome

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_7,

STAGING

TNM STAGING FOR NON-SMALL CELL LUNG CANCER (7TH EDITION)

T stage

- **T1** <3 cm without bronchoscopic evidence of invasion more proximal than the lobar bronchus
  - **T1a** ≤2 cm
  - **T1b** >2–3 cm
- **T2** ≤7 cm with any of the following: involving main bronchus ≥2 cm distal to the carina; involving the visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
  - **T2a** >3–≤5 cm
  - **T2b** >5–7 cm
- **T3** >7 cm or invades chest wall, diaphragm, mediastinal pleura, parietal pericardium or main bronchus <2 cm to carina; atelectasis/obstructive pneumonitis of entire lung; separate tumor nodule(s) within the same lobe
- **T4**=invasion of mediastinum, heart, great vessels, carina, trachea, esophagus, or vertebral body; ipsilateral tumor nodule(s) in different lobes

N stage

- **N1**=ipsilateral peribronchial and hilar LN
- **N2**=ipsilateral mediastinal and subcarinal LN
- **N3**=ipsilateral supraclavicular and scalene or any contralateral LN

M stage (typically involves pleural fluid, lungs, brain, liver, adrenals, bones, and skin)

- **M1a**=malignant pleural effusion, pericardial effusion, separate tumor nodule(s) in contralateral lobe
- **M1b**=distant metastasis

STAGE GROUPINGS FOR NON-SMALL CELL LUNG CANCER

Stage	TNM @=any	Median survival (months)	5-year survival
IA	T1aN0M0, T1bN0M0	60	50%
IB	T2aN0M0	43	43%
IIA	T1N1M0, T2aN1M0, T2bN0M0	34	36%
IIB	T2bN1M0, T3N0M0	18	25%
IIIA	T3N1M0, T1-3N2M0, T4N0-1M0	14	19%
IIIB	T@N3M0,T4N2M0	10	7%
IV	T@N@M1	6	2%

STAGING FOR SMALL CELL LUNG CANCER

- **LIMITED STAGE** (40%)—tumor confined to the hemithorax, mediastinum, and supraclavicular nodes, which can be encompassed within a tolerable radiation therapy port

STAGING (CONT'D)

- **EXTENSIVE STAGE** (60%)—non-limited stage, including pleural effusion

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, INR, PTT, Ca, albumin, CEA
- **IMAGING**—CXR (compared to old) and CT chest
- **BIOPSY**—bronchoscopy with lavage/wash/brushings/biopsy, endoscopic U/S with biopsy, 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
- **BONE SCAN**—if bone pain, elevated ALP or Ca, ≥N2)
- **CT HEAD OR MR HEAD**—if ≥N2 or symptomatic NSCLC, all SCLC
- **REPEATED SPUTUM CYTOLOGY**—sens 60–80% for central lesions, 15–30% for peripheral lesions

DIAGNOSTIC AND PROGNOSTIC ISSUES

REGIONAL LYMPH NODE CLASSIFICATION—based on mediastinoscopy. Nodes are designated 1–14. N3 node (supraclavicular)=position 1, N2 nodes=position 2–9, and N1 nodes=position 10–14

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
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

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

EASTERN CO-OPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

- **0**—normal. KPS 100%
- **1**—limited activity, otherwise ambulatory. KPS 80–90%
- **2**—resting <50% of day. KPS 60–70%
- **3**—resting >50% of day. KPS 40–50%
- **4**—bed-bound. 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_aO_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 IA**—**lobectomy/pneumonectomy**
- **STAGE IB**—**lobectomy/pneumonectomy.** Consider adjuvant **chemotherapy** (cisplatin–vinorelbine ×4) if high-risk features (e.g. >4 cm, high grade)
- **STAGE II**—**lobectomy/pneumonectomy** + adjuvant **chemotherapy** (cisplatin–vinorelbine ×4)
- **STAGE IIIA** (N2 disease)—**concurrent chemoradiation** (cisplatin–etoposide ×4), followed by either **pneumonectomy/lobectomy** or **radiation boost**
- **STAGE IIIA** (unresectable) **AND IIIB**—no surgery. **Concurrent chemoradiation** (cisplatin–etoposide ×4) with potential chance of cure. Can consider sequential chemo-radiation but may have reduced chance of cure
- **STAGE IV**—**palliative radiation** should be administered before chemotherapy if patients present with hemoptysis, SVC syndrome, severe bone pain, or obstructive pneumonia. Palliative **chemotherapy** (cisplatin–pemetrexed ×4 (for non-squamous histologies), cisplatin–gemcitabine ×4 (for squamous histology), cisplatin–vinorelbine ×4, or carboplatin–paclitaxel ×4) ± bevacizumab. For patients who have not progressed after 4 cycles of platinum-based induction chemotherapy, consider maintenance pemetrexed until disease progression. For recurrent disease after platinum-based therapy, consider docetaxel (for squamous cell histology), pemetrexed, or erlotinib (for adenocarcinoma histology)

MANAGEMENT (CONT'D)

SMALL CELL LUNG CANCER

- **LIMITED STAGE**—**radiation** + **concurrent chemotherapy** (cisplatin + etoposide ×4) + **prophylactic cranial irradiation** if good partial/complete response
- **EXTENSIVE STAGE**—**palliative chemotherapy** (cisplatin + etoposide ×4, cisplatin + irinotecan ×4, etoposide ×4) + **prophylactic cranial irradiation** if partial/complete response. For recurrent disease after platinum-based therapy, consider topotecan, cisplatin + irinotecan ± ifosfamide, gemcitabine + irinotecan, gemcitabine + paclitaxel

TREATMENT ISSUES

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 LN metastasis, trachea/contralateral 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

PREDICTIVE FACTORS FOR EGFR INHIBITORS—clinical factors include women, Asian, never smokers, and adenocarcinoma. With all 4 factors, response rate 50% (compared to 10% normally). Pathologic predictive factors include EGFR mutation and high EGFR gene copy number

Related Topics

Dyspnea (p. 3)
Horner's Syndrome (p. 13)
SVC Syndrome (p. 228)
Solitary Pulmonary Nodule (p. 13)
Smoking Cessation (p. 418)
Superior Vena Cava Syndrome (p. 228)
Pre-Operative Assessment (p. 422)

Mesothelioma

NEJM 2005 353:15

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **EPITHELIOID**—tubulopapillary, glandular, or solid. 50–60%
- **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

STAGING

TNM STAGING

T stage

- **T1**=invasion limited to ipsilateral pleura (T1a=parietal pleura, T1b=parietal pleura with focal visceral pleura involvement)
- **T2**=invades ipsilateral visceral pleura diffusely, lung, or diaphragm
- **T3**=invades ipsilateral endothoracic fascia, mediastinal fat, soft tissues of chest wall (solitary), pericardium (non-transmural)
- **T4**=invades contralateral pleura or lung by direct extension, soft tissues of chest wall (diffuse or multifocal), rib, any mediastinal organs, diaphragm, spine, pericardium, myocardium, brachial plexus

N stage

- **N1**=ipsilateral bronchopulmonary or hilar LN
- **N2**=ipsilateral mediastinal LN
- **N3**=contralateral mediastinal internal mammary, supraclavicular, or scalene LN

STAGING (CONT'D)

M stage

- **M1**=distant metastasis

STAGE GROUPINGS

Stage	TNM @=any
IA	T1aN0M0
IB	T1bN0M0
II	T2N0M0
III	T1-2N1-2M0, T3N0-2M0
IV	T4N@M0, T@N3M1, T@N@M1

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bili
- **IMAGING**—CXR, CT chest/abd, or MRI chest
- **BIOPSY**—thoracentesis (sens 33–84%, cytology is usually inadequate), thoracoscopy with pleural biopsy

SPECIAL

- **SERUM MESOTHELIN-RELATED PROTEIN** (SMRP)—sens 75–84%
- **PET SCAN**—if surgical candidate

PROGNOSTIC ISSUES

ADVERSE PROGNOSTIC FACTORS—male, poor performance status, sarcomatoid subtype, leukocytosis, anemia, thrombocytosis, advanced stage, high PET ratios

PROGNOSIS—**stage I**=16 months median survival, $\geq$3 adverse prognostic factors= $<$6 months median survival, **stage II–IV**=10 months median survival

MANAGEMENT

STAGE I, II (resectable disease)—**surgery** (extrapleural pneumonectomy, debulking) is controversial and of questionable benefit. It should be considered for highly selected patients (age $<$55, performance status $\leq$1, stage I or II and 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 vitamin B12 and folic acid supplementation or cisplatin– gemcitabine). Second-line options include repeating cisplatin–gemcitabine, cisplatin–pemetrexed, and vinorelbine. **Pleurodesis** should be considered

Thymoma and Thymic Carcinoma

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

STAGING

YAMAKAWA–MASAOKA TNM STAGING
T stage

- **T1**=intact capsule
- **T2**=macroscopically invades surrounding fatty tissue or mediastinal pleura, microscopically invades capsule
- **T3**=invades pericardium, great vessels, lung
- **T4**=pleural or pericardial dissemination

N stage

- **N1**=anterior mediastinal LN
- **N2**=other intrathoracic LN
- **N3**=extrathoracic LN

M stage (drop metastasis in pleural space)

- **M1**=distant metastasis

STAGING (CONT'D)

STAGE GROUPINGS

Stage	TNM @=any	5-year survival
I	T1N0M0	95%
II	T2N0M0	85%
III	T3N0M0	70%
IVA	T4N0M0	50%
IVB	T@N1-3M0, T@N@M1	

Related Topic
Myasthenia Gravis (p. 318)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bili
- **IMAGING**—CXR, CT chest
- **BIOPSY**

MANAGEMENT

STAGE I, II, III (resectable disease)—**resection** (usually including adjacent lung parenchyma and pericardium) ± **adjuvant radiation** ± **(neo) adjuvant chemotherapy** (cisplatin–etoposide, cisplatin–doxorubicin–cyclophosphamide)
STAGE IV (unresectable disease)—**palliative radiation** ± **palliative chemotherapy** (cisplatin–etoposide, cisplatin–doxorubicin–cyclophosphamide)

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 NEJM 2004 350:14

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
ATYPICAL HYPERPLASIA—3–5× increased risk of breast cancer
CARCINOMA IN SITU—ductal (DCIS), lobular (LCIS)
MALIGNANT—breast cancer (see below for details)

PATHOPHYSIOLOGY

CLASSIFICATION OF PRE-MALIGNANT LESIONS

- **DUCTAL CARCINOMA IN SITU** (DCIS)—precursor lesion to invasive cancer
- **LOBULAR CARCINOMA IN SITU** (LCIS)—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 (1% 1 year of development of invasive cancer)

PATHOPHYSIOLOGY (CONT'D)

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+ 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**—phylloides, post-radiation

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
- **FAMILY HISTORY** (10%)—affected relatives, BRCA1 and BRCA2 mutations, 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

BRCA BREAST CANCERS—BRCA1 is associated with basal-like subtype and triple negative (ER negative, PR negative, Her2 negative) phenotype. BRCA2 is associated with luminal subtype. Phase II data have shown that these tumors are particularly sensitive to platinum-based chemotherapy and poly(ADP-ribose) polymerase (PARP) inhibitors due to defects in DNA homologous recombination repair from BRCA mutation

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE BREAST CANCER?

PHYSICAL—the value of inspection is unproved. Palpation with clinical breast examination (CBE) includes proper positioning of the patient, use of a vertical strip pattern, proper position and movement of the fingers (pads of 2^{nd}–4^{th} fingers rolling motion), thoroughness of search, and spending at least 3 min per breast (sens 54%, spc 94%, LR+ 10.6, LR– 0.47)

APPROACH—"screening by both clinical breast examination and mammography is associated with decreased breast cancer mortality. Clinical breast examination alone detected between 3–45% of breast cancers that were missed by screening mammography. While clinical breast examination alone cannot rule out disease, the high specificity of certain abnormal findings significantly increases the probability of breast cancer"

JAMA 1996 282:13

CLINICAL FEATURES (CONT'D)

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**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—CXR, mammogram (15% false negative), U/S 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

SPECIAL

- **BONE SCAN**—if stage II or above
- **TUMOR MARKERS**—CA 15-3 if metastatic disease

TNM STAGING

TNM STAGING

T stage (same clinical and pathologic staging)

- **T1** <2 cm (T1mic=microinvasion ≤0.1 cm, T1a >0.1–0.5 cm, T1b >0.5–1 cm, T1c >1–2 cm)
- **T2** >2–5 cm
- **T3** >5 cm
- **T4**=invades skin or chest wall (T4a=extends to chest wall, but not including pectoralis muscle; T4b=edema with peau d'orange or ulceration of the skin, or satellite skin nodules confined to the same breast; T4c=both T4a and T4b; T4d=inflammatory carcinoma)

N stage (axillary, internal mammary, supraclavicular)

- **N1**
  - **cN1**=ipsilateral mobile axillary lymph node(s)
  - **pN1mi**=micrometastasis 0.2–2 mm
  - **pN1a**=1–3 axillary lymph node(s)
  - **pN1b**=internal mammary lymph nodes with microscopic disease detected by SLND but not clinically apparent
  - **pN1c**=N1a and N1b
- **N2**
  - **cN2a**=ipsilateral fixed/matted axillary lymph node(s)

TNM STAGING (CONT'D)

- **cN2b**=ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node
- **pN2a**=4–9 axillary lymph nodes
- **pN2b**=ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node

- **N3**
  - **cN3a**=ipsilateral infraclavicular lymph node(s)
  - **cN3b**=ipsilateral internal mammary and axillary lymph node(s)
  - **cN3c**=ipsilateral supraclavicular lymph node(s)
  - **pN3a**=10 or more axillary lymph nodes or metastasis to the infraclavicular lymph nodes
  - **pN3b**=metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary node, or in >3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
  - **pN3c**=ipsilateral supraclavicular lymph node

M stage (lungs, liver, bones, brain)

- **M1**=distant metastasis. Micrometastasis early, relatively slow growing, and variable course

STAGE GROUPINGS

Stage	TNM @=any	5-Year survival
I	T1N0M0	100%
IIA	T0-1N1M0, T2N0M0	90%
IIB	T2N1M0, T3N0M0	80%
IIIA	T0-2N2M0, T3N1-2M0	70%
IIIB	T4N0-2M0	50%
IIIC	T@N3M0	40%
IV	T@N@M1	20%

DIAGNOSTIC AND PROGNOSTIC ISSUES

MAMMOGRAPHIC FINDINGS OF BREAST CANCER—spiculated, crab-like, puckering lesions, architectural distortion, clustered microcalcifications

SCREENING—monthly self-breast examination, annual clinical breast examination, annual mammogram starting age 40

POOR PROGNOSTIC FACTORS—young age, advanced stage (especially nodal status and tumor size), high grade, Her2/neu+, ER–, PR–, lymphatic/vascular invasion

VAN NUYS PROGNOSTIC INDEX (VNPI)—provides the risk of local recurrence after DCIS excision

- **SIZE OF TUMOR**—1 ≤15 mm, 2=16–40 mm, 3 >40 mm
- **MARGIN WIDTH**—1 >10 mm, 2=1–10 mm, 3 <1 mm

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **GRADE**—1=non-high grade, no comedo necrosis, 2=non-high grade with comedo necrosis, 3=high grade with or without comedo necrosis
- **AGE**—1 >60, 2=40–60, 3 <40 years old
- **INTERPRETATION**—add up the four factors

VNPI score	Risk of relapse	Treatment recommendation
≤6	Low	Lumpectomy only
7–9	Mod	Lumpectomy plus radiation
≥10	High	Consider mastectomy

MANAGEMENT

DCIS

- **RESECTION**—breast-conserving surgery, plus adjuvant radiation (if tumor >1 cm, comedo type, or close margins <5 mm), or mastectomy if large lesions (>3–5 cm)
- **ADJUVANT HORMONAL**—tamoxifen may be considered after breast-conserving surgery for selected individuals if ER/PR positive

LCIS

- **RESECTION**—observation, breast-conserving surgery or bilateral mastectomy for selected individuals
- **HORMONAL**—tamoxifen or raloxifene may be used for prevention of invasive breast cancer in selected individuals

STAGE I AND II

1. **RESECTION**—breast-conserving surgery or mastectomy, plus sentinel biopsy or axillary lymph node dissection. If sentinel lymph node positive, proceed to axillary dissection
2. **ADJUVANT SYSTEMIC THERAPY**—anthracycline ± taxane (see below for details) ± trastuzumab
3. **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 node, positive margins, or lymphovascular invasion
4. **ADJUVANT HORMONAL**—give if ER/PR positive (see below for details)

STAGE III

1. **NEOADJUVANT SYSTEMIC THERAPY**—anthracycline plus taxane (see below for details) ± trastuzumab. Adjuvant therapy may also be considered if tumor resectable upfront
2. **RESECTION**—breast-conserving surgery or mastectomy, plus axillary lymph node dissection
3. **ADJUVANT RADIATION**—almost always given for stage III disease
4. **ADJUVANT HORMONAL**—give if ER/PR positive (see below for details)

MANAGEMENT (CONT'D)

STAGE IV

1. **HORMONAL**—if ER/PR positive, non-visceral disease (i.e. bony, sometimes lung), non-bulky and not highly symptomatic, consider aromatase inhibitors, tamoxifen, or fulvestrant. Oophorectomy or LHRH agonists for premenopausal women
2. **PALLIATIVE CHEMOTHERAPY**—for visceral or ER/PR negative disease. Choices include anthracyclines, taxanes, gemcitabine, capecitabine, and vinorelbine
3. **BIOLOGICAL THERAPY**—for Her2+ disease, add trastuzumab to chemotherapy and continue maintenance trastuzumab until disease progression. The role of newer targeted therapies including lapatinib (dual tyrosine kinase inhibitor of EGFR and HER2) and bevacizumab (anti-VEGF) is expanding in pre-treated patients
4. **PALLIATIVE RADIATION**—for symptom control
5. **BISPHOSPHONATES**—if bone metastasis, *pamidronate* 90 mg IV over 1–2 h q1month, or *zoledronate* 4 mg IV

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

Related Topics
BRCA Mutations (p. 224)
Cancer Screening (p. 222)

BREAST SURGERY OVERVIEW

COMPLETE SURGERY—modified radical mastectomy, radical mastectomy. Indications for mastectomy include multicentric disease, diffuse malignant-appearing microcalcifications on mammography, prior breast radiation, and pregnancy. Relative indications include large tumor (>5 cm), connective tissue disease (radiation contraindicated), and patient preference. Poorer cosmesis compared to breast-conserving surgery

BREAST CONSERVING SURGERY—excisional biopsy, lumpectomy, partial mastectomy, quadrantectomy, wide local excision

SURGICAL MARGIN—positive margin is defined as tumor touching ink and would require either re-excision (preferred) or radiation (boost). Close margin is defined as tumor <2 mm from ink mark

AXILLARY LYMPH NODE DISSECTION (ALND)—used in all invasive carcinoma or in situ disease >5 cm. May be avoided if sentinel lymph node negative

BREAST SURGERY OVERVIEW (CONT'D)

SENTINEL LYMPH NODE BIOPSY—indicated for size <3 cm and clinically N0 tumors. Contraindications include locally advanced breast cancer, multifocal cancers, previous disruptive breast procedures, palpable axillary nodes, and adverse reactions to dyes. Proceed to ALND if positive nodes, unable to identify sentinel node, or any two of the following features (grade 3, lymphovascular invasion, T2 tumor)

HORMONAL THERAPY OVERVIEW

HORMONAL REGIMENS

- **OVARIAN ABLATION** (premenopausal only)—oophorectomy, radiation, LHRH agonists (*goserelin* 3.6 mg IM every month, leuprolide). Combined 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** (*letrozole* 2.5 mg PO daily, *anastrozole* 1 mg PO daily). Side effects include hot flashes, mood swings, vaginal dryness, myalgia/arthralgia, headache, osteoporosis, dyslipidemia, weight gain, and potentially CAD
- **ANTIESTROGEN**—*fulvestrant* 250–500 mg IM monthly is equivalent to aromatase inhibitors in first-line metastatic setting
- **OTHERS**—*megestrol acetate* 160 mg PO daily, methyltestosterone

PREDICTIVE FACTORS FOR HORMONAL THERAPY—degree of response to tamoxifen varies (ER+PR+ >ER+PR– >ER–PR+ >ER–PR–). Hormonal therapy not given to patients with ER– and PR– cancers. Her2+ may also interfere with ER pathways

APPROACH IN THE ADJUVANT SETTING—for premenopausal women, consider tamoxifen ×5 years. For postmenopausal women, consider tamoxifen ×2–3 years, followed by exemestane or anastrozole to complete 5 years of adjuvant hormonal therapy, letrozole ×5 years, anastrozole ×5 years, or tamoxifen ×5 years followed by letrozole ×5 years. Consider aromatase inhibitors as first hormonal agent if >10% risk of relapse in first 2 years (e.g. ≥4 positive

HORMONAL THERAPY OVERVIEW (CONT'D)

nodes, low ER or grade 3 disease). Potential benefits are as follows:

- **RELATIVE RISK REDUCTION IN MORTALITY**—32% for all regimens
- **RELATIVE RISK REDUCTION IN RECURRENCE**—40% for tamoxifen, 56% for aromatase inhibitor regimens

APPROACH IN THE METASTATIC SETTING—patients with slowly progressive disease, no visceral involvement, and minimal symptoms may be best served with a trial of endocrine therapy. For premenopausal women, consider ovarian ablation + tamoxifen → aromatase inhibitor 1 → aromatase inhibitor 2 → fulvestrant → megestrol. For postmenopausal women, aromatase inhibitor 1 → tamoxifen → aromatase inhibitor 2 → fulvestrant → megestrol. Time

HORMONAL THERAPY OVERVIEW (CONT'D)

to progression is 8 months with tamoxifen and 10 months with aromatase inhibitors

ADJUVANT CHEMOTHERAPY OVERVIEW

WHO SHOULD GET ADJUVANT CHEMOTHERAPY: THE ST. GALLEN GUIDELINE

- **LOW RISK**—node negative and age $\geq$35, tumor $\leq$2 cm, grade 1, no lymphatic/vascular invasion, Her2/neu negative
- **INTERMEDIATE RISK**—node negative and at least one of age $<$35, tumor $>$2 cm, grade 2–3, lymphatic/vascular invasion, Her2/neu positive, or node positive (1–3 nodes) and Her2/neu negative
- **HIGH RISK**—node positive (1–3 nodes) and Her2/neu positive, node positive (4 or more nodes)

APPROACH TO SYSTEMIC THERAPY FOR BREAST CANCER

	ER/PR +ve	ER/PR unknown	ER/PR–ve
Low risk	H or nil	H or nil	N/A
Intermediate risk	H or Cx→H	Cx→H	Cx
High risk	Cx→H	Cx→H	Cx

where Cx=chemo, H=hormonal therapy

ADJUVANT CHEMOTHERAPY OVERVIEW (CONT'D)

WHO SHOULD GET ADJUVANT CHEMOTHERAPY: THE NCCN GUIDELINE

- **ALL HISTOLOGIC SUBTYPES EXCEPT TUBULAR OR COLLOID CANCERS**—adjuvant chemotherapy should be given if $\geq$1 cm or node positive. Consider chemotherapy if 0.6–1 cm and high grade or lymphovascular invasion. Add trastuzumab if Her2/neu positive
- **TUBULAR OR COLLOID CANCERS**—adjuvant chemotherapy should be given if $\geq$3 cm or node positive. Consider chemotherapy if 1–2.9 cm

ADJUVANT REGIMENS

- **FIRST GENERATION**—CMF PO, AC$\times$4, FEC50$\times$6
- **SECOND GENERATION**—CAF$\times$6, FAC$\times$6, CEF$\times$6, FEC100$\times$6, AC$\times$4+D$\times$4, DC$\times$4
- **THIRD GENERATION**—DAC$\times$6, FEC100$\times$3+D$\times$3, AC$\times$4+T$\times$4 (dose dense), FEC$\times$4+T$\times$8
- **NOTE**—A=doxorubicin, C=cyclophosphamide, D=docetaxel, E=epirubicin, F=5-fluorouracil, M=methotrexate, T=paclitaxel

ESTIMATED BENEFITS OF ADJUVANT CHEMOTHERAPY

RELATIVE RISK REDUCTION FOR MORTALITY

	Postmenopausal	Premenopausal
1st gen.	8% ER+, 15% ER–	30%
2nd gen.	26% ER+, 32% ER–	44%
3rd gen.	40% ER+, 45% ER–	55%

ADJUVANT CHEMOTHERAPY OVERVIEW (CONT'D)

RELATIVE RISK REDUCTION FOR RECURRENCE

	Postmenopausal	Premenopausal
1st gen.	12% ER+, 23% ER–	37%
2nd gen.	30% ER+, 38% ER–	50%
3rd gen.	43% ER+, 50% ER–	59%

ADVERSE EFFECTS OF ADJUVANT CHEMOTHERAPY

- **ALOPECIA**—anthracycline or taxane regimens (100%), CMF (50%)
- **FEBRILE NEUTROPENIA**—DAC (40%) and dose dense regimens require GCSF. CEF $>$FEC; FAC $>$FEC; ACT $>$AC/CMF
- **NAUSEA AND VOMITING**—CMF $>$anthracyclines
- **OTHER ACUTE SIDE EFFECTS**—fatigue and weight gain. With taxanes, may experience myalgia, arthralgia, and neuropathy (motor, sensory)
- **PREMATURE OVARIAN FAILURE**—CMF $>$CEF/FEC $>$AC; DAC $>$FAC
- **OTHER LONG-TERM SIDE EFFECTS**—cardiotoxicity (dose dependent and increases with age, $\sim$1% with anthracycline doses used in adjuvant regimens), secondary cancers (AML, MDS with alkylating agents, $\sim$1–2% depending on regimen)

PREDICTIVE FACTORS FOR ADJUVANT CHEMOTHERAPY BENEFIT—younger age, high grade, ER negative, Her2 positive (possibly for anthracycline and taxane-based regimens)

APPROACH IN THE ADJUVANT SETTING—consider first generation chemotherapy if risk of relapse

ADJUVANT CHEMOTHERAPY OVERVIEW (CONT'D)

20–40%, second generation if risk 40–50%, third generation if risk >50%. Chemotherapy usually starts 4–10 weeks after surgery. Adjuvant! online (www.adjuvantonline.com) is a useful web-based resource for estimating survival and treatment benefits. Consider anthracycline and docetaxel for node-positive breast cancer, anthracycline ± paclitaxel + traustuzumab for Her2-positive breast cancer, dose dense anthracycline and docetaxel (e.g. ddACT) for ER-negative patients, CMF or DC if anthracycline contraindicated or preexisting heart disease, and FAC or CAF for post-menopausal women

WHICH REGIMEN SHOULD BE USED?

FOR NODE-NEGATIVE WOMEN

	Premenopausal	Postmenopausal
ER–	ddACT	ddACT
ER+	FEC, CEF	If G3 or large T, FAC, FEC, AC, DC
Lower risk	AC	No chemo

ADJUVANT CHEMOTHERAPY OVERVIEW (CONT'D)

FOR NODE-POSITIVE WOMEN

	Premenopausal	Postmenopausal
ER–	FECD (DAC), ddACT	FECD, ddACT
ER+	FECD (DAC), FEC, CEF	FAC, FECD, FEC, AC
Lower risk	AC, DC, or no chemo	AC, DC or no chemo

NEOADJUVANT CHEMOTHERAPY FOR LOCALLY ADVANCED BREAST CANCER

- **DEFINITION**—T3N1, T4, N2, or N3 disease
- **NEOADJUVANT REGIMENS**—anthracycline plus docetaxel regimens (ACD, DAC, FECD), ACDH or DCH (docetaxel, carboplatin, and trastuzumab) for Her2 positive disease

ADVANTAGES AND DISADVANTAGES OF NEOADJUVANT AND ADJUVANT THERAPY

Neoadjuvant	Adjuvant
Clinical staging is less accurate	Accurate pathological staging
Pathological confirmation of chemotherapy efficacy	No confirmation
Definitive treatment delayed	Definitive treatment early on
Reduced tumor improves local control	No reduction of tumor before surgery
Surgery refusal in patients with complete response	All patients undergo surgery
Timely application of chemotherapy	Delayed or no chemotherapy in patients with post-op complications
Better performance status allowing aggressive therapy	Impaired performance status post-op
Intact blood/lymph vessels allowing optimal drug concentrations	Impaired blood/lymph vessel supply in pelvis

PALLIATIVE CHEMOTHERAPY OVERVIEW

PALLIATIVE REGIMENS—doublet regimens include doxorubicin plus paclitaxel, capecitabine plus docetaxel, docetaxel plus gemcitabine, paclitaxel plus gemcitabine, and weekly paclitaxel plus bevacizumab. Single agents include capecitabine, vinorelbine, and taxane

APPROACH IN THE METASTATIC SETTING—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. Choice 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 and modest gains in overall survival but more toxicities. Single agents are tolerated better with limited alopecia and are particularly appropriate for patients who are elderly or have poor performance status. At eventual progressive disease, change

PALLIATIVE CHEMOTHERAPY OVERVIEW (CONT'D)

chemotherapy to non-cross-resistance drugs. Use single agent only as no evidence for enhanced overall survival with doublets beyond first line

BIOLOGICAL THERAPY OVERVIEW

HER2/NEU STATUS—15–20% positive. Her2 positivity is a poor prognostic factor, but predicts response to trastuzumab and anthracycline chemotherapy

APPROACH—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

ADVERSE EFFECTS—infusion reactions (40%, usually with first administration), cardiotoxicity, and pulmonary (rare)

BIOLOGICAL THERAPY OVERVIEW (CONT'D)

DISTINGUISHING FEATURES BETWEEN CARDIOTOXICITY DUE TO ANTHRACYCLINE AND TRASTUZUMAB

	Anthracycline	Trastuzumab
Mechanism	Lipid peroxidation and vacuolation → myocyte fibrosis	Unknown
Structural damage	Present	Not seen
Cardiomyopathy	Dilated	Dilated
Dose dependent	Yes	No
Prevention	Dexrazoxone Weekly Treatment Liposomal Doxorubicin Limit dose	None
Treatment	Stop therapy Cannot give more	Stop therapy May restart
Course	Irreversible	Reversible

MANAGEMENT OF BRAIN METASTASES

APPROACH—steroids, resection plus radiation, or radiation alone if resection not possible. Principles are similar for CNS recurrence

- **SURGERY**—consider resection if solitary lesion or primary lesion causing neurological complications. Surgery plus radiation is associated with better overall survival than radiation alone for eligible candidates (10 vs. 6 months)

MANAGEMENT OF BRAIN METASTASES (CONT'D)

- **RADIATION**—may be re-irradiated if over 1 year from first whole brain radiation
- **STEREOTACTIC RADIATION**—less generalized toxicity. If <3 lesions and all <3 cm [<1.2 in.]
- **CHEMOTHERAPY**—limited role with high-dose methotrexate and possibly capecitabine

Esophageal Cancer NEJM 2003 349:23

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **ADENOCARCINOMA**—75% in distal esophagus
- **SQUAMOUS**—evenly distributed between upper, middle, and lower third esophagus
- **MELANOMA**
- **LEIOMYOSARCOMA**
- **LYMPHOMA**
- **CARCINOID**

RISK FACTORS

	Squamous	Adeno
Frequency	50%	50%
Barrett's 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×

PATHOPHYSIOLOGY (CONT'D)

	Squamous	Adeno
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's node, hepatomegaly, pleural effusion

CONSTITUTIONAL—anorexia, fatigue, weight loss

Related Topics
Barrett's Esophagus (p. 113)
Esophageal Dysphagia (p. 112)
Gastric Cancer (p. 197)

STAGING

TNM STAGING

T stage

- **T1**=invades lamina propria or submucosa
- **T2**=invades muscularis propria
- **T3**=invades adventitia
- **T4**=invades into adjacent structures (trachea, mediastinum)

N stage (cervical paraesophageal, right recurrent laryngeal, left paratracheal, upper and lower paraesophageal, infraaortic, infracarinal and lower posterior mediastinal regions)

- **N1**=regional LN

M stage (spreads rapidly and early. Over 50% unresectable/metastatic disease at presentation)

- **M1a**=cervical (proximal esophagus) or celiac (distal esophagus) LN metastasis
- **M1b**=distant metastasis

STAGE GROUPINGS

Stage	TNM @=any	5-year survival
0	TisN0M0	>95%
I	T1N0M0	50–80%
IIA	T2-3N0M0T	30–40%
IIB	T1-2N1M0	10–30%
III	T3N1M0 T4N0-1M0	10–15%
IVA	T@N@M1a	<5%
IVB	T@N@M1b	<1%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CEA
- **IMAGING**—CXR, barium swallow, CT chest and abd, endoscopic U/S (excellent for staging), PET scan (preoperative workup)
- **BIOPSY**—gastroscopy ± laparoscopy

DIAGNOSTIC AND PROGNOSTIC ISSUES

SCREENING (for Barrett's)—endoscopy with biopsy every 3–5 year, yearly if low-grade dysplasia

POOR PROGNOSTIC FACTORS—weight loss >10%, dysphagia, large tumors, advanced age, lymphatic micrometastases

MANAGEMENT

NUTRITIONAL SUPPORT—dietician consult. Consider supplemental feeding if significant weight loss, but only if benefits greater than risk

MANAGEMENT (CONT'D)

RESECTABLE (T1–2, N0, 20%)—**surgical resection** (right transthoracic approach, transhiatal approach). **Definitive chemoradiation** (5-fluorouracil plus cisplatin, 5000 cGy) may be a reasonable alternative to surgery, particularly for older individuals, medically inoperable patients, and cervical esophageal carcinoma (difficult resection). **Neoadjuvant chemotherapy** (ECF×3 (E=epirubicin, C=cisplatin, F=infusional 5-fluorouracil)) + **surgical resection** followed by ECF×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 (T3–4, N1, 65%, median survival 12–14 months)

- **ADENOCARCINOMA**—primary chemoradiation if localized. See also metastatic, unresectable cancer
- **SQUAMOUS CELL CARCINOMA**—chemoradiation (5-fluorouracil plus cisplatin, 5000 cGy). Palliative surgical resection may be considered for selected patients (increased local control), although squamous cell carcinomas are very sensitive to chemoradiation, and thus surgery may not be needed

METASTATIC, UNRESECTABLE (M1, 15%, median survival 9–12 months)

- **PALLIATIVE CHEMOTHERAPY**—similar to gastric cancer. Standard regimens include ECF, DCF (D=docetaxel, C=cisplatin, F=5-fluorouracil), ECX and EOX, EOF (X=capecitabine, O=oxaliplatin). For patients with poor performance status, consider CF, FOLFIRI (5-fluorouracil–leucovorin–irinotecan), or 5-fluorouracil or irinotecan alone. No standard for second line, which may include FOLFIRI, irinotecan alone, or taxane alone. Response rate 10–30% for single agents and 30–50% for combination therapy
- **PALLIATIVE RADIATION**—brachytherapy, external beam radiation
- **PALLIATIVE PROCEDURES**—dilatation and endoluminal stent if obstruction, phototherapy, G-tube insertion

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 at 6 months, 18 months, then every 2–3 years may be considered

Gastric Cancer

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
H. pylori	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

- **PERSONAL**—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**—*H. pylori* (L), EBV, hiatus hernia (U), pernicious anemia (3–18×), chronic gastritis, gastric polyps, previous partial gastrectomy where U=upper stomach, L=lower stomach

CLINICAL FEATURES

LOCOREGIONAL—epigastric pain, nausea and vomiting, dysphagia, upper GI bleed (melena, hematemesis), anemia, abdominal mass

METASTATIC—hepatomegaly, Virchow's node (left supraclavicular LN), Irish's node (left axillary LN), 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's, carcinoid

STAGING

TNM STAGING

T stage

- **T1**=invades lamina propria or submucosa
- **T2**=invades muscularis propria or subserosa (T2a= muscularis propria, T2b=subserosa)
- **T3**=invades serosa (visceral peritoneum)
- **T4**=invades 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**=1–6 LN
- **N2**=7–15 LN
- **N3**= >15 LN

M stage (liver, lung, peritoneum, left supraclavicular LN, left axillary LN, umbilicus, ovary)

- **M1**=distant metastasis

STAGE GROUPINGS

Stage	TNM @=any	Freq	5 year survival
IA	T1N0M0	10%	78%
IB	T2N0M0, T1N1M0		58%
II	T3N0M0, T2N1M0, T1N2M0	20%	34%
IIIA	T4N0M0, T3N1M0, T2N2M0	40%	20%
IIIB	T3N2M0		8%
IV	T4N@M0, T@N3M0, T@N@M1	30%	7%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CEA, CA 19–9
- **IMAGING**—CXR, barium swallow, endoscopic U/S, CT abd, U/S 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

POOR PROGNOSTIC FACTORS—advanced stage, high grade, proximal location

Related Topics
Dyspepsia (p. 113)
Leser-Trelat Sign (p. 368)
MALT (p. 177)
Melena (p. 118)

MANAGEMENT

STAGE IA—gastrectomy (total or subtotal) with **D1 dissection**

STAGE IB, II, III

- **OPTION 1—neoadjuvant ECF×3** (epirubicin, cisplatin, infusional 5-fluorouracil) + **surgery** + **adjuvant ECF×3**; 43% of patients able to complete treatment
- **OPTION 2—gastrectomy** (total or subtotal) with D1 dissection + **adjuvant chemoradiation** (5-fluorouracil)
- **INSUFFICIENT EVIDENCE**—D2 dissection, 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

STAGE IV (M1, MEDIAN SURVIVAL 10 MONTHS)

- **PALLIATIVE CHEMOTHERAPY**—standard regimens include ECF (E=epirubicin, C=cisplatin, F=infusional 5-fluorouracil), DCF (D=docetaxel, C=cisplatin, F=5-fluorouracil), ECX, EOX, EOF (X=capecitabine, O=oxaliplatin). For patients with poor performance status, consider CF, FOLFIRI (5-fluorouracil–leucovorin–irinotecan), 5-fluorouracil alone, or irinotecan alone. No standard for second line, which may include FOLFIRI, irinotecan alone, or taxane alone. Recent findings from the TOGA trial demonstrate improved survival with the addition of trastuzumab to chemotherapy in HER2-positive gastric cancer (positivity rate 15–20%)
- **PALLIATIVE RADIATION**—for bony metastasis or bleeding tumors
- **PALLIATIVE SURGERY**—gastrojejunostomy, partial gastrectomy to bypass obstruction

TREATMENT ISSUES

VITAMIN B12 DEFICIENCY—may develop after a few years in patients who received subtotal or total gastrectomy

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

FOLLOW-UP—no agreed upon surveillance program. q3month for first year, then every 6 months for a total of 5 years. Endoscopy at 6 months, 18 months, then every 2–3 years (variable guidelines)

Colorectal Cancer

NEJM 2005 352:5

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **ADENOCARCINOMA**—mucinous subtype, signet-ring cells, adenosquamous, medullary
- **CARCINOID**—mostly involving appendix and rectum, less malignant
- **RARE**—squamous cell, small cell, undifferentiated
- **ADENOMATOUS POLYP**—pre-malignant

RISK FACTORS

- **PERSONAL**—age
- **FAMILY HISTORY**—affected relatives (2×), 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 (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's syndrome, Turcot's syndrome, flat adenoma syndrome
- **ENVIRONMENTAL**—decreased fiber intake

PATHOPHYSIOLOGY (CONT'D)

- **DISEASES**—prior colon cancer, polyps, ovarian, breast, endometrial cancer, Crohn's, 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 peritoneal reflection	<12 cm [<4.7 in.] from anal verge or below peritoneal reflection

PATHOPHYSIOLOGY (CONT'D)

	Colon cancer	Rectal cancer
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). MSI is characterized by a decreased response to 5-fluorouracil-based adjuvant chemotherapy but improved prognosis

K-RAS MUTATION—about 40% of colon cancer has mutation in KRAS, which plays a key role in signal transduction downstream of EGFR. Tumors with wild-type K-ras have been shown to be more responsive to EGFR-based therapy (panitumumab, cetuximab) compared to mutant. This makes biologic sense as a mutated KRAS could continue to activate cell proliferation despite inhibition of EGFR

CLINICAL FEATURES

LOCOREGIONAL—bowel habit Δ, hematochezia, 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

T stage

- **T1**=invades submucosa
- **T2**=invades muscularis propria
- **T3**=invades 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 → supraclavicular)

- **N1**=1–3 LN
- **N2**=≥4 LN

M stage (liver, lung, bone, brain)

- **M1**=distant metastasis

STAGING (CONT'D)

STAGE GROUPINGS

Stage	TNM @=any	Frequency	5 year survival
I	T1–2N0M0	15%	90%
IIA	T3N0M0	20%	85%
IIB	T4N0M0		70%
IIA	T1–2N1M0	40%	80%
IIIB	T3–4N1M0		60%
IIIC	T@N2M0		45%
IV	T@N@M1	25%	5%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CEA, CA19–9
- **IMAGING**—barium enema, CT abd, CXR, MRI, and endorectal U/S in rectal cancer
- **BIOPSY**—colonoscopy with biopsy, laparoscopy, laparotomy

MANAGEMENT OF COLON CANCER

STAGE I—**surgical resection** only

STAGE II—**surgical resection**. **Adjuvant chemotherapy** (capecitabine, 5-fluorouracil–leucovorin, consider FOLFOX if high risk) may be given if adverse prognostic features (T4, perforation, obstruction, poorly differentiated, signet ring cell and mucinous histology, lymphovascular invasion, inadequate LN 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—if metastasis limited to liver and potentially resectable, consider liver **resection** plus perioperative chemotherapy. **Radiofrequency ablation** could be considered if patient unfit for surgery. If non-resectable disease, **palliative chemotherapy** (FOLFIRI–bevacizumab or FOLFOX–bevacizumab. Capecitabine or 5-fluorouracil/LV if patient unfit. Raltitrexed if 5-fluorouracil intolerant. Cetuximab–irinotecan or single-agent panitumumab in third line if KRAS wild type)

Related Topics
Cancer Screening (p. 222)
Chemotherapy-Induced Diarrhea (p. 231)
Oral Mucositis (p. 230)
Hematochezia (p. 120)
Hereditary Cancers (p. 224)

MANAGEMENT OF RECTAL CANCER

HIGHLY RESECTABLE (stage I)—**transanal excision** only if <30% circumference, <3 cm [<1.2 in.], margins >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. Otherwise, **total mesorectal excision** via low anterior resection or abdominoperineal resection

RESECTABLE (stage II and some stage III with no high-risk feature (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×12 if pathologic node positive (i.e. node positive); capecitabine ×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) + **total mesorectal excision** + **adjuvant chemotherapy** for 4 months. 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

*NOTE: FOLFOX=5-fluorouracil, leucovorin, and oxaliplatin; FOLFIRI=5-fluorouracil, leucovorin, and irinotecan; 5-fluorouracil/LV=5-fluorouracil and leucovorin

TREATMENT ISSUES

ESTIMATED BENEFITS OF ADJUVANT CHEMOTHERAPY FOR STAGE III COLORECTAL CANCER

RELATIVE RISK REDUCTION FROM MAYO CLINIC DATABASE

	Recurrence	Death
5-FU vs. control		
Node –ve	17%	14%
Node +ve	40%	34%

TREATMENT ISSUES (CONT'D)

	Recurrence	Death
FOLFOX vs. 5-FU		
Node –ve	18%	18%
Node +ve	24%	24%

RELATIVE RISK REDUCTION FROM ADJUVANT ONLINE

	Recurrence	Death
5-FU benefit		
Node –ve	20%	18%
Node +ve	43%	38%
FOLFOX benefit		
Node –ve	39%	24%
Node +ve	59%	48%

COLORECTAL CANCER SURVEILLANCE—for patients with stage II and III disease who would be candidate for salvage treatment if recurrence, ASCO suggests medical visit with history and physical examination every 3–6 months ×3 years, then every 6 months for the next 2 years, and then yearly after. Perform CEA every 3 months for at least 3 years. CT chest/abd (+ CT pelvis for rectal cancer) yearly ×3 years. Colonoscopy 3 years after initial diagnostic colonoscopy, then every 5 years. Proctosigmoidoscopy every 6 months for 5 years if rectal cancer but radiation not given

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

LIVER RESECTION CRITERIA

- **RESECTABLE DISEASE**—involvement of <70% of liver and <6 segments, no involvement of major vessels including SMA, SMV, hepatic vein, hepatic artery, portal vein, and no metastases elsewhere. An evaluation by a hepatobiliary surgeon should always be considered
- **OPERABLE CANDIDATE**—relatively young, no major comorbidities, performance status 0–1
- **PREDICTIVE FACTORS OF RECURRENCE POST-LIVER METASTASECTOMY**—tumor >5 cm [>2 in.], >1 liver lesion, lymph node involvement, relapse-free survival <1 year, CEA >200 μg/L within 1 month post-surgery

Carcinoid Tumors

NEJM 1999 340:11

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 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. 124)
MEN syndrome (p. 348)

PATHOPHYSIOLOGY (CONT'D)

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 (10% of small intestine in the presence of liver metastases, $<1\%$ appendix, none in the rectum are associated with the carcinoid syndrome); 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's, 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**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, serum chromogranin A, 24 h urine 5-HIAA (sens 73%, spc 100%)

INVESTIGATIONS (CONT'D)

- **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 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 μg SC div 2–4 doses, *octreotide depot* 10–30 mg IM every 28 days, lanreotide, *loperamide* 4 mg ×1 dose, then 2 mg q4h PRN, maximum 16 mg/day, *atropine–diphenoxylate* 1–2 tabs q6–8h, 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 hepatic metastasis
- **CHEMOTHERAPY**—limited activity, streptozocin/5-fluorouracil or doxorubicin, interferon α (now rarely used). Consider temozolomide, cisplatin, and etoposide for patients with poorly differentiated tumors
- **TARGET RADIOTHERAPY WITH RADIOLABELED SOMATOSTATIN ANALOGUES**—difficult to access as only few institutions offer this therapy
- **HEPATIC METASTASES**—resection, radiofrequency ablation and cryoablation, hepatic artery embolization

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 hormones

- **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 50 μg as test dose (may cause gastric atony and skin toxicity), then 100–150 μg SC BID–TID. May double dose 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

PATHOPHYSIOLOGY (CONT'D)

MOLECULAR BIOLOGY—characteristic c-kit/CD117 (90%) and/or PDGFRa 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**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—CT abd/pelvis ± MRI, U/S 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—segmental resection without regional lymphadenectomy. Adjuvant *imatinib* 400 mg PO daily is recommended for at least 12 months for patients with intermediate- to 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, sunitinib should be considered

Anal Cancer

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY (WHO)

- **ANAL CANAL**
  - **SQUAMOUS CELL CARCINOMA (75%)**—large cell keratinizing (distal to the dentate line) or non-keratinizing (above the dentate line).
  - **ADENOCARCINOMA (20%)**—rectal type, of anal glands, within anorectal fistula
  - **SMALL CELL CARCINOMA**
  - **UNDIFFERENTIATED**
- **ANAL MARGIN (PERIANAL SKIN)**
  - **SQUAMOUS CELL CARCINOMA**
  - **GIANT CONDYLOMA**
  - **BASAL CELL CARCINOMA**
  - **OTHERS**—Bowen's disease, Paget disease

RISK FACTORS

- **PERSONAL**—sexual activity (HPV, number of sexual partners, receptive anal intercourse, history of STD, genital warts)
- **ENVIRONMENTAL**—smoking
- **DISEASES**—HIV and other causes of chronic immunosuppression (e.g. solid organ transplantation).

LYMPHATIC DRAINAGE

- **TUMORS ORIGINATING ABOVE THE DENTATE LINE**—drain to the perirectal and paravertebral LN

PATHOPHYSIOLOGY (CONT'D)

- **TUMORS ORIGINATING BELOW THE DENTATE LINE**—drain to the inguinal and femoral LN

CLINICAL FEATURES

LOCOREGIONAL—rectal bleeding (45%), anal pain, and sensation of rectal mass (30%). Squamous cell carcinoma may be associated with a history of anorectal condyloma (50%), while tumor of perianal skin can be associated with pruritus ani
METASTATIC—RUQ pain, dyspnea
CONSTITUTIONAL—weight loss, anorexia, fatigue

STAGING

TNM STAGING
T stage

- **T1** ≤2 cm
- **T2** >2 cm but ≤5 cm
- **T3** >5 cm
- **T4**=invades adjacent organ(s) (involvement of sphincter muscle(s) alone is not classified as T4)

N stage

- **N1**=perirectal LN
- **N2**=unilateral internal iliac LN and/or inguinal LN
- **N3**=perirectal and inguinal LN and/or bilateral internal iliac and/or inguinal lymph nodes

STAGING (CONT'D)

M stage

- **M1**=distant metastasis

STAGE GROUPINGS

Stage	TNM @=any	5-year survival
I	T1N0M0 (10%)	85%
II	T2-T3N0M0 (55%)	75%
III	T1–3N1M0 (27%)	54%
IVA	T4N@M0	17%
IVB	T@N@M1 (6%)	17%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin

INVESTIGATIONS (CONT'D)

- **IMAGING**—CXR, CT chest, CT, or MRI abd/pelvis ± PET/CT
- **BIOPSY**—mass biopsy

MANAGEMENT

SQUAMOUS CELL CANCER OF THE ANAL CANAL—chemoradiation (5-fluorouracil–mitomycin). If evidence of progression or persisting disease at 12 weeks after treatment, consider salvage abdominoperineal resection. For metastatic disease, consider palliative chemotherapy (5-fluorouracil–cisplatin), regional therapy for isolated hepatic metastases

PRIMARY ADENOCARCINOMA OF THE ANAL CANAL—managed like rectal cancer

CANCER OF THE PERIANAL SKIN—treated like skin counterpart

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 mucous 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

PATHOPHYSIOLOGY (CONT'D)

RISK FACTORS

- **PERSONAL**—Ashkenazi Jewish origin, low socioeconomic status, habitation of industrialized societies, obesity, and low physical activity
- **FAMILY HISTORY**—hereditary non-polyposis colon cancer (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

LOCOREGIONAL—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's syndrome, polymyositis, dermatomyositis, panniculitic arthritis–eosinophilia syndrome, depression

STAGING

TNM STAGING

T stage

- **T1** $\leq$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

STAGING (CONT'D)

N stage (portal, peripancreatic, periaortic, celiac axis LN)
- **N1**=regional LN

M stage (liver, lungs, bone, pleura, adrenal)
- **M1**=distant metastasis

STAGE GROUPINGS

Stage	TNM @=any	Freq.	Median survival (months)
IA	T1N0M0	10%	17
IB	T2N0M0		
IIA	T3N0M0		
IIB	T1-3N1M0	20–30%	8–9
III	T4N@M0		
IV	T@N@M1	50–60%	4–6

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CA 19–9, CEA
- **IMAGING**—CXR, CT abd (allows for establishment of resectability criteria, >90% accurate in the staging), U/S abd, endoscopic U/S, MRCP
- **BIOPSY**—percutaneous needle biopsy (only if unresectable disease), endoscopic U/S-guided biopsy, ERCP (also useful for biliary obstruction), laparoscopy, laparotomy

DIAGNOSTIC 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

MANAGEMENT

RESECTABLE (T1-3N0–1, 10–20%)—**Whipple's 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)
- **PALLIATIVE CHEMOTHERAPY**—gemcitabine ± erlotinib. No standard in second line. Consider 5-fluorouracil-based therapy
- **CHEMORADIATION** (5-fluorouracil)—in selected patients with limited advanced unresectable cancer
- **PAIN CONTROL**—opioids, percutaneous celiac ganglion ablation
- **PALLIATIVE RADIATION**—controversial with no clear benefit
- **PALLIATIVE PROCEDURES**—if biliary obstruction, consider ERCP stent placement or percutaneous transhepatic cholangiography with drainage

TREATMENT ISSUES

RESECTABLE DISEASE CRITERIA[a]
1. No liver, peritoneal, or other metastases
2. No involvement of celiac axis, superior mesenteric artery, and hepatic artery
3. 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)

[a]If in doubt, patients should be evaluated by a hepatobiliary surgeon

Related Topics
Cachexia (p. 397)
Cancer Pain (p. 391)
Jaundice (p. 138)

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 carcinoma without cirrhosis as the virus can integrate into host genome. Environmental toxins include aflatoxin, the blue-green 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

CLINICAL FEATURES (CONT'D)

disease (ascites, encephalopathy, jaundice, and variceal bleeding)

METASTATIC—bone pain, dyspnea

CONSTITUTIONAL—weight loss, fever due to central tumor necrosis

PARANEOPLASTIC SYNDROME—hypoglycemia, erythrocytosis, hypercalcemia, water 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**=regional LN

M stage

- **M1**=distant metastasis

STAGE GROUPINGS

Stage	TNM @=any	5-year survival
I	T1N0M0	55%
II	T2N0M0	37%
IIIA	T3N0M0	
IIIB	T4N0M0	16%
IIIC	T@N1M0	
IV	T@N@M1	<5%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, albumin, AFP
- **IMAGING**—CXR, CT abd (biphasic or triphasic), U/S abd, MRI abd, liver/spleen scan (if suspect FNH)

SPECIAL

- **BIOPSY**—liver biopsy if AASLD clinical criteria (atypical vascular pattern on imaging + AFP >100 U/L) not met or if biopsy would have an impact on management options

DIAGNOSTIC ISSUES

CT SCAN—characteristic features for hemangioma, FNH (central scar)

LIVER SPLEEN SCAN—useful for distinguishing focal nodular hyperplasia and hepatoma

DIAGNOSTIC ISSUES (CONT'D)

GALLIUM SCAN—useful for identifying hepatoma and abscesses (increased blood flow)

APPROACH TO HEPATOMA—start with U/S 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

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. For unresectable disease up to 3 lesions <3 cm, consider liver transplant if no comorbidity, and percutaneous ethanol injection/radiofrequency ablation if significant comorbidities; 5-year survival 50–70%

INTERMEDIATE STAGE (multinodular disease, Child–Pugh A-B, and ECOG 0)—chemoembolization. Median survival 6–16 months

ADVANCED STAGE (portal invasion, N1, M1, Child–Pugh A–B, or ECOG 1–2)—for patients with Child–Pugh A disease, consider sorafenib. Chemoembolization may also represent an option for some patients. Median survival 6–16 months

TERMINAL STAGE (Child–Pugh C or ECOG >2)—best supportive care. Median survival <3 months

Barcelona Clinic Treatment Algorithm

TREATMENT ISSUES

CRITERIA FOR RESECTABLE DISEASE—well-compensated cirrhosis, single lobe involvement, no vascular invasion, N0, M0

CRITERIA FOR PERCUTANEOUS ETHANOL ABLATION—1 lesion <5 cm or 3 lesions <3 cm, accessible, no ascites, not coagulopathic, non-resectable or refuses surgery, awaiting transplantation. Radiofrequency ablation is not recommended for these patients as potential spread of cancer along the percutaneous track

FOLLOW-UP OF RESECTABLE DISEASE—AFP every 3 months for 2 years, then every 6 months. CT abd every 6 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

SPECIFIC ENTITIES (CONT'D)

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 ultrasound. If fail to regress, consider resection

Related Topics
Hepatitis B (p. 130)
Hepatitis C (p. 131)
Hepatic Failure (p. 128)
Chronic Liver Disease (p. 132)

Renal Cancer

NEJM 2005 335:12
Cancer 2006 107:10

DIFFERENTIAL DIAGNOSIS OF SOLID RENAL MASS

RENAL MALIGNANCIES
ANGIOMYOLIPOMA—distinctive fat density on CT. Association with tuberous sclerosis
ONCOCYTOMA—a homogeneous, well-circumscribed solid mass with a central scar
XANTHOGRANULOMATOUS PYELONEPHRITIS—variant of chronic pyelonephritis

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **RENAL CELL CARCINOMA** (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
- **TRANSITIONAL CELL 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'S TUMOR**—nephroblastomas. In children mostly

RISK FACTORS

- **PERSONAL**—age, obesity
- **ENVIRONMENTAL**—smoking (2x), phenacetin
- **FAMILY HISTORY**—affected relatives
- **DISEASES**—von Hippel–Lindau syndrome, hereditary type 2 papillary renal cell carcinoma, Birt–Hogg–Dube syndrome, 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 inferior 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's syndrome, without liver metastases)

TNM STAGING

TNM STAGING

T stage
- **T1**= <7 cm (T1a=<4 cm, T1b=4–7 cm)
- **T2**= >7 cm
- **T3**=extends into surrounding structures but not Gerota fascia (T3a=invades adrenal gland or perinephric tissues, T3b=extends into renal veins or vena cava below diaphragm, T3c=extends into vena cava above diaphragm)
- **T4**=invades beyond Gerota fascia

N stage
- **N1**=single LN
- **N2**= >1 LN

M stage (lungs, liver, bones, brain)
- **M1**=distant metastasis

STAGE GROUPINGS

Stage	TNM @=any	5-year survival
I	T1N0M0	96%
II	T2N0M0	82%
III	T1-3N1M0, T3N0M0	64%
IV	T4N@M0, T@N2M0, T@N@M1	23%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, urinalysis (hematuria, proteinuria)
- **URINE CYTOLOGY**
- **IMAGING**—CXR, US abd, CT abd/pelvis (most useful), IVP, bone scan (if suspicious), CT head (if suspicious)
- **NEPHRECTOMY**—for solitary renal mass, needle biopsy is generally not done because of its low specificity and potential for seeding, while nephrectomy is both diagnostic and therapeutic

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIAGNOSTIC NEPHRECTOMY CRITERIA—diameter >3 cm, enhancement with contrast, poorly defined margins, or areas of necrosis all suggest malignancies and resection is strongly recommended. Biopsy prior to surgery is usually not required

ADVERSE PROGNOSTIC FACTORS—>10 cm, stage III–IV, Fuhrman's grade 3–4 (based on nuclear size and shape, and nucleolar appearance, a score of 1–4 is given)

MSK PROGNOSTIC SCORE FOR METASTATIC RENAL CELL CARCINOMA—Karnofsky performance status <80%, LDH >1.5× upper normal limit, calcium >2.5 mmol/L [>10 mg/dL], hemoglobin <lower normal limit, absence of nephrectomy

Factors	Risk group	Freq.	1-year survival	3-year survival
0	Good	25%	71%	31%
1–2	Inter.	53%	42%	7%
3–5	Poor	22%	12%	0%

JCO 1999 17:8

MANAGEMENT

STAGE I, II—**radical nephrectomy** ± regional node dissection

STAGE III—**radical nephrectomy** ± regional node dissection ± renal vein or vena cava evacuation

MANAGEMENT (CONT'D)

STAGE IV

- **PALLIATIVE RESECTION**—nephrectomy (particularly if primary is symptomatic), systemic therapy intended, limited metastatic disease, good performance status, and good surgical candidate; resection of solitary metastasis may also be considered
- **PALLIATIVE TARGETED THERAPY**
  - **FIRST LINE**—for good- or intermediate-risk disease, consider sunitinib or interferon plus bevacizumab. For poor-risk disease (MSK score ≥3), consider temsirolimus or sunitinib
  - **SECOND LINE**—sorafenib should be considered for cytokine refractory disease
- **PALLIATIVE RADIATION**—control of bleeding, pain or bone metastases
- **PALLIATIVE IMMUNOTHERAPY**—recombinant IL-2 or INFα, response rate 15–20%

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, hemangioblastomas of the cerebellum and spinal cord, and retinal hemangiomas. HIF1α is hydroxylated in normoxic conditions, which is then ubiquitinated by VHL protein complex and destroyed. Accumulation of HIF1α happens with hypoxic conditions or mutated VHL protein, which then heterodimerizes with HIF1β and activates transcription of various genes such as VEGF. Development of targeted therapy for renal cell carcinoma was facilitated by our understanding of the VHL–HIF1α–VEGF pathway

Bladder Cancer

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **TRANSITIONAL CELL** (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

PATHOPHYSIOLOGY (CONT'D)

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×), 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

PATHOPHYSIOLOGY (CONT'D)

- **DISEASES** (usually squamous cell carcinoma)—schistosomiasis, chronic bladder infection, Balkan endemic nephropathy

CLINICAL FEATURES

LOCOREGIONAL—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

TNM STAGING

TNM STAGING
T stage
- **Ta**=non-invasive papillary carcinoma
- **Tis**=carcinoma in situ (CIS), flat tumor
- **T1**=invades lamina propria
- **T2**=invades detrusor muscle (T2a=invades inner half superficial muscle, T2b=invades outer half deep muscle)
- **T3**=invades perivesical tissue (T3a=microscopic, T3b=macroscopic)
- **T4**=invades surrounding tissue (T4a=prostate, uterus, vagina, T4b=pelvic wall, abdominal wall)

N stage
- **N1**=single LN, $\leq$2 cm
- **N2**=single LN 2–5 cm, or multiple LN $\leq$5 cm
- **N3**=any LN $>$5 cm

M stage (bone, liver, lungs)
- **M1**=distant metastasis

STAGE GROUPINGS

Stage	TNM @=any	5-year survival
0a	TaN0M0	$>$90%
0is	TisN0M0	
I	T1N0M0	85%
II	T2a-bN0M0	60%
III	T3a-bN0M0, T4aN0M0	35%
IV	T4bN0M0, T@N1-3M0 T@N@M1	15%

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—IVP or triphasic CT abd/pelvis
- **URINE CYTOLOGY**—sens 70%
- **CYSTOSCOPY WITH BIOPSY**

PROGNOSTIC ISSUES

RISK FACTORS FOR RECURRENCE OF SUPERFICIAL BLADDER TUMOR POST-RESECTION—previous recurrence, large size, high, grade, advanced stage (T1 $>$Tis $>$Ta) multiple tumors, diffuse CIS
ADVERSE PROGNOSTIC FACTORS—squamous cell carcinoma or adenocarcinoma, invasion of muscle, lymphatics, or perivesical fat

MANAGEMENT

SUPERFICIAL
- **STAGE 0A, 0IS, I**—**transurethral resection** (TUR) $\pm$ fulguration $\pm$ **intravesicular therapy** (BCG$\times$6 [bacillus Calmette–Guerin], mitomycin C, thiotepa, doxorubicin, epirubicin, Epodyl) $\pm$ intravesicular interferon. **Radical cystectomy** may be done if multifocal CIS

INVASIVE
- **STAGE II**, **STAGE III**—**radical cystectomy** $\pm$ **pelvic lymph node dissection** or **curative radiation**, **(neo)adjuvant chemotherapy** (gemcitabine–cisplatin [GC], methotrexate–vinblastine–doxorubicin–cisplatin [MVAC], cisplatin–methotrexate–vinblastine [CMV])
- **STAGE IV**—palliative chemotherapy (GC, MVAC, CMV)

Prostate Cancer

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **ADENOCARCINOMA** (>95%)
- **PROSTATE INTRAEPITHELIAL NEOPLASM** (PIN)
- **TRANSITIONAL CELL CARCINOMA**
- **SMALL CELL CARCINOMA**
- **SQUAMOUS CELL CARCINOMA**
- **SARCOMA**

GLEASON SCORE—assigned by a pathologist based on the aggressiveness of the predominate population (1–5) plus second most common population (1–5) with a total of between 2 and 10

RISK FACTORS

- **PERSONAL**—male, age, race (black >Caucasian >Asian)
- **FAMILY HISTORY**—affected relatives (2–5×)
- **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 common as the metastatic lesions tend to be osteoblastic instead of lytic

CONSTITUTIONAL—weight loss, anorexia, fatigue

PARANEOPLASTIC—systemic fibrinolysis, neuromuscular syndromes

INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS)

- **SCORING**—symptoms of incomplete emptying, urinary frequency, intermittency, urgency, weak stream, straining and nocturia over the last month. Each symptom assigned a score from 0 to 5, with a total score ranging between 0 and 35
- **INTERPRETATION**—mild=0–7, moderate=8–19, severe=20–35

STAGING

TNM STAGING

T stage

- **T1**=clinically inapparent tumor (**T1a**=incidental finding by TURP in <5% of tissue, **T1b**=incidental finding by TURP in >5% of tissue, **T1c**=incidental finding by needle biopsy due to ↑ PSA)
- **T2**=confined within prostate (**T2a**=invades less than or equal to half of one lobe, **T2b**=invades more than half of one lobe, **T2c**=invades both lobes)

STAGING (CONT'D)

- **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**=regional LN

M stage (bone, liver. Biologically heterogeneous with variable course)

- **M1**=distant metastasis

GRADE

- **G1**=Gleason score 2–4 and well differentiated
- **G2**=5–6 and moderately differentiated
- **G3–4**=7–10 and poorly/undifferentiated

STAGE GROUPINGS

Stage	TNM	5 year survival
I	T1aN0M0+G1	>95%
II	T1aN0M0+G2–4	70%
	T1b-cN0M0, T2N0M0	
III	T3N0M0	60%
IV	T4N0M0, T@N1M0, T@N@M1	30%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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), transrectal U/S
- **BIOPSY**—U/S-guided transrectal biopsy (6–12 core needles)

Related Topics
Cancer Screening (p. 222)
Tumor Markers (p. 220)

DIAGNOSTIC AND PROGNOSTIC ISSUES

PROSTATE-SPECIFIC ANTIGEN—a serine protease that liquidifies semen physiologically. Elevated in prostate cancer, prostatitis, BPH, endoscopy, prostate surgery, prostate biopsy (remains elevated for 6–8 weeks), and with increasing age

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

(age 40–50 normal <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, and following treatment response

- **FREE PSA**—proportion of PSA unbound to antichymotrypsin or α2 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
- **SCREENING**—if 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
- **BIOCHEMICAL RELAPSE**—for patients with previous prostatectomy, PSA relapse is indicated by any detectable value, particularly if >1 ng/mL. For patients with previous external beam radiation or brachytherapy, PSA relapse is indicated by PSA >2 ng/mL from nadir

ADVERSE PROGNOSTIC FACTORS—pre-treatment PSA, Gleason score, stage

RISK CATEGORIES FOR LOCALIZED DISEASE

Risk category	PSA (ng/mL)	Gleason score	Stage
Low (highly curable)	≤10	2–6	≤T2b
Intermediate (curable)[a]	10–20	7	T2c
High (rarely curable)	>20	8–10	≥T3

[a]If only one of PSA or Gleason score meets criteria, considered low intermediate risk. If both PSA or Gleason score meet criteria, considered high intermediate risk

MANAGEMENT

LOCALIZED DISEASE (T1-3N0M0)

- **LOW RISK**—consider active surveillance if significant comorbidities or <10-year life expectancy. Patients on active surveillance should have PSA testing every 6 months and prostate biopsy yearly, and consider treatment with disease progression (i.e. meet intermediate-risk criteria, decrease in PSA doubling time <3 years, DRE changes, or prostate biopsy demonstrating Gleason score ≥7, >2 scores positive, >50% involvement in core sample). Curative options include brachytherapy and radical prostatectomy, which are preferred over external beam radiation
- **INTERMEDIATE RISK**—consider brachytherapy or radical prostatectomy for low intermediate risk group. LHRH agonist ×6 months combined with external beam radiation (starting at 3 months) for high intermediate risk group
- **HIGH RISK**—usually LHRH agonist ×1 year combined with external beam radiation (starting at 6–8 months)
- **RELAPSE**—may consider salvage (i.e. external beam radiation for patients with radical prostatectomy or brachytherapy) for young and fit patients. Otherwise, treat as advanced disease

ADVANCED DISEASE (T4, N1–3, M1)—**life-long castration** (surgical or medical with LHRH agonists [*leuprolide* 22.5 mg IM q3month, *goserelin* 10.8 mg SC q3month] plus flutamide for first few weeks to control flare response). Note that up-front combined androgen blockade may be "considered" an option as per ASCO. Early initiation of androgen deprivation therapy may provide disease-specific survival but not overall survival benefit compared to starting treatment when patient become symptomatic, and thus not recommended. With disease progression, consider **combined androgen blockade** with antiandrogen (*bicalutamide* 50 mg PO daily, *flutamide* 250 mg PO TID, nilutamide) added onto surgical/medical castration long term. With progression, consider **anti-androgen withdrawal**. With further progression to castration-resistant (formerly hormone refractory) prostate cancer, consider **palliative chemotherapy** (docetaxel–prednisone). Patients who were on an LHRH agonist should remain on it to potentially slow disease progression. **Alternative systemic agents** (of questionable benefit) include mitoxantrone, *megestrol acetate* 40 mg PO QID, *ketoconazole* 400 mg PO TID, aminoglutethimide, *prednisone* 5 mg PO BID, and finasteride (α5 reductase inhibitor). Abiraterone is being investigated as a promising agent. **Palliative radiation**, bisphosphonates (zoledronic acid), and strontium infusion can be useful for bone metastasis

TREATMENT ISSUES

COMPARISON OF TREATMENTS FOR LOCALIZED DISEASE[a]

	Impotence	Urinary incontinence	Urinary irritation	GI irritation
Prostatectomy[b]	50–90%	10–20%	15–60%	2–17%
Brachytherapy	50%	1–2%	12–30%	10%
External RT[c]	50%	1–2%	2–30%	30%

[a] side effects at 5 years are listed
[b] symptoms tend to decrease over time
[c] symptoms tend to increase over time

TREATMENT ISSUES (CONT'D)

RADICAL PROSTATECTOMY

- **BENEFITS**—5-year disease-free survival 85%
- **INDICATIONS**—preferred for patients with low-risk disease, life expectancy >20 years, or significant urinary symptoms
- **CONTRAINDICATIONS**—age >70, high-risk disease
- **ADVERSE EFFECTS**—urinary (frequency, urgency, nocturia, dysuria, incontinence), impotence

BRACHYTHERAPY—implant of radioactive seeds

- **BENEFITS**—5-year disease-free survival 96%
- **INDICATIONS**—eligibility criteria include PSA ≤15 ng/mL, Gleason score ≤7, stage ≤T2c, prostate volume ≤60 mL, and life expectancy >5 years
- **CONTRAINDICATIONS**—significant urinary symptoms (as prostate swells significantly shortly after procedure), prior TURP
- **ADVERSE EFFECTS**—urinary (frequency, urgency, nocturia, dysuria, incontinence), GI (diarrhea, tenesmus), and impotence; 3% require indwelling urinary catheter for >3 weeks and <1% chance of severe GI symptoms requiring colostomy. The symptoms typically peak at 6 weeks and generally resolve over time; 50% of patients return to baseline symptoms at 3 months and 95% by 1 year

EXTERNAL BEAM RADIATION

- **BENEFITS**—5-year disease-free survival 80%

TREATMENT ISSUES (CONT'D)

- **INDICATIONS**—preferred for patients with high-risk disease or older
- **CONTRAINDICATIONS**—pelvic kidney, inflammatory bowel disease, connective tissue disease (SLE, scleroderma), or prior radiation to same region
- **ADVERSE EFFECTS**—urinary (frequency urgency, nocturia, dysuria, incontinence), GI (diarrhea, rectal bleeding), and impotence. Urethral stricture (1%), bowel obstruction (0.1%). Also risk of late-onset second malignancy

LHRH AGONISTS

- **INDICATIONS**—high intermediate or high-risk localized disease, salvage setting, or advanced disease setting. Requires the use of an antiandrogen (flutamide) for first few weeks to counter flare response
- **ADVERSE EFFECTS**—fatigue, hot flushes, mood changes, weight gain, decreased libido, impotence, 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 bone density scan

TIME LINE—median time from castration to androgen independence 1.5 year. Median time from androgen independence to death 1.5 year

Testicular Cancer — EGCCCG Guidelines Ann Onc 2004 15

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, αFP nega4tive and sometimes slightly βhCG positive. Few metastasize. Very radiosensitive and very chemosensitive
  - **NON-SEMINOMA** (60%)—age twenties to thirties, pure or mixed, more metastasize. Chemosensitive. Include the following subtypes

PATHOPHYSIOLOGY (CONT'D)

  - **EMBRYONAL CELL CARCINOMA**—neoplastic counterpart of inner cell mass of embryo. May be βhCG+, αFP+
  - **YOLK SAC TUMOR**—neoplastic counterpart of yolk sac. Usually αFP+
  - **CHORIOCARCINOMA**—neoplastic counterpart of chorionic villus. Usually βhCG+
  - **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

PATHOPHYSIOLOGY (CONT'D)

- 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

RISK FACTORS

- **FAMILY HISTORY**—affected relatives
- **DISEASES**—prior testicular cancer, cryptorchidism (10–40×), testicular feminization syndromes, Klinefelter syndrome

CLINICAL FEATURES

LOCOREGIONAL—testicular mass ± pain, acute epididymitis (25% of embryonal cell tumor and mixed teratoma), back pain (10%), gynecomastia (βhCG), infertility (3%)

METASTATIC—dyspnea, cough, headaches, stroke

CONSTITUTIONAL—weight loss, anorexia, fatigue

STAGING

TNM STAGING

T stage

- **T1**=limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade into tunica albuginea but not tunica vaginalis

STAGING (CONT'D)

- **T2**=limited to testis and epididymis with vascular/lymphatic invasion or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
- **T3**=invades the spermatic cord ± vascular/lymphatic invasion
- **T4**=invades the scrotum ± vascular/lymphatic invasion

N stage (pelvic → paraaortic LN)

- **N1**=1–5 LN, all È2 cm
- **N2**=1 or more LN 2–5 cm or >5 LN È5 cm
- **N3**=any LN >5 cm

M stage

- **M1a**=non-regional LN or lung
- **M1b**=sites other than non-regional LN or lung (e.g. bone)

SERUM MARKER DESIGNATION

	αFP (ng/mL)	βhCG (IU/L)	LDH
S1	<1000	<5000	<1.5×
S2	1000–10,000	5000–50,000	1.5–10×
S3	>10,000	>50,000	>10×

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 group	Non-seminoma	Seminoma
Good (90% 5-year survival)	Testicular or retroperitoneal tumor, S1, and absence of non-pulmonary metastases	Any location, any marker, and absence of non-pulmonary metastases
Intermediate (80% 5-year survival)	Testicular or retroperitoneal tumor, S2, and absence of non-pulmonary metastases	Any location, any marker, and any non-pulmonary metastases
Poor (50% 5-year survival)	Testicular, retroperitoneal, or mediastinal tumor, S3, or non-pulmonary metastases	Not applicable

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, αFP, βhCG, LDH, TSH, T3, T4, total testosterone, LH, FSH
- **IMAGING**—testicular U/S, CXR, CT abd/pelvis, CT head (if advanced disease with intermediate or poor prognosis), bone scan (if suspect metastasis)
- **RADICAL INGUINAL ORCHIECTOMY**

SPECIAL

- **SEMEN ANALYSIS**—if fertility a consideration

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, and monitoring treatment response

- **LDH**—less specific, indicates tumor bulk
- **βhCG**—elevated in trophoblastic tumor, choriocarcinoma. Half-life 24 h
- **αFP**—elevated in yolk sac tumor. Half-life 2–3 days

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

Tumor	βhCG	αFP
Non-seminoma	↑ in up to 85%	↑ in up to 80%
Seminoma	↑ in 15–25%	Normal

PROGNOSTIC FACTORS—vascular invasion is most important indicator for relapse in non-seminoma

MANAGEMENT

NOTE: all cases should be discussed with an interdisciplinary team experienced in the management of testicular cancer

EARLY SEMINOMA

- **STAGE I—orchiectomy** + one of adjuvant **radiation** (paraaortic/paracaval LN, 3–4% relapse) or adjuvant **carboplatin** (1–2 cycles, 3–4% relapse) or **surveillance** (15–20% relapse (higher risk of recurrence if >4 cm or rete testis involvement)
- **STAGE IIA—orchiectomy** + **radiation** (paraaortic/ipsilateral iliac LN, 6-year RFS 95%)
- **STAGE IIB—orchiectomy** + one of **radiation** (paraaortic/ipsilateral iliac LN, 6-year RFS 89%) or **chemotherapy** (if radiation not given, BEP×3 or EP×4, where B=bleomycin, E=etoposide, P=cisplatin)

EARLY NON-SEMINOMA

- **STAGE I WITH NO VASCULAR INVASION** (14–22% relapse)—**orchiectomy** + one of **surveillance** (14–22% relapse) or **chemotherapy** (if surveillance not chosen, BEP×2) or nerve-sparing retroperitoneal [NSRP] **LN dissection** (if both surveillance and chemotherapy not chosen). Surveillance is recommended
- **STAGE I WITH VASCULAR INVASION** (48% relapse)—**orchiectomy** + one of **chemotherapy** (BEP×2, 3% relapse) or **surveillance** (if chemotherapy not given, 48% relapse) or **NSRP-LN dissection** (if both surveillance and chemotherapy not chosen, 10% relapse). Surveillance is recommended
- **STAGE IIA, MARKER NEGATIVE—orchiectomy** + one of
- **NSRP-LN dissection** → if pathologic stage IIA or IIB, BEP×2; if stage I, surveillance only, or **surveillance** (follow-up every 6 weeks) → if regression, follow-up only; if no change, NSRP-LN dissection or close follow-up; if progressive disease, BEP×3 or NSRP-LN dissection
- **STAGE IIA, MARKER POSITIVE—orchiectomy** + **BEP×3** + **resection** if residual tumor
- **STAGE IIB—orchiectomy** + **BEP×3** + **resection** if residual tumor

ADVANCED SEMINOMA AND NON-SEMINOMA (IIC, IIIA-C)

- **GOOD RISK—orchiectomy** + **chemotherapy** (BEP×3 or EP×4)
- **INTERMEDIATE/POOR RISK—orchiectomy** + **chemotherapy** (BEP×4)

MANAGEMENT (CONT'D)

- **RESIDUAL TUMOR POST-CHEMOTHERAPY—marker normalized** (proceed to resection → if necrosis (40%), differentiated teratoma (40%) or <10% viable tumors, follow-up only; if >10% viable tumors, consolidative chemotherapy with VIP×2; if incomplete resection of viable tumor, treat as marker increased), **marker elevated but plateau** (follow-up 4–12 weeks → treat as marker normalized or marker increased depending on trend), **marker increased after short interval** (salvage chemotherapy with PEI×4, VIP×4, VeIP×4, TIP×4)
- **NOTE**—B=bleomycin, E/V=etoposide (VP16), P=cisplatin, I=ifosfamide, Ve=vinblastine, T=taxol

RELAPSED SEMINOMA—if systemic relapse, consider BEP×4. If locoregional relapse, consider BEP or radiotherapy. Salvage chemotherapy regimens after first line chemotherapy include PEI×4, VIP×4, or VeIP×4 or TIP×4

RELAPSED NON-SEMINOMA—salvage chemotherapy regimens after first-line chemotherapy include PEI×4, VIP×4, or VeIP×4 or TIP×4. For late relapses, patients with negative tumor markers should have immediate radical surgery. If unresectable disease, consider salvage chemotherapy and then resection if possible. If unresectable disease and localized, consider radiotherapy

TREATMENT ISSUES

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 chemotherapy 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 cryoconservation 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. 297)

Ovarian Cancer

PATHOPHYSIOLOGY

HISTOLOGIC TYPE

- **EPITHELIAL** (90%)
  - **SEROUS CYSTADENOCARCINOMA** (75–80%)
  - **MUCINOUS CYSTADENOCARCINOMA** (10%)
  - **ENDOMETRIOID CARCINOMA** (10%)
  - **CLEAR CELL** (<5%)
  - **UNDIFFERENTIATED** (<1%)
  - **BRENNER'S TUMOR** (<1%)
  - **MIXED EPITHELIAL TUMOR**
  - **MALIGNANT MIXED MULLERIAN TUMORS** (carcinosarcomas)
  - **UNCLASSIFIED**
- **GERM CELL TUMORS**
  - **DYSGERMINOMA** (ovarian counterpart of seminoma of the testes)
  - **ENDODERMAL SINUS TUMOR**
  - **EMBRYONAL CARCINOMA**
  - **POLYEMBRYOMA**
  - **CHORIOCARCINOMA**
  - **TERATOMA**
  - **MIXED**
- **SEX CORD STROMAL TUMORS**
  - **SERTOLI–LEYDIG CELL TUMOR**
  - **GRANULOSA STROMAL CELL TUMOR**
  - **GYNANDROBLASTOMA**
  - **ANDROBLASTOMA**
  - **UNCLASSIFIED**

RISK FACTORS FOR EPITHELIAL OVARIAN CANCER

- **PERSONAL**—Ashkenazi Jews (BRCA1/2), HNPCC, Caucasian, nulliparity (incessant ovulation)
- **FAMILY HISTORY**—breast cancer, ovarian cancer
- **DISEASES**—breast cancer, endometrial cancer

CLINICAL FEATURES

SYMPTOMS

- **LOCOREGIONAL**—bowel obstruction, constipation, abdominal pain, abdominal mass, abdominal bloating/distension, renal failure, urinary frequency
- **METASTATIC**—cough
- **CONSTITUTIONAL**—weight loss, weight gain (if ascites and edema), anorexia, fatigue
- **PARANEOPLASTIC**—neurologic (peripheral neuropathy, dementia, ALS-like syndrome, cerebellar ataxia), Cushing's syndrome, hypercalcemia (clear cell), thrombophlebitis

STAGING

FIGO STAGING

STAGE I (15%)—limited to the ovaries; 80% 5-year survival

- **IA**=one ovary involved with no ascites
- **IB**=both ovaries involved with no ascites
- **IC**=IA or IB with tumor on the ovary surface, ruptured capsule, positive pelvic washings

STAGE II (15%)—pelvic extension; 60% 5-year survival

- **IIA**=extension to uterus or tubes
- **IIB**=extension to other pelvic tissues
- **IIC**=IIA or IIB with tumor on the ovary surface, ruptured capsule, positive pelvic washings

STAGE III (65%)—peritoneal implants outside the pelvis with extensions to small bowel, omentum, or liver (serosal surface only); 30% 5-year survival

- **IIIA**=tumor grossly limited to the true pelvis with negative nodes, but microscopic seeding of abdominal peritoneal surfaces
- **IIIB**=abdominal peritoneal implants <2 cm
- **IIIC**=abdominal peritoneal implants >2 cm, retroperitoneal/inguinal lymph nodes

STAGE IV (5%)—distant metastasis; 10% 5-year survival

- **IV**=liver parenchyma, peripheral superficial lymph nodes, cytology positive pleural effusion

OVERALL SURVIVAL BY STAGE

Stage	FIGO stage	Freq	5-year survival
I	IA–C	35%	80–90%
II	IIA–C	5%	60–70%
III	IIIA-C	40%	30–50%
IV	IV	10%	20%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, albumin, CA125, βhCG, αFP
- **IMAGING**—CXR, U/S abd, CT abd/pelvis
- **BIOPSY**—laparoscopy, staging laparotomy

DIAGNOSTIC AND PROGNOSTIC ISSUES

DISTINGUISHING FEATURES BETWEEN OVARIAN CANCER AND BENIGN CYSTS—any of the following features should prompt consideration of ovarian cancer and biopsy: any postmenopausal women, >8 cm in premenopausal women, solid, or cystic but still present after 2 months of oral contraceptive pills, presence of ascites

ADVERSE PROGNOSTIC FACTORS—advanced stage, high grade, residual disease after debulking (38 vs. 60 months), poor performance status

Related Topics
BRCA Mutations (p. 225)
Cancer Screening (p. 222)
Tumor Markers (p. 220)

MANAGEMENT

EPITHELIAL OVARIAN TUMORS

- **STAGE IA–B, GRADE 1**—total abdominal hysterectomy/bilateral salpingo-oophorectomy (TAH/BSO). If premenopausal, consider unilateral oophorectomy to preserve fertility until childbearing is completed
- **STAGE IA–B GRADE 2–3, IC, II**—TAH/BSO, adjuvant chemotherapy (carboplatin–paclitaxel ×6)
- **STAGE III**—debulking, retroperitoneal lymph node dissection, plus adjuvant chemotherapy (if optimal debulking with residual disease <1 cm, consider intraperitoneal chemotherapy or carboplatin–paclitaxel ×6; if suboptimal debulking, consider carboplatin–paclitaxel ×6). For those who derived a complete response to carboplatin and paclitaxel, consolidation chemotherapy with 12 cycles of paclitaxel may be considered
- **STAGE IV—first-line** palliative chemotherapy includes carboplatin–paclitaxel ×6. **Second-line** chemotherapy includes ongoing doublet therapy (if greater than 6 months since last line of platinum-based therapy; regimens include carboplatin-paclitaxel, carboplatin–liposomal doxorubicin, and carboplatin–gemcitabine) or single agent therapy using carboplatin, paclitaxel, cisplatin, topotecan, etoposide, gemcitabine, vinorelbine, ifosfamide, or liposomal doxorubicin. In platinum-resistant disease, single-agent therapy is recommended. Platinum resistance is commonly defined as clinical evidence of disease progression <6 months from last platinum therapy

GERM CELL TUMORS—surgery is mainstay. May consider unilateral salphingo-oophorectomy to preserve fertility in young women. For advanced disease consider BEP (bleomycin–etoposide–cisplatin) chemotherapy after surgery. The treatment paradigm is based entirely on germ cell tumors of the testicle (p. 212)

SEX CORD STROMAL TUMORS—surgery is mainstay. Excellent prognosis

TREATMENT ISSUES

OVARIAN CANCER SURGERY—for both staging and cytoreduction. Key features include (1) obtaining free fluid or lavage for cytology, (2) systematic exploration of all intra-abdominal organs, surfaces and retroperitoneum for pelvic and paraaortic lymph nodes, (3) biopsy of any suspicious areas or random biopsies from peritoneum of the cul-de-sac, paracolic gutters, bladder, intestinal mesentery and lymph nodes, (4) biopsy of diaphragm, (5) resection of omentum, and (6) total abdominal hysterectomy and bilateral salpingo-oophorectomy. For patients who had a good response to neoadjuvant chemotherapy (no prior maximal surgical effort), surgical resection to remove residual macroscopic disease is generally recommended

Endometrial Cancer

PATHOPHYSIOLOGY

HISTOLOGIC TYPE OF UTERINE CANCER

- **ENDOMETRIAL CARCINOMAS** (97%)
  - **ADENOCARCINOMA** (>95%)
  - **CLEAR CELL CARCINOMA**—associated with more aggressive disease and worse prognosis, but more responsive to chemotherapy
  - **PAPILLARY SEROUS CARCINOMA**—associated with more aggressive disease and worse prognosis
  - **SMALL CELL CARCINOMA**
  - **MALIGNANT MIXED MULLERIAN TUMORS**
- **UTERINE SARCOMA** (3%)

RISK FACTORS

- **PERSONAL**—age, excess estrogen (early menarche, late menopause, nulliparity, obesity with conversion of androstenedione to estrone by aromatase in adipose tissue)

PATHOPHYSIOLOGY (CONT'D)

- **FAMILY HISTORY**—HNPCC
- **DISEASES**—ovarian granulosa cell and theca cell tumors (produce estrogen), polycystic ovary disease (chronic anovulation), diabetes (2×), tamoxifen (3–7×), unopposed estrogen administration (i.e. without progesterone, 6×)

CLINICAL FEATURES

SYMPTOMS

- **LOCOREGIONAL**—abnormal vaginal bleed (97%, particularly in postmenopausal women), pelvic pain, pelvic mass, constipation, bowel obstruction, abdominal pain, abdominal bloating/distension, renal failure, urinary frequency
- **METASTATIC**—dyspnea, cough, abdominal pain, seizures, bony pain
- **CONSTITUTIONAL**—weight loss, anorexia, fatigue

PROGNOSTIC ISSUES

ADVERSE PROGNOSTIC FACTORS—advanced stage, high grade, papillary serous carcinoma, small cell carcinoma, vascular invasion, ER negative, PR negative, DNA ploidy

STAGING

REVISED FIGO STAGING 2009

STAGE I—confined to the corpus uteri

- **IA**=no or less than half myometrial invasion
- **IB**=invasion equal to or more than half of the myometrium

STAGE II—involves cervical stroma

- **II**=invades cervical stroma, but does not extend beyond the uterus

STAGE III—local and regional spread of the tumor

- **IIIA**=invades the serosa of the corpus uteri and/or adnexae
- **IIIB**=vaginal and/or parametrial involvement
- **IIIC**=metastases to pelvic and/or para-aortic LN
  - **IIIC1**=pelvic nodes
  - **IIIC2**=para-aortic lymph nodes with or without positive pelvic lymph

STAGE IV—extends outside the true pelvis

- **IVA**=invasion of bladder and/or bowel mucosa
- **IVB**=distant metastases, including intra-abdominal metastases and/or inguinal LN

GRADE

- **G1**=well differentiated (≤5% of solid growth pattern)
- **G2**=moderately differentiated (6–50%)
- **G3**=undifferentiated (>50%)

STAGING (CONT'D)

OVERALL SURVIVAL BY STAGE

Surgical stage	Freq	5 year survival
IA–B	75%	80–90%
II	11%	70%
IIIA–C	11%	50%
IVA–B	3%	20–30%

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, CA 125
- **IMAGING**—CXR
- **BIOPSY**—endometrial curettage with endocervical sampling, dilation and curettage, colonoscopy (if symptomatic or relevant family history suggestive of HNPCC)

SPECIAL

- **ADDITIONAL IMAGING**—transvaginal U/S (not routinely required), CT abd/pelvis (not routinely required), MR pelvis with gadolinium (most sensitive but not routinely required)

MANAGEMENT

STAGE I—TAH/BSO ± lymphadenectomy (highly controversial). If high-risk features such as stage 1C (>50% muscle invasion), grade 3, vascular invasion, papillary serous or clear cell histology, consider **adjuvant radiotherapy** to pelvis to reduce local recurrence rate

STAGE II—surgery (TAH/BSO ± lymphadenectomy), followed by **adjuvant radiotherapy** to pelvis to reduce local recurrence rate

STAGE III—surgery (TAH/BSO ± lymphadenectomy), followed by **adjuvant chemotherapy** (generally a platinum taxane combination with or without doxorubicin)

STAGE IV OR LOCALLY RECURRENT DISEASE

- **EXENTERATION**—potentially curable if isolated central recurrence
- **PELVIC RADIATION**—if central local recurrence and not previously irradiated
- **HORMONAL AGENTS**—for grade 1–2 disease, consider hormonal therapy with *megestrol acetate* 160 mg PO daily, *medroxyprogesterone* 1 g IM weekly ×6 weeks and then monthly, or *tamoxifen* 20 mg PO daily. Response rate 20–30%, response duration 4 months. Predictors for hormonal therapy include well-differentiated tumors (G1–2), ER/PR+ tumors, and long progression-free survival before recurrence

MANAGEMENT (CONT'D)

- **CHEMOTHERAPY**—regimens include carboplatin–paclitaxel, paclitaxel–doxorubicin–carboplatin (TAP), paclitaxel–doxorubicin–cisplatin, and paclitaxel-doxorubicin. Highest response rate is ~55% with TAP. TAP is the only regimen associated with a survival benefit in clinical trial

TREATMENT ISSUES

INDICATIONS FOR PELVIC AND PARAAORTIC LYMPHADENECTOMY—this is an area of controversy. Two large trials have demonstrated no therapeutic benefit to lymphadenectomy. This has not been uniformally accepted by the surgical community

INDICATIONS FOR PRIMARY RADIOTHERAPY—elderly or women with multiple comorbidities and cannot tolerate. Outcome inferior to surgery

Cervical Cancer

PATHOPHYSIOLOGY

HISTOLOGIC TYPE

- **SQUAMOUS** (80%)—starts at squamocolumnar junction. Slow progression from CIN to carcinoma over 15 years
- **ADENOCARCINOMA** (20%)
- **SARCOMA**

HPV AND CERVICAL CANCER—types 16, 18, 45, 31, 33, 52, 58, 35 are associated with cervical cancer, and type 18 is particularly strongly associated with poorly differentiated carcinoma with nodal metastases. Viral proteins implicated in carcinogenesis include E6 and E7. Types 6 and 11 are usually associated with condyloma acuminate

RISK FACTORS—early age at first intercourse, early first pregnancy, multiple sexual partners, male partners with multiple sexual partners, venereal diseases (especially HPV related), HIV, smoking

CLINICAL FEATURES

SYMPTOMS

- **LOCOREGIONAL**—may be asymptomatic, abnormal vaginal bleeding, postcoital spotting, vaginal discharge (may be malodorous), pelvic pain
- **METASTATIC**—cough, jaundice, bony pain
- **CONSTITUTIONAL**—weight loss, anorexia, fatigue

Related Topic
Cancer Screening (p. 222)

TNM STAGING

TNM STAGING

T stage

- **T1a**=microscopic only (T1a1=stromal invasion ≤3 mm and ≤7 mm in lateral spread, T1a2=stromal invasion 3–5 mm and ≤7 mm in lateral spread)
- **T1b**=microscopic or macroscopic (T1b1=≤4 cm, T1b2 >4 cm)

TNM STAGING (CONT'D)

- **T2**=beyond cervix but not pelvic wall (T2a=proximal 2/3 of vagina, T2b=with parametrial invasion)
- **T3**=invades distal vagina, pelvic wall, or causes hydronephrosis (T3a=lower third of vagina, T3b=extends to pelvic wall or causes hydronephrosis)
- **T4**=spread to bladder or rectum

N stage

- **N1**=regional LN

M stage (lung, liver, bone)

- **M1**=distant metastasis

STAGE GROUPINGS

Stage	TNM @=any	5 year survival
IA1	T1a1N0M0	95%
IA2	T1a2N0M0	
IB1	T1b1N0M0	80%
IB2	T1b2N0M0	
IIA	T2aN0M0	60%
IIB	T2bN0M0	
IIIA	T3aN0M0	30%
IIIB	T3bN@M0, T1a1–3aN1M0	
IVA	T4N@M0	5%
IVB	T@N@M1	

INVESTIGATIONS

BASIC

- **BLOOD TESTS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bili
- **IMAGING**—CXR, CT abd/pelvis
- **SPECIAL**—pap smear → if lesion suspected, colposcopy, cone biopsy, loop electrosurgical excision, endocervical curettage

MANAGEMENT

STAGE IA1—**simple hysterectomy**, excisional conization. If lymphovascular invasion, treat as IA2 disease

MANAGEMENT (CONT'D)

STAGE IA2, IB1—radical hysterectomy, bilateral pelvic and paraaortic lymphadenectomy

STAGE IB2, IIA—chemoradiation with cisplatin ± 5–FU. Alternatively, **radical hysterectomy**, bilateral pelvic and paraaortic lymphadenectomy, followed by **adjuvant radiation or chemoradiation** with cisplatin ± 5–FU

STAGE IIB, III, IVA (locally advanced)—**chemoradiation** with cisplatin ± 5–FU ± additional brachytherapy

STAGE IVB—palliative chemotherapy (cisplatin–topotecan, cisplatin–paclitaxel, cisplatin, carboplatin, bleomycin, mitomycin C), palliative radiation

MANAGEMENT (CONT'D)

RECURRENCE—for locally recurrent disease, pelvic **exenteration** (32–62% 5-year survival). For recurrence in the pelvis following radical surgery, **chemoradiation** with cisplatin or 5–FU ± mitomycin C (40–50% cure). If distant recurrence, treat with **palliative chemotherapy**

HPV VACCINATION—may offer primary prevention although clinical data lacking at this time. Current vaccines are created against common serologic types only, including HPV 6, 11, 16, and 18

Cancer of Unknown Origin

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. 220)

IMMUNOHISTOCHEMICAL MARKERS

- **CARCINOMA**—cytokeratin negative, common leukocyte antigen, S100, vimentin negative. Breast cancer may be ER/PR positive
- **LYMPHOMA**—common leukocyte antigen

PATHOPHYSIOLOGY (CONT'D)

- **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**—CBCD, 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**—tissue biopsy

MANAGEMENT

TREAT UNDERLYING CAUSE—see table below for tailored treatment of cancer of unknown primary based on most likely tumor type

SUPPORTIVE—symptom control, consider palliative care consult

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	Quadroscopy, 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, U/S breast, MRI breast	Mastectomy with axillary dissection or whole breast irradiation, adjuvant chemotherapy. If lytic metastasis in post-menopausal women, consider hormonal treatment

MANAGEMENT (CONT'D)

Presentation	Likely primary	Key history and physical	Investigations	Empiric treatment(s)
Squamous cell carcinoma with inguinal lymphadenopathy	Cervical/rectal 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)	Treated as ovarian with carboplatin, paclitaxel
Liver metastasis	GI (colorectal [usually otherwise well], pancreatic, esophageal, gastric, hepatic [orientals or cirrhosis], lung, breast	General	CEA, CA 19-9, CA 15-3, AFP, colonoscopy	Gemcitabine, pemetrexed
Lung nodule(s)	Metastasis (lower lobes, multiple), lung cancer (upper lobe, single)	Smoking history	CT chest	Platinum-based doublet chemotherapy
Malignant pleural effusion	Lung adenocarcinoma, mesothelioma	Smoking, asbestos exposure	Thoracentesis	Thoracentesis
Blastic bone metastasis	Prostate (most common), lung, breast	DRE	PSA, plain X-rays of bones, bone scan	Hormonal therapy if suspect prostate cancer

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

PROSTATE SPECIFIC ANTIGEN (PSA) (CONT'D)

UTILITY IN PROSTATE CANCER

- **SCREENING**—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. 210)

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 performed every 3 months for at least 3 years if the

CARCINOEMBRYONIC ANTIGEN (CEA) (CONT'D)

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

CA 125 (CONT'D)

ELEVATED—epithelial ovarian cancer (sens 50% in stage I, 85% in all), breast cancer, colorectal 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 ultrasound
- **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 (GI)	CEA, CA 19-9
Pancreas	CA 19-9, CEA
Liver	αFP
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	αFP, βhCG, LDH
GTN	βhCG
Carcinoid tumor	Chromogranin, 5-HIAA
Non-Hodgkin's	LDH
Hodgkin's	ALP
Myeloma	M-protein, β2 microglobulin

UTILITY OF SPECIFIC TUMOR MARKERS

Tumor marker	Tumor type	Screen	Diagnosis	Prognosis	Response	Follow-up (recurrence)
PSA	Prostate	√?	√	√	√	√
CEA	Colorectal	×	×	√	√	√
CA 19–9	Pancreas	×	×?	×	√?	√?
CA 15–3	Breast	×	×	×	M	x
CA 125	Ovary	×?	x?	√	√	√?
αFP	Germ cell	×	√	√	√	√
	Liver	×?	√	√	√	×
βhCG	Germ cell	×	√	√	√	√
	GTN	×	√	√	√	√
LDH	Germ cell	×	√	√	√	√
	Lymphoma	×	×	√	√	×

√=useful, ?=controversial, x=not useful, M=metastatic setting only

Cancer Screening

Canadian Association of Gastroenterology Guidelines for Colon Cancer Screening 2004 NEJM 2009 361:12

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 which 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

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
- **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

PRINCIPLES OF SCREENING (CONT'D)

- **LUNG**—CXR, sputum cytology, CT chest. No role for routine screening at this time
- **COLORECTAL**—fecal occult blood (FOB) sigmoidoscopy, double-contrast barium enema, colonoscopy, CT colonography
- **PROSTATE**—DRE, PSA
- **OVARIAN**—U/S, 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. 220). Evidence for survival benefit conflicting

OVERALL—for men who have life expectancy >10 years and who desire screening after extensive counseling on the risks and benefits, start monitoring PSA at age 50. Perform PSA annually if PSA >1 ng/mL and every 4 years if PSA <1 ng/mL. Combine with annual DRE

Related Topics
Tumor Markers (p. 220)
Hereditary Cancer Syndromes (p. 224)

COLON 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) → repeat in 5 years; positive in 7–25% → 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) → repeat in 10 years; positive (i.e. ≥1 polyp) in 20–50% → 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,

COLON CANCER SCREENING (CONT'D)

patient would need to undergo optical colonoscopy (ideally on standby) for resection. Risk of radiation exposure

FECAL OCCULT TEST (FOB)—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 years if done biennially. Negative test in 90–98% of cases (15–50% negative even with cancer) → repeat in 1–2 years; positive in 2–10% → proceed to colonoscopy

FECAL IMMUNOCHEMICAL TEST (FIT)—detects human globin. More specific and less sensitive than FOB

STOOL DNA TEST (sDNA)—need to provide entire stool sample. Insufficient evidence to support benefit

OVERALL APPROACH

- **AVERAGE RISK**—start screening at age 50 with *one* of colonoscopy every 10 years, flexible sigmoidoscopy every 5 years, FOB or FIT every 1–2 years, or double-contrast barium enema every 5 years. Both FOB and FIT detect primarily cancer, while the rest detect mostly polyps (i.e. earlier stage and thus preferred). Insufficient data to recommend routine CT colonoscopy or stool DNA testing
- **POLYPS ON COLONOSCOPY**—1–2 tubular adenomas → colonoscopy in 5 years; >2 adenomas → colonoscopy in 3 years; incomplete exam, numerous polyps, advanced adenoma, large sessile adenoma → 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 → 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. For AAPC, colonoscopy annually beginning at 16–18 years of age
- **IBD** (ulcerative colitis or Crohn's 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

BREAST CANCER SCREENING

BREAST SELF-EXAMINATION (BSE)—no survival benefit demonstrated on its own

CLINICAL BREAST EXAMINATION (CSE)—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 U/S—may represent an alternative in women with dense breasts and increased risk of breast cancer who cannot tolerate MRI. No survival benefit demonstrated

OVERALL—mammogram should be done every 1–2 years for women aged 40 or greater for as long as women is in good health, with CBE annually and BSE q6months. 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 U/S—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 individuals not recommended. For those at high risk (family history, BRCA mutation), the decision should be individualized and may consist of transvaginal U/S 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

CERVICAL CANCER SCREENING (CONT'D)

- **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

CERVICAL CANCER SCREENING (CONT'D)

OVERALL—should be performed annually within 3 years of vaginal intercourse or no later than age 21. May decrease frequency of screening to every 3 years if 2 consecutive negative smears, up until age 69. Women with 3 normal Pap tests in a row may get screened every 2–3 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)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A FAMILY HISTORY OF CANCER?

	Sens	Spc	LR+	LR–
Accuracy of self-reported family history of cancer in a first-degree relative by healthy individuals				
Colon cancer	53–86%	92–99%	23	0.25
Breast cancer	82%	91%	8.9	0.20
Endometrial ca	33%	98%	14	0.68
Ovarian cancer	50%	99%	34	0.51
Prostate cancer	70%	94%	12.3	0.32
Accuracy of self-reported family history of cancer in a first-degree relative by cancer patients				
Colon cancer	57–90%	96–99%	23	0.29
Breast cancer	85–98%	96–99%	41	0.07
Endometrial ca	29–56%	97–98%	20	0.55
Ovarian cancer	67–83%	96–99%	44	0.21
Prostate cancer	69–79%	93–99%	24	0.21

HEREDITARY NON-POLYPOSIS COLON CANCER (HNPCC) GENETIC TESTING CRITERIA (FOR PREMENOPAUSAL WOMEN ≤50 YEARS)

(1) at least three relatives must have a cancer associated with HNPCC (colon, endometrial, ovarian, stomach, small bowel, hepatobiliary, ureter, renal pelvis, brain)
(2) one should be a first-degree relative of the other 2. At least two successive generations should be affected
(3) at least one of the relatives with cancer associated with HNPCC should have received the diagnosis before age 50 years

HEREDITARY BREAST/OVARIAN CANCER GENETIC TESTING CRITERIA

(1) two breast cancers in a first- or second-degree relative and mean age at diagnosis of 40 years
(2) one breast cancer and one ovarian cancer in a first- or second-degree relative and mean age at diagnosis of 41–50 years
(3) two or more breast cancers and one ovarian cancer in a first- or second-degree relative
(4) ovarian cancer in two relatives

APPROACH—"patient-reported family cancer histories for first-degree relatives are accurate and valuable for breast and colon cancer risk assessments. Negative family history reports for ovarian and endometrial cancers are less useful, although the prevalence of these malignancies within families is low"

JAMA 2004 292:12

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 (19% by age 40, 50% by age 50, 85% by age 70), ovarian (14–45% lifetime risk), prostate (8–16%), colon (6%)	Breast (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	
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**—tamoxifen or raloxifene are not 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's 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 colonoscopy every 1–2 years starting at 20–25 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 U/S) 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-oopherectomy at around age 35 or at the end of childbearing

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

GENETICS—autosomal dominant, 5q21–q22

PATHOPHYSIOLOGY—adenomatosis polyposis coli (APC) gene, a tumor suppressor gene that 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's syndrome)

FEATURES—colon polyps (more than 100), duodenal adenomatous polyps, extraintestinal manifestations

FAMILIAL ADENOMATOUS POLYPOSIS (FAP) (CONT'D)

(Gardner's syndrome) such as desmoid tumors, sebaceous or epidermoid cysts, lipomas, osteomas, supernumerary teeth, gastric polyps ,and juvenile nasopharyngeal angiofibromas

SURVEILLANCE (all at-risk family member)—sigmoidoscopy or colonoscopy annually starting age 10–12. Upper endoscopy. 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

Antineoplastic Agents

Chemotherapeutic agents	Activity[a]	Myelo. supp.	Emetogenic risk	Alopecia	Other major toxicities[b]	Dose modification[c]
Alkylating agents						
Cyclophosphamide (Cytoxan, IV/PO)	BR, GYN, NHL, BMT	+++	++(+)	+++	**Hemorrhagic cystitis**, muco, sterility	Renal, hepatic
Ifosfamide (IV)	T, SA, NHL	+++	++	+++	**Hemorrhagic cystitis**, neuro	Renal
Melphalan (PO)	MM, BMT	++	+	+	Mucositis, sterility	Renal
Chlorambucil (PO)	NHL, CLL	++	–	+	Mucositis, sterility	–
Bulsulfan (PO)	BMT	+++	+	++	Pulmonary	Renal
Carmustine (BCNU, IV)	CNS, NHL	+++	+++	+	Pulmonary, renal, muco, diarrhea, LFT	Renal
Lomustine (CCNU, PO)	CNS, NHL	+++	++	++	Pulmonary, renal, muco, diarrhea, LFT	Renal
Dacarbazine (DTIC, IV)	NHL, melanoma, SA	++	+++	+	Flu-like symptoms, LFT, photo	Renal, hepatic
Temozolomide (PO)	CNS, melanoma	++	++	+	Photosensitivity	Renal, hepatic
Streptozocin (IV)	Carcinoid, islet cell	+	+++	+	**Renal**, diarrhea, LFT, hypoglycemia	Renal
Antimetabolites						
Methotrexate (IV/PO)	ALL, chorio, leptomeningeal	++	+	+	**Muco**, diarrhea, LFT, **renal**, pulm, neuro	Renal, hepatic
Pemetrexed (IV)	LU, mesothelioma, BR	++	+	+	**Mucositis**, diarrhea, hand–foot	Renal
Raltitrexed (IV)	GI, BR	++	+	+	Mucositis, diarrhea, LFT, **fatigue**	Renal
5-Fluorouracil (IV)	GI, BR	+	+	++	Muco, **diarrhea**, hand–foot, cerebellar	Hepatic
Capecitabine (xeloda, PO)	GI, BR	++	+	+	Muco, **diarrhea**, LFT, hand–foot, neuro	Renal
Cytosine arabinoside (Ara-C, IV)	ALL, NHL, leptomeningeal	+++	+(+)	++	Mucositis, diarrhea, **cerebellar**	Renal, hepatic, neuro
Gemcitabine (IV)	GI, LU, BR, NPC, bladder	++	+	++	Diarrhea, LFT, flu-like, rash	Renal, hepatic
Hydroxyurea (PO, IV)	AML, CML	++	+	+	Mucositis, rash	Renal
6-Thioguanine (6-TG, IV)	AML	++	+	+	Mucositis, diarrhea, LFT	Hepatic
6-Mercaptopurine (6-MG, IV)	ALL	++	+	+	Mucositis, diarrhea, LFT	Renal, hepatic
Fludarabine (IV, PO)	NHL, CLL	++	+	+	Neuro, AIHA, LFT	Renal
2-Chlorodeoxyadenosine (cladribine, IV)	NHL, hairy cell leukemia	++	+	+	Constipation, fever	–
Topoisomerase inhibitors						
Doxorubicin (hydroxydaunomycin, IV)	BR, SA	+++	++	+++	**Cardiac**	Hepatic
Doxorubicin (liposomal, IV)	KS, OV	++	+	+++	**Cardiac**, infusion, skin	Hepatic
Daunorubicin (IV)	AML, neuroblastoma	+++	++	+++	**Cardiac**	Hepatic
Idarubicin (PO)	AML	+++	++	+++	Cardiac (less)	Hepatic, renal
Epirubicin (IV)	BR	+++	++	+++	Cardiac	Hepatic
Mitoxantrone (IV)	AML, BR, prostate	++	+	+	Cardiac, LFT	Hepatic
Etoposide (IV/PO)	LU, T, NHL	++	+	+++	Neuro, LFT	Hepatic, renal
Topotecan (IV)	OV, LU	+++	+	+++	Diarrhea, constipation, fever	Renal
Irinotecan (IV)	GI, LU, GYN	++	+	+++	**Diarrhea**, constipation, fever	Hepatic
Platinating agents						
Cisplatin (IV)	Bladder, LU, T, OV	++	+++	+	**Renal, neuro, ototoxicity**	Renal, neuro
Carboplatin (IV)	Bladder, LU, T, OV	++	++	+	Renal, neuro, ototoxicity (less)	Renal
Oxaliplatin (IV)	GI	+	++	+	**Neuro**, diarrhea	Neuro, renal
Antimicrotubular agents						
Vincristine (oncovin, IV)	NHL	–	+	++	**Neuro**, constipation	Hepatic, neuro
Vinblastine (IV)	T, NHL	++	+	++	Cramps, neuro, constipation	Hepatic, neuro
Vinorelbine (navelbine, IV)	LU, BR	++	+	+++	Neuro, constipation, diarrhea	Hepatic
Docetaxel (taxotere, IV)	BR, LU, prostate, OV	++	+	+++	Infusion, neuro, nails, myalgia, arthralgia, **edema**	Hepatic
Paclitaxel (taxol, IV)	BR, LU, prostate, OV	++	+	+++	Neuro, nails, myalgia, arthralgia	Hepatic, neuro

Antineoplastic Agents (Cont'd)

Chemotherapeutic agents	Activity[a]	Myelo. supp.	Emetogenic risk	Alopecia	Other major toxicities[b]	Dose modification[c]
Others						
Bleomycin (IV)	Testicular	+	+	++	Pulmonary, hemorrhagic cystitis	Renal
Mitomycin C (IV)	GI, BR, GU	+++	+	+	Pulmonary, HUS, GU irritation	Renal

[a] BR=breast, chorio=choriocarcinoma, BMT=bone marrow transplant, CML=chronic myelogenous leukemia, CNS=brain tumor, GI=gastrointestinal, GIST=gastrointestinal stromal tumor, GYN=gynecological, KS=Kaposi sarcoma, LU=lung, OV=ovarian, MM=multiple myeloma, NHL=non-Hodgkin's lymphoma, NPC=nasopharyngeal carcinoma, SA=sarcoma, T=testicular, TCL=T-cell lymphoma

[b] LFT=elevated liver enzymes/hepatic dysfunction, muco=mucositis, photo=photosensitivity

[c] Dose modification may be required for **dose-limiting toxicities** (in **bold**) and also potentially renal and hepatic dysfunction

Hormonal and targeted agents	Activity	Cytopenia	Other major toxicities
Monoclonal antibodies			
Alemtuzumab (Campath)—anti-CD52 (SC/IV)	NHL, TCL	+++	Infusion rx'n, infections (e.g. CMV, HSV, TB, fungal), pancytopenia
Bevacizumab (Avastin)—anti-VEGF (IV)	GI	–	Infusion rx'n, HTN, bleed, thrombosis, GI perforations, proteinuria
Cetuximab (Erbitux)—anti-EGFR (IV)	GI, H&N	–	Infusion rx'n, rash, nail/hair changes, mucositis, diarrhea, hypomagnesemia
Gemtuzumab (Mylotarg)—anti-CD33 (IV)	AML	+++	Infusion rx'n, N&V, diarrhea, fever, LFT
Panitumumab (Vectibix)—anti-EGFR (IV)	GI	–	Rash, nail/hair changes, mucositis, diarrhea, hypomagnesemia
Rituximab (Rituxan)—anti-CD20 (IV)	NHL	+	Infusion rx'n, infections (e.g. JC virus, CMV, PJP), cardiac arrhythmia
Trastuzumab (Herceptin)—anti-Her2 (IV)	BR	–	Infusion rx'n, cardiomyopathy
Tyrosine kinase inhibitors			
Sunitinib (Sutent)—VEGFR inhibitor (PO)	Renal, GIST	+	Fatigue, diarrhea, acral erythema, nail/hair changes, HTN, bleed, hypothyroidism, hypophosphatemia
Sorafenib (Nexavar)—VEGFR inhibitor (PO)	Renal, liver	+	Fatigue, diarrhea, acral erythema, nail/hair changes, HTN, bleed, hypothyroidism, hypophosphatemia
Imatinib (Gleevec)—bcr/abl, c-kit inhibitor (PO)	CML, GIST	+	Periorbital edema, nausea, diarrhea, muscle cramps, bowel perforation, fatigue
Erlotinib (Tarceva)—EGFR inhibitor (PO)	Lung	–	Rash, nail/hair changes, mucositis, diarrhea, interstitial lung dx
Gefitinib (Iressa)—EGFR inhibitor (PO)	Lung	–	Rash, nail/hair changes, mucositis, diarrhea, interstitial lung dx
LHRH agonists			
Goserelin (Zoladex) (IM)	Prostate, BR	–	Hot flashes, mood changes, sexual dysfunction, diarrhea, anemia, loss of muscle mass, osteoporosis
Leuprolide (Lupron) (IM)	Prostate, BR	–	
Selective estrogen receptor modulators			
Tamoxifen (Nolvadex)	BR	–	Hot flashes, mood Δ, vaginal dryness/discharge, thromboembolism, hypercalcemia, endometrial cancer
Aromatase inhibitors			
Anastrozole (Arimidex)—non-steroidal (PO)	BR	–	Hot flashes, mood Δ, arthralgia, vaginal dryness and discharge, osteoporosis for all aromatase inhibitors
Letrozole (Femara)—non-steroidal (PO)	BR	–	
Exemestane (Aromasin)—steroidal (PO)	BR	–	
Other hormonal agents			
Bicalutamide (Casodex)—anti-androgen (PO)	Prostate	–	Hot flashes, mood changes, sexual dysfunction, diarrhea, anemia, loss of muscle mass, osteoporosis
Flutamide (Eulexin)—antiandrogen (PO)	Prostate	–	
Finasteride (Proscar)—α5 reductase inhibitor	Prostate	–	Postural hypotension, sexual dysfunction, dizziness
Megestrol (Megace)—progestin (PO)	BR, endometrial	–	Vaginal bleed and irregularities, nausea, weight gai
Fulvestrant (Faslodex)—ER blocker (PO)	BR	–	Hot flashes, nausea, diarrhea, back pain, pharyngitis
Others			
Thalidomide (Thalomid)—anti-angiogenic (PO)	Myeloma	++	Sedation, fatigue, constipation, rash, peripheral neuropathy, thromboembolism
Bortezomib (Velcade)—proteasome inhibitor (IV)	Myeloma, NHL	++	GI symptoms, fatigue, cytopenia, peripheral neuropathy
Interferon—immune modulatory (IV)	Melanoma, renal	++	Fatigue, fever, myalgia, LFT, mood changes
Temsirolimus (Torisel)—mTOR inhibitor (IV)	Renal	+	Rash, mucositis, fatigue, hyperglycemia, hypophosphatemia, hypertriglyceridemia

Oncologic Emergencies

INFUSION REACTIONS

TREAT UNDERLYING CAUSE—stop infusion
ABC—**O_2** to keep sat >94%, *salbutamol* 2 puffs INH q1h PRN, *ipratropium* 2 puffs INH q6h PRN. ***Diphenhydramine*** 50 mg IV ×1 dose, ***hydrocortisone*** 100 mg IV ×1 dose. **If hypotensive**, give normal saline 500–1000 mL IV bolus and consider *epinephrine* 0.1–0.25 mg slow IV push (1 mg in 10 mL of NS, give 1–2.5 mL). May restart chemotherapy slowly for most drugs (infusion at 25% rate ×5 min, then 50% rate ×5 min, then 75% rate ×5 min, then complete infusion at 100% rate)
PROPHYLAXIS (before treatment)—*dexamethasone* 20 mg PO 12 h and 6 h prior and 10 mg IV 30 min prior, *diphenhydramine* 50 mg IV 30 min prior, *ranitidine* 50 mg IV over 10 and 30 min prior, *ephedrine* 30 mg PO 30 min prior. See p. 372 for more details on anaphylaxis

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's lymphoma, multiple myeloma, cancer of unknown primary, colorectal cancer, sarcoma
CLINICAL FEATURES—**back pain** (particularly may worsen with recumbency), **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's sign**, **retention/incontinence** (urinary, bowel), **gait ataxia**
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, bone scan, CT, MRI). MRI and myelogram are best. Strongly consider imaging of T- and L-spine regardless of clinical findings
TREATMENTS—**corticosteroid** (*dexamethasone* 10 mg IV/PO ×1 dose, then 8 mg IV/PO BID. **Treat underlying cause urgently** (radiation ± radical resection, chemotherapy for chemosensitive tumors)

MALIGNANT CAUDA EQUINA SYNDROME

PATHOPHYSIOLOGY—compression of lumbosacral nerves roots (lower motor neurons, mostly below L1 level)
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 of blood within the SVC. Venous collaterals establish alternative pathways, 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), 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 or refractory disease

NEJM 2007 356:18

Related Topics
Febrile Neutropenia (p. 236)
Spinal Cord Compression (p. 228)

HYPERCALCEMIA

PATHOPHYSIOLOGY—local osteolytic hypercalcemia 20% (cytokines), humoral hypercalcemia of malignancy 80% (PTHrP), 1,25$(OH)_2$vitD-secreting lymphomas, and ectopic hyperparathyroidism (PTH) are all known mechanisms. Median survival of 1 month post-presentation with hypercalcemia

CLINICAL FEATURES—bony pain, abdominal pain, constipation, polyuria, renal failure, renal stones, confusion

DIAGNOSIS—Ca, PO_4, albumin, PTH, 1,25$(OH)_2$vitD, bone scan

SYMPTOM CONTROL—NS 200–500 mL/h IV ± ***furosemide*** 20–40 mg IV TID PRN. 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), **steroids** (*prednisone* 60 mg PO daily ×10 days, *hydrocortisone* 200–500 mg IV daily), ***plicamycin*** 25 μg/kg in 1 L NS over 4–6 h, ***calcitonin*** 200U SC/IM BID

TREAT UNDERLYING CAUSE

See HYPERCALCEMIA for more details (p. 353)

NEJM 2005 352:4

TUMOR LYSIS SYNDROME

PATHOPHYSIOLOGY—treatment-induced lysis of tumor cells, leading to release of cell contents → hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, 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 (aggressive lymphomas, ALL, AML, solid tumors)

DIAGNOSIS—a clinical diagnosis with a combination (but not necessary 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 PO_4 (>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 and consider rasburicase (promotes uric acid degradation). Monitor urine output, K, Ca, PO_4, Cr, uric acid, and LDH q6h. Treatment of uric acid nephropathy with aggressive hydration, furosemide diuresis, rasburicase, and dialysis as a last resort

Febrile Neutropenia

See FEBRILE NEUTROPENIA (p. 236)

Chemotherapy-Induced Nausea and Vomiting

NEJM 2008 358:23; JCO 2006 24:18

PATHOPHYSIOLOGY

REFLEX PATHWAY—see p. 111

RISK FACTORS—female, <50 years, previous treatment-related nausea and vomiting, concomitant radiation, and chemotherapy. Alcohol use predicts lower likelihood of chemotherapy-induced nausea and vomiting (CINV)

NCI-CTC GRADING V4.0

Grade	Nausea
1	Loss of appetite without alteration in eating habits
2	Oral intake decreased without significant weight loss, dehydration, or malnutrition
3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
4	Not applicable

Grade	Vomiting
1	1–2 episodes (separated by 5 min) in 24 h
2	3–5 episodes in 24 h
3	≥6 episodes in 24 h; tube feeding, TPN, or hospitalization indicated
4	Life-threatening consequences; urgent intervention required

Related Topic
Nausea and Vomiting (p. 111)

EMETOGENIC LEVELS OF INTRAVENOUSLY ADMINISTERED ANTINEOPLASTIC AGENTS

HIGH RISK (>90%)—carmustine, cisplatin, cyclophosphamide (>1.5 g/m^2), dacarbazine, mechlorethamine, streptozocin

MODERATE RISK (31–90%)—carboplatin, cyclophosphamide (≥1.5 g/m^2), cytarabine (>1 g/m^2), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin

LOW RISK (10–30%)—bortezomib, cetuximab, cytarabine (≥1 g/m^2), docetaxel, etoposide, fluorouracil, gemcitabine, ixabepilone, lapatinib, methotrexate, mitomycin, mitoxantrone, paclitaxel, pemetrexed, topotecan, temsirolimus, trastuzumab

MINIMAL RISK (<10% risk of CINV in the absence of antiemetic prophylaxis)—bevacizumab, bleomycin, busulfan, cladribine, fludarabine, vinblastine, vincristine, vinorelbine

MANAGEMENT

PREVENTION IS KEY

ANTICIPATORY NAUSEA AND VOMITING (–3 to –4 h)—consider use of distraction and benzodiazepines

ACUTE NAUSEA AND VOMITING (0 – 24 h)—5HT3 antagonists and steroids are key. NK1 antagonists may be added for patients on highly emetogenic chemotherapy

DELAYED NAUSEA AND VOMITING (>24 h)—associated with cisplatin, cyclophosphamide, ifosfamide at higher doses and doxorubicin. NK1 antagonists, 5HT3 antagonists, and steroids are all effective

CHRONIC NAUSEA AND VOMITING—unlikely to be due to chemotherapy alone. Multi-factorial interventions required. Avoid long-term use of 5HT3/NK1 antagonists

MANAGEMENT (CONT'D)

TREATMENT OVERVIEW FOR PREVENTING ACUTE AND DELAYED CINV

Risk	NK1 antagonist	5HT3 antagonist	Steroid	Etc[a]
High[b]	✓	✓	✓	✓
Moderate		✓	✓	✓
Low			✓	✓
Minimal				✓

[a]choices include *metoclopramide* 10 mg PO q4h PRN and *prochlorperazine* 10 mg PO q4h PRN

[b]highly emetogenic chemotherapy or doxorubicin/cyclophosphamide (AC) combination chemotherapy

TREATMENT ISSUES

HIGH-RISK CHEMOTHERAPY OR AC COMBINATION CHEMOTHERAPY—*aprepitant* 125 mg PO on day 1, then 80 mg PO days 2–3, PLUS *ondansetron* 8–12 mg IV or 16–24 mg PO on day 1, PLUS *dexamethasone* 12 mg PO/IV on day 1, then 8 mg PO days 2–4 PLUS *metoclopramide* 10 mg PO q4h PRN or *prochlorperazine* 10 mg PO q4h PRN

MODERATE-RISK CHEMOTHERAPY—*ondansetron* 8 mg IV or 8 mg PO BID on day 1, then 8 mg PO BID on days 2–3, PLUS *dexamethasone* 12 mg PO/IV on day 1, then 8 mg PO or 4 mg PO BID days 2–3 PLUS *metoclopramide* 10 mg PO q4h PRN or *prochlorperazine* 10 mg PO q4h PRN

LOW-RISK CHEMOTHERAPY—*dexamethasone* 8 mg PO/IV day 1 PLUS *metoclopramide* 10 mg PO q4h PRN or *prochlorperazine* 10 mg PO q4h PRN

LOW, RISK CHEMOTHERAPY—*metoclopramide* 10 mg PO q4h PRN or *prochlorperazine* 10 mg PO q4h PRN

NOTE—for patients with significant nausea and vomiting despite proper oral antiemetic use, consider admission for intravenous hydration and medication administration

Oral Mucositis

PATHOPHYSIOLOGY

RISK FACTORS FOR ORAL MUCOSITIS

- **PERSONAL**—younger age, poor oral hygiene, smoking, alcohol use
- **CHEMOTHERAPY**—bleomycin, capecitabine, chlorambucil, cytarabine, doxorubicin, etoposide, methotrexate, vinblastine, 5-fluorouracil
- **TARGETED AGENTS**—RAD001
- **RADIATION**—head and neck region

COMPLICATIONS OF ORAL MUCOSITIS—severe pain, bleeding, superinfections (bacteremia, febrile neutropenia)

NCI-CTC GRADING V4.0

Grade	Oral mucositis
1	Asymptomatic or mild symptoms; intervention not indicated
2	Moderate pain; not interfering with oral intake; modified diet indicated
3	Severe pain; interfering with oral intake
4	Life-threatening consequences; urgent intervention indicated

MANAGEMENT

CRYOTHERAPY—sucking on ice chips during chemotherapy is a reasonable preventative strategy for patients on 5-fluorouracil, edatrexate, or high-dose melphalan

ORAL HYGIENE—soft tooth brush, flossing, mouth rinses q4h (0.9% saline, baking soda, or salt and baking soda solution by mixing one teaspoon of baking soda and half teaspoon of salt in 1/L of water), denture care (if applicable)

DOSE ADJUSTMENTS—dose reduction or treatment termination may be considered in severe cases

SUPPORTIVE MEASURES—ensure adequate hydration and monitor nutritional intake. Assess patients for diarrhea as well. Providing optimal pain control is key

MANAGEMENT (CONT'D)

- **TOPICAL ANALGESIA**
  - **MAGIC/MIRACLE MOUTHWASH**—generally includes lidocaine for pain control. For a 100 mL solution, mix hydrocortisone 25 mg, glycerin 95% 2 mL, normal saline 52 mL, lidocaine 2% 25 mL, and nystatin 2083,300 IU or 20.833 mL. Use 10 mL squish and spit q4h–q6h
  - **MORPHINE SULFATE MOUTHWASH**—2 mg/mL in 15 mL of water, swish and spit, q4h to q6h
  - **LIDOCAINE VISCOUS 2%**—10 mL, swish and spit, q4h PRN
- **SYSTEMIC OPIOIDS**—morphine 5 mg IV q4h PRN or 10 mg PO q4h PRN, titrating up as needed
- **INFECTIONS**—**oral candidiasis** (*nystatin* 500,000 IU swish and swallow QID, clotrimazole troches, or fluconazole), **HSV infections** (acyclovir or valacyclovir after cultures taken)

Chemotherapy-Induced Diarrhea JCO 2004 22:14

PATHOPHYSIOLOGY

RISK FACTORS FOR CHEMOTHERAPY-INDUCED DIARRHEA

- **CHEMOTHERAPY**—5-fluorouracil, capecitabine, irinotecan (active metabolite SN 30), cisplatin, docetaxel, paclitaxel, doxorubicin, cyclophosphamide, methotrexate, cytosine arabinoside, and topotecan
- **TARGETED AGENTS**—imatinib, erlotinib, sunitinib, sorafenib

NCI-CTC GRADING V4.0

Grade	Chemotherapy-Induced Diarrhea
1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline
2	Increase of 4–6 stools per day over baseline; moderate increase in ostomy output compared to baseline
3	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization; severe increase in ostomy output compared to baseline; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated

MANAGEMENT

DOSE ADJUSTMENTS—dose reduction or treatment termination may be considered in severe cases

FIRST LINE—*loperamide* 4 mg PO, followed by 2 mg every 2 h (or 4 mg every 4 h) until 12 h has elapsed without any diarrhea

SECOND LINE—*octreotide* 100–150 μg SC as needed. Octreotide is a somatostatin analogue that decreases both intestinal transit time and fluid secretion into the small intestine

NOTE—ensure adequate hydration and assess other related symptoms such as oral mucositis, nausea, and vomiting. Remember to stop all laxatives

Notes

8

INFECTIOUS DISEASES

Section Editor: Dr. Mark Joffe

Fever of Unknown Origin

Infect Dis Clin North Am 2007;21:4

DIFFERENTIAL DIAGNOSIS

This list is not exclusive, but highlights some important causes of FUO after the common causes of fever have been excluded:

INFECTIONS—**TB** (pulmonary, extrapulmonary, miliary), **abscess** (liver, splenic, perinephric, psoas, diverticular, pelvis), **osteomyelitis**, **endocarditis**

NEOPLASTIC—**hematologic** (lymphoma, leukemia, multiple myeloma, myelodysplastic syndrome), **solid tumors** (renal cell, hepatoma)

COLLAGEN-VASCULAR—**vasculitis** (giant cell arteritis, Still's disease, polyarteritis nodosa, Takayasu's arteritis, Wegener's granulomatosis, mixed cryoglobulinemia), **lupus**, **rheumatoid arthritis**

DRUGS—**antimicrobials** (sulfonamides, penicillins, nitrofurantoin, antimalarials), **antihistamines**, **antiepileptics** (barbiturate, phenytoin), **NSAIDs/ASA**, **antihypertensives** (hydralazine, methyldopa), **antiarrhythmics** (quinidine, procainamide), **antithyroid**, **iodides**, **quinine**, **illicit** (cocaine)

UNCOMMON CAUSES OF FUO—central fever, **endocrine** (hypothalamic dysfunction, hyperthyroidism, pheochromocytoma, adrenal insufficiency), **infections** (dental abscess, Q fever, leptospirosis, psittacosis, tularemia, melioidosis, syphilis, gonococcemia, chronic meningococcemia, Whipple's disease, yersiniosis, brucellosis), **hereditary periodic fever syndromes** (familial Mediterranean fever, PFAPA syndrome [Periodic Fever with Aphthous Stomatitis and Adenitis], TNFR-1-associated periodic syndrome, hyper-IgD syndrome, Muckle–Wells syndrome, familial cold autoinflammatory syndrome), **alcoholic hepatitis**, **hematoma**, **factitious fever**

PATHOPHYSIOLOGY

DEFINITIONS

- FEVER OF UNKNOWN ORIGIN **(FUO)**
  - CLASSIC DEFINITION **(1961)**—≥38.3°C [≥101°F], duration ≥3 weeks, diagnosis uncertain after 7 days of investigation in hospital

PATHOPHYSIOLOGY (CONT'D)

- NEW DEFINITIONS
  - **FUO**—≥38.3°C [≥101°F], duration ≥3 weeks, diagnosis uncertain after 3 days in hospital or three outpatient visits
  - NOSOCOMIAL **FUO**—hospitalized patients, ≥38.3°C [≥101°F], diagnosis uncertain after 3 days and infection not present or incubating on admission
  - IMMUNE-DEFICIENT **(NEUTROPENIC) FUO**—>38.3°C [≥101°F], >3 days, neutrophil count ≤500/mm^3. See p. 234 for details
  - **HIV-RELATED FUO**—HIV patients, ≥38.3°C [≥101°F], duration ≥3 weeks for outpatients or ≥3 days for inpatients
- FEVER, **NYD**—persistent fever that has not yet met the definition for FUO

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—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, CK, serum protein electrophoresis, urinalysis, ESR, CRP, ANA, ENA, RF, C3, C4, ANCA, cryoglobulin

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_8,

INVESTIGATIONS (CONT'D)

- **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

SPECIAL

- **ECG**
- **TUBERCULIN SKIN TEST**
- **BIOPSY**—affected tissue

DIAGNOSIS AND PROGNOSTIC ISSUES

DIAGNOSIS—the most important diagnostic strategy is a careful history and physical examination with frequent reassessment

PROGNOSIS—up to 30–50% will not have a diagnosis despite detail workup; adults who remain undiagnosed have good prognosis

MANAGEMENT

EMPIRIC ANTIBIOTICS—ONLY if suspect infectious etiology and therapy cannot be delayed due to severity of patient's disease (see EMPIRIC ANTIBIOTICS p. 257). In general, therapeutic trials of antimicrobials or steroids are discouraged

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**—meningococcemia (purpura), disseminated gonococcal infection
- **GRAM-NEGATIVE BACILLI**—*Salmonella typhi, Pseudomonas* (ecythema gangrenosum), *Vibrio vulnificus*
- **ENDOCARDITIS**
- **SPIROCHETES**—*Borrelia burgdorferi* (Lyme erythema migrans), *Treponema pallidum* (chancre, secondary syphilis)
- **RICKETTSIAL**—Rocky Mountain spotted fever, ehrlichiosis, typhus
- **VIRAL EXANTHEM**—acute HIV, mononucleosis, rubella, measles, roseola, erythema infectiosum, chickenpox, shingles, coxsackie virus, echovirus
- **FUNGAL**—Blastomyces, Coccidioides, Histoplasma

RHEUMATOLOGIC

- **SEROPOSITIVE**—lupus, dermatomyositis
- **SERONEGATIVE**—inflammatory bowel disease, reactive arthritis
- **VASCULITIS**—Wegener's, polyarteritis nodosa
- **BEHCET'S DISEASE**

MALIGNANCY—lymphoma, leukemia, metastatic, paraneoplastic

MEDICATIONS—penicillins, cephalosporins, sulfas, barbiturates, phenytoin, procainamide, quinidine

OTHERS—sarcoidosis, erythema nodosum; Sweet's 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
- **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

CLINICAL FEATURES (CONT'D)

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**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, ESR, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S, monospot test, CMV IgM, EBV, HIV, and other serologies

SPECIAL

- **LUMBAR PUNCTURE**—if suspect meningococcus
- **SKIN BIOPSY**—dermatology consult
- **INFLAMMATORY WORKUP**—CRP, ANA, ENA, RF

MANAGEMENT

ISOLATION PRECAUTIONS—droplet/airborne plus contact precautions for uncertain diagnosis; for purpura with bacterial sepsis, institute droplet and contact isolation precautions. See p. 269 for more details

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

RICKETTSIAL INFECTIONS (WITHIN NORTH AMERICA)

- **THEMES**—all transmitted by ticks, except Q fever. 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 can be treated with doxycycline
- **ROCKY MOUNTAIN SPOTTED FEVER**—*Rickettsia rickettsii* transmitted by ticks. Most common in mid-Atlantic states. Rash begins on extremities and moves centrally. Treat with doxycycline
- **MURINE TYPHUS**—flea vector. Rash begins centrally and moves peripherally. Treat with doxycycline or chloramphenicol
- **EHRLICHIA**—*E. 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 one-third. Human granulocytic anaplasmosis is caused by a related *Ehrlichia* and produces similar illness without rash. Transmitted by Ixodes tick and co-infection with Lyme disease possible. Treat with doxycycline
- **Q FEVER**—*Coxiella burnetii* transmitted by respiratory spread from infected animal body fluids (e.g. cattle, sheep, goats, cats). No rash. Fever, pneumonitis, hepatitis, endocarditis, CNS symptoms. Treat with doxycycline

SPECIFIC ENTITIES (CONT'D)

LYME DISEASE

- **PATHOPHYSIOLOGY**—*Borrelia burgdorferi* transmitted by 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

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ERYTHEMA MIGRANS?

	Sens
History (US studies)	
Systemic symptoms	65%
Fatigue	47%
Headache	36%
Myalgias	35%
Arthralgias	35%
Fever	33%
Pruritus	33%
Stiff neck	31%
History of a tick bite	26%
Dysesthesia	20%
Nausea and vomiting	11%
Physical (US studies)	
Solitary lesion	81%
Lymphadenopathy	22%
Multiple lesions	21%
Central clearing of rash	19%

APPROACH—"no single component of the history or physical examination emerges as one that makes the diagnosis of erythema migrans highly likely. These signs and symptoms have not been examined in combination. Laboratory testing has limited utility. In endemic areas, the combination of history of a tick bite, a solitary lesion of appropriate size, morphology and presence of systemic symptoms is consistent with erythema migrans. In non-endemic areas, these same factors are also suggestive of this diagnosis and should prompt further investigation"

JAMA 2007 297:23

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—seology (anti-B. burgdorferi ELISA). If positive, confirm with Western blot
- **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, amoxicillin)
- **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

SPECIFIC ENTITIES (CONT'D)

BABESIOSIS (malaria like; does not cause rash)

- **PATHOPHYSIOLOGY**—*B. microti* (USA) or *B. 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**—endemic in southern New England, southern New York, Wisconsin, and Minnesota
- **DIAGNOSIS**—blood smear, PCR, serology
- **TREATMENTS**—atovaquone plus azithromycin

Related Topic
Exanthematous Lesions (p. 364)

Fever and Joint Pain

See JOINT PAIN AND FEVER (p. 276)

Sepsis

See SEPSIS (p. 97)

Febrile Neutropenia — IDSA Guidelines 2002

DIFFERENTIAL DIAGNOSIS

BACTERIAL

- **GRAM POSITIVE**—*S. aureus*, coagulase-negative staphylococci, *Streptococcus pneumoniae*, corynebacterium
- **GRAM NEGATIVE**—*Enterobacter, Escherichia. coli, K. pneumoniae, Pseudomonas, C. difficile,* anaerobes
- **TB**

VIRAL—HSV, VZV, CMV, EBV, HHV6, enterovirus, RSV

FUNGAL—Candida, Aspergillus, Cryptococcus, Fusarium

REACTIVATION OF LATENT INFECTION—Histoplasma, Coccidioides, Toxoplasma, Tuberculosis

PATHOPHYSIOLOGY

DEFINITION—single temp >38.3°C [101°F] or >38°C [100.4°F] for >1 h, ANC $<0.5\times10^9$/L or $<1.0\times10^9$/L + expected nadir $<0.5\times10^9$/L

PATHOPHYSIOLOGY (CONT'D)

ABSOLUTE NEUTROPHIL COUNT (ANC)—neutrophils + bands

PATHOGENESIS—chemotherapy-induced injury to mucosal barriers, immune defects due to drugs or underlying disease and invasive devices. With the 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. Digital rectal examination is not recommended as potential rectal tear

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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

SPECIAL

- **SINUS X-ray**

MANAGEMENT

LOW RISK (ANC $>0.1\times10^9$/L, peak temperature $<39^\circ$C [102.2°F], no significant symptoms or signs, no significant comorbidities, nearly normal renal and hepatic function, neutropenia <7 days)—*ciprofloxacin* 500 mg PO BID + *amoxicillin–clavulanate* 500 mg PO q8h. May send home with follow-up

HIGH RISK—admit for intravenous antibiotics

- **FIRST LINE**—one of *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, *piperacillin* 3 g IV q4h plus *tobramycin* 2–2.5 mg/kg IV q8h, *clindamycin* 600 mg IV q8h plus *tobramycin* 7 mg/kg IV q24h, or *piperacillin/tazobactam* 4.5 g IV q8h plus *gentamicin* 2–2.5 mg/kg IV q8h
- **SECOND LINE**—add ***vancomycin*** 1 g IV q12h if suspect line infection, known colonization MRSA, Gram-positive blood culture, or hypotension
- **THIRD LINE**—add **antifungal** if febrile after 5 days (*fluconazole* 400 mg IV daily, *itraconazole* 200 mg IV daily, *amphotericin B* 0.5–1 mg/kg IV daily over 4 h, *caspofungin* 70 mg on first day followed by 50 mg IV daily)

GCSF SUPPORT—see TREATMENT ISSUES below

MANAGEMENT (CONT'D)

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
  - **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 $\geq0.5\times10^9$/L for 2 consecutive days, afebrile for ≥48 h, cultures negative, and no obvious signs of infection, or if (2) ANC $<0.5\times10^9$/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 $\geq0.5\times10^9$/L for 4–5 consecutive days
  - **CONTINUE ANTIBIOTICS**—if ANC $<0.5\times10^9$/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—*meperidine* 50 mg IV, *acetaminophen* 2 tabs PO, *hydrocortisone* 25 mg IV 30 min before dose, and repeat ×1 1–2 h after administration

ASCO 2006 GUIDELINE FOR GCSF USE

- **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 (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

TREATMENT ISSUES (CONT'D)

primary prophylaxis was not received), in which a reduced dose may compromise disease-free survival overall survival, or treatment outcome

- **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 ($<0.1\times10^9$/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

J Clin Oncol 2006 24:19

SPECIFIC ENTITIES

NECROTIZING ENTEROCOLITIS (typhlitis)

- **PATHOPHYSIOLOGY**—mucosal injury in patients with profound neutropenia → impaired host defense → 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
- **TREATMENTS**—bowel rest, NG suction, IV fluids, nutritional support, broad spectrum antibiotics (including metronidazole for *C. difficile* and amphotericin B/fluconazole for fever >72 h), GCSF. Surgical indications include peritonitis, perforation, persistent GI bleeding, or clinical deterioration

Related Topics
Chemotherapy (p. 226)
Neutropenia (p. 148)
Sepsis (p. 97)
Stem Cell Transplant (p. 180)

Fever with Travel History

NEJM 2002 347:7
http://www.cdc.gov

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**—coccidioidomycosis
- **PARASITIC**—malaria, angiostrongyliasis, trypanosomiasis

FEVER WITH RESPIRATORY INVOLVEMENT

- **BACTERIAL**—*S. pneumoniae*, mycoplasma, Legionella, Q fever, typhoid fever, scrub typhus
- **MYCOBACTERIAL**—tuberculosis
- **VIRAL**—influenza, parainfluenza, metapneumovirus, respiratory syncytial virus, adenovirus, dengue
- **FUNGAL**—histoplasmosis, coccidioidomycosis

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **PARASITIC**—malaria, Loeffler's syndrome (migration of larval helminths such as ascaris, strongyloides, and hookworm)

FEVER WITH RASH—see FEVER AND RASH (p. 234)

HEMORRHAGIC FEVER

- **BACTERIAL**—rickettsial, meningococcemia, leptospirosis
- **VIRAL**—dengue, yellow fever, Ebola fever, Lassa fever
- **PARASITIC**—malaria

FEVER WITH SEXUAL OR BLOOD EXPOSURES—syphilis, CMV, EBV, HIV, HBV

FEVER WITH EOSINOPHILIA—parasitic (acute hookworm, ascaris, strongyloides, acute schistosomiasis, visceral larva migrans, lymphatic filariasis, acute trichinosis)

DIFFERENTIAL DIAGNOSIS (CONT'D)

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*, *Salmonella, Shigella, Vibrio, Aeromonas, Plesiomonas, C. difficile*
- **VIRAL**—Caliciviruses (Norwalk, Norwalk-like), rotaviruses, enteroviruses
- **PARASITIC**—*Giardia lamblia, Cryptosporidium parvum, Entamoeba histolytica, Cyclospora cayetanensis, Isospora belli, E. 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, *M. avium* complex
- **FUNGAL**—*Paracoccidioides brasiliensis, Histoplasma capsulatum*
- **PARASITIC**—*G. lamblia, E. histolytica, C. parvum, C. cayetanensis, Trichuris trichiura, Strongyloides stercoralis*, Schistosomiasis, *Capillaria philippinensis, Fasciolopsis buski, Metagonimus yokogawai,* Echinostoma
- **NON-INFECTIOUS**—small-bowel overgrowth syndrome, disaccharidase deficiency, tropical sprue, irritable bowel syndrome, inflammatory bowel disease, cancer, laxative use, endocrinopathy, dysmotility, idiopathic

www.phac-aspc.gc.ca/publicat/ccdr-rmtc/06vol32/acs-01/index-eng.php

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, 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**—CBCD, 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 ×1 within 12–24 h if initially negative result), serologies (HIV, dengue, rickettsiae, schistosomiasis, strongyloidiasis, leptospira, HAV, HBV, HCV, Hepatitis E)
- **IMAGING**—CXR, U/S 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—ciprofloxacin and imodium if diarrhea develops

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

SCHISTOSOMIASIS

- **PATHOPHYSIOLOGY**—trematode worms *S. haematobium, S. mansoni, S. intercalatum* in sub-Saharan Africa, *S. mansoni* in part of South America, *S. japonicum* in Asia, *S. 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, mekongi, japonicum, and intercalatum*) bladder (*S. hematobium*), where females lay eggs → excreted into feces or urine → mature to cercariae
- **CLINICAL FEATURES**—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, occult blood, fibrosis) or genitourinary tract symptoms (hematuria, dysuria, calcification, fibrosis), and rarely CNS (seizures, focal deficit, transverse myelitis) involvement

SPECIFIC ENTITIES (CONT'D)

- **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 Katyama fever

MALARIA—the most important cause of fever in returning travelers. *P. 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**—anopheline mosquito bite transmits sporozoites → travel to liver and invade hepatocytes → divide and form schizonts which contain merozoites (asymptomatic) → rupture after 6–16 days and release merozoites into the bloodstream → infect erythrocytes and mature from ring forms to trophozoites to mature schizonts (asexual form) over 48 (*P. vivax, P. ovale, P. falciparum*) or 72 (*P. malariae*) hours → merozoites released from erythrocytes (fever, anemia, lactic acidosis, cytokine release) and infect new red cells → 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. In contrast, *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* is acquired mostly from sub-Saharan Africa, while *P. vivax* is 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 universally fatal if untreated
- **DIAGNOSIS**—thick and thin smear (need to repeat over 48 h to rule out malaria)
- **PROPHYLAXIS**—the relative risk of contracting malaria varies by geographic region: Caribbean 4, North Africa 7, South America 8, Southeast Asia 12, Central America 38, South Asia 54, Oceania 77, and sub-Saharan Africa 208. 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 destinations with chloroquine-sensitive *P. falciparum* (e.g. 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). Atavaquone–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 2010 risk assessment and prophylaxis recommendations are available online at
  http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/malaria-risk-information-and-prophylaxis.aspx
- **TREATMENTS**—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

NEJM 2008 359:6
www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s1/index-eng.php

RICKETTSIAL INFECTIONS (OUTSIDE OF NORTH AMERICA)

- **PATHOPHYSIOLOGY**—African tick typhus (*Rickettsia africae*), Mediterranean tick typhus (R. conorii), and scrub typhus (*Orientia tsutsugamushi*) are all transmitted by ticks
- **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 OF NORTH AMERICA)—see **FEVER AND RASH** (p. 234)

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's 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

SPECIFIC ENTITIES (CONT'D)

TYPHOID FEVER

- **PATHOPHYSIOLOGY**—acquired after exposure to food or water contaminated by *Salmonella typhi*
- **CLINICAL FEATURES**—mainly in developing countries. 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

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, splenic, thyroid, epidural). May develop into chronic hepatosplenic disease

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—blood cultures, serology
- **TREATMENTS**—doxycycline plus streptomycin or rifampin

DENGUE FEVER (break-bone fever)

- **PATHOPHYSIOLOGY**—flavivirus transmitted by mosquito → flu-like illness 4–7 days later → may develop 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. Leukopenia and thrombocytopenia
- **DIAGNOSIS**—serology
- **TREATMENTS**—supportive

CHIKUNGUNYA FEVER

- **PATHOPHYSIOLOGY**—mosquito-borne viral infection acquired in Africa and Asia. Large outbreaks ongoing 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

NEJM 2007 356:8

Pneumonia

See PNEUMONIA (p. 6)

Endocarditis

See ENDOCARDITIS (p. 52)

Meningitis NEJM 2006 354:1

DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS

★DIMS★

DRUGS—neuroleptic malignant syndrome, serotonin syndrome, sympathomimetics, alcohol withdrawal

INFECTIOUS

- **MENINGITIS**—bacterial (*S. pneumoniae, N. meningitidis, H. influenzae, L. monocytogenes, Klebsiella, E. coli, Serratia, Pseudomonas*), viral (enterovirus, VZV, influenza, mumps, HIV), TB, fungal (*Cryptococcus*)

DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS (CONT'D)

- **ENCEPHALITIS**—HSV, West Nile, St. Louis, Equine, La Crosse
- **ABSCESS**—bacterial

METABOLIC—thyroid storm

STRUCTURAL

- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral
- **CEREBRAL INFARCT**

DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS (CONT'D)

- **TUMOR**
- **PITUITARY APOPLEXY**
- **VASCULAR**—TTP/HUS, lupus, vasculitis, granulomatous angiitis

PATHOPHYSIOLOGY

ASSOCIATIONS WITH SPECIFIC ORGANISMS

- **AGE 0–4 WEEKS**—*S. agalactiae, E. coli, Listeria 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, S. epidermidis*, aerobic Gram-negative bacilli*

PATHOPHYSIOLOGY (CONT'D)

- **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

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	50%	
Nausea and vomiting	30%	
Neck pain	28%	
Physical		
Fever	85%	
Neck stiffness	70%	
Altered mental status	67%	
Focal neurological findings	23%	
Rash	22%	
Kernig sign (patient lying supine with hip flexed >90°. Extension of knee from this position elicits resistance or pain in lower back or posterior thigh)	9%	100%
Brudzinski 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%

APPROACH—"absence of all 3 signs of the classic triad of fever, neck stiffness, and altered mental status virtually eliminates a diagnosis of meningitis. Fever is most sensitive of triad, stiff neck and altered mental status second and helpful to exclude meningitis in low risk patients. Kernig and Brudzinski signs appear to have low sensitivity and high specificity. Jolt accentuation of headache may be a useful adjunctive maneuver for patients with fever and headache. In patients at sufficient risk of meningitis, a positive test result may aid in the decision to proceed to lumbar puncture, whereas a negative test result essentially excludes meningitis"

JAMA 1999 282:2

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, Cr/urea, INR, PTT, AST, ALT, ALP, bilirubin, fibrinogen, urinalysis
- **MICROBIOLOGY**—blood C&S, sputum Gram stain/AFB/C&S, urine C&S

INVESTIGATIONS (CONT'D)

- **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, with culture. Suspect viral infection if high lymphocytes, *normal* glucose, and normal/high protein (**NEJM 2006 355:e12**)

- **OPENING PRESSURE**—normal is 60–250 mmH_2O. Causes of elevated opening pressure include meningitis, pseudotumor cerebri, intracranial hemorrhage, tumors, and idiopathic
- **CELL COUNT AND DIFFERENTIAL**—normal WBC is $<5/mm^3$. This can increase to 1000–5000/mm^3 for bacterial meningitis (neutrophils mainly) and 50–1000/mm^3 for viral meningitis (lymphocytes mainly). Other causes include seizure, intracerebral hemorrhage, tumor, and "traumatic tap" (correct by +1 WBC for every 500–1000 RBCs)
- **XANTHOCHROMIA**—lysed RBC. 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
- **CULTURE**—gold standard with sensitivity of 70–85% in untreated bacterial meningitis and 50% in partially treated cases. Viral, TB, and fungal cultures may be done as well
- **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 hemorrhages, multiple sclerosis, and Guillain–Barre 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

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 ≥500/μL	15
CSF lactate ≥3.5 mmol/L [≥32 mg/dL]	21

JAMA 2006 296:16

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

CT HEAD—indicated before lumbar puncture only if age >60, immunocompromised, history of CNS disease, seizures within 1 week, focal neurological abnormalities, papilloedema, obtunded or unconscious, inability to answer two questions correctly, or inability to follow two commands correctly

NEJM 2001 345:24

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*

NEJM 2004 351:18

MANAGEMENT

ACUTE—ABC, O_2, 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 ×4days). ***Cefotaxime*** 2 g IV q6h or ***ceftriaxone*** 2 g IV q12h. Add ***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 ***ceftazidime*** 2 g IV q8h 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 ×14–21 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, and leptomeningeal carcinomatosis

RECURRENT MENINGITIS—**congenital predisposition** (myelomeningocele, dermal sinus), **acquired** (trauma, tumor, shunt), **immunologic 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**—lumbar puncture (mild lymphocytic pleocytosis <500 cells/μL, erythrocytes, xanthochromia, ↑ protein, normal glucose, PCR for HSV1 and HSV2), MRI (hyperintense lesion in the inferior medial temporal lobe, often extending into the insula)
- **TREATMENTS**—*acyclovir* 30 mg/kg/day ×14 days

SPECIFIC ENTITIES (CONT'D)

WEST NILE VIRUS ENCEPHALITIS

- **PATHOPHYSIOLOGY**—flavivirus West Nile virus transmitted by mosquitoes between late spring and early autumn
- **CLINICAL FEATURES**—wide spectrum from asymptomatic to severe neurologic disorder. Fever, erythematous rash, meningitis, encephalitis, and flaccid paralysis. Risk of progression to severe neurological disease about 1/150, highest in the elderly
- **DIAGNOSIS**—lumbar puncture (viral picture, PCR for West Nile virus), IgM antibody to West Nile virus in serum or cerebrospinal fluid (samples from the acute and convalescent phases, submitted at least two weeks apart)
- **TREATMENTS**—supportive. Prevention is key

SPECIFIC ENTITIES (CONT'D)

Related Topics
Delirium (p. 380)
Infection Control (p. 269)

Urinary Tract Infections and Sexually Transmitted Infections

Urol Clin N Am 2008;35:1;
Can J Infect Dis Med Microbiol 2005;16:6;
www.phac-aspc.gc.ca/std-mts/sti-its/guide-lignesdir-eng.php

DIFFERENTIAL DIAGNOSIS OF DYSURIA

★SUV★

SEXUALLY TRANSMITTED DISEASES—*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, HSV

URINARY TRACT INFECTIONS (urethritis, cystitis, pyelonephritis, perinephric abscess)—**bacterial** (**★KEEPS★** ***K****lebsiella,* ***E.*** *coli,* ***E****nterococci,* ***P****roteus,* ***S****taphylococcus 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 (polycystic kidney disease, nephrolithiasis, neurogenic bladder, diabetes, immunosuppression, pregnancy, indwelling urinary catheter, recent urinary tract instrumentation)

UNCOMPLICATED UTI—absence of risk factors above. In women, uncomplicated UTIs are usually treated for 3 days (or 5–7 days with nitrofurantoin)

PYELONEPHRITIS—usually 18–40-year-old women, fever, costovertebral angle tenderness, blood and urine cultures indicated. Challenges differentiating between cystitis and pyelonephritis

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 include duration of catheterization, errors in catheter care, diabetes mellitus, and female sex

CLINICAL FEATURES OF URINARY TRACT INFECTIONS

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS WOMAN HAVE ACUTE UTI?

	LR+	LR–
History		
Dysuria	1.5	0.5
Frequency	1.8	0.6
Hematuria	2.0	0.9
Fever	1.6	0.9
Flank pain	1.1	0.9
Lower abdominal pain	1.1	0.9
Vaginal discharge	0.3	3.1
Vaginal irritation	0.2	2.7
Back pain	1.6	0.8
Physical		
Vaginal discharge	0.7	1.1
CVA tenderness	1.7	0.9
Urine dipstick		
Leukocyte esterase or nitrite positive	4.2	0.3

APPROACH—"four symptoms (dysuria, frequency, hematuria, back pain) and one sign (CVA tenderness) increased the probability of UTI and may effectively rule in if all present. However, no combinations reliably rule out UTI. Urinalysis is moderately powerful and should be considered in women with appropriate urinary tract symptoms. If the dipstick leukocyte esterase or nitrite is positive, the probability of UTI is high, especially when combined with other positive findings from the history and physical. If dipstick is negative but probability of disease is still relatively high, a urine culture should be considered to rule out infection"

JAMA 2002 287:20

INVESTIGATIONS FOR URINARY TRACT INFECTIONS

BASIC

- **LABS**—CBCD, lytes, Cr/urea
- **MICROBIOLOGY**—urinalysis (nitrite or leukocyte esterase sens 75%, spc 82%), urine C&S (pyuria sens 95%, spc 71%; bacteria sens 40–70%, spc 85–95%. Not necessary if symptomatic uncomplicated UTI)

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

URINE CULTURE—not always needed if symptomatic and biochemical evidence (i.e. leukocyte esterase) of uncomplicated UTI (see Clinical Features). However, antimicrobial resistance is increasing, so culture and sensitivity may become more important

MANAGEMENT OF URINARY TRACT INFECTIONS

UNCOMPLICATED UTI IN WOMEN—*trimethoprim–sulfamethoxazole* (DS-160/800 mg) 1 tab PO BID ×3 days, *ciprofloxacin* 250–500 mg PO BID ×3 days, *levofloxacin* 250–500 mg PO daily ×3 days, *nitrofurantoin macrocrystals* 50 mg PO QID ×5–7 days, *nitrofurantoin monohydrate macrocrystals* 100 mg PO BID ×5–7 days, *amoxicillin–clavulanate* 500 mg PO BID ×7 days, *fosfomycin trometamol* 3 g PO ×1 dose

COMPLICATED UTI—treatment duration 7–14 days

RECURRENT UTI (consider below measures if >3 episode of UTI/year)—**daily low-dose prophylaxis** (*trimethoprim–sulfamethoxazole DS* ½ tab PO qhs or 1 tab 3×/week ×6 months, *nitrofurantoin* 50 mg or macrocrystals 100 mg PO qhs ×6 months), **post-coital prophylaxis** (*trimethoprim–sulfamethoxazole* DS ½-1 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 ×2 days

ACUTE UNCOMPLICATED PYELONEPHRITIS—treat empircally with oral fluoroquinolones ×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 ×14 d. Most otherwise healthy, non-pregnant women with pyelonephritis can be treated on an outpatient basis. Otherwise, treat with IV antibiotics, at least initially (aminoglycoside ± ampicillin, third-generation cephalosporin, or carbapenem)

MANAGEMENT OF URINARY TRACT INFECTIONS (CONT'D)

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 16 weeks. Treat all bacteriuria with amoxicillin or nitrofurantoin ×3–7 days even if asymptomatic as there is a 20–40% risk of pyelonephritis. 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 antifungal cream (3–14 days) or *fluconazole* 150 mg PO ×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

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 (STIs)

URETHRITIS IN MEN/CERVICITIS IN WOMEN

- **PATHOPHYSIOLOGY**—*N. gonorrhea*, *Chlamydia 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 (*cefixime* 400 mg PO ×1, *ceftriaxone* 125 mg IM ×1), anti-chlamydial (*azithromycin* 1 g PO ×1, or *doxycycline* 100 mg PO BID ×7 days). If gonorrhea identified, empirically treat for both gonococcus and chlamydia since dual infection is common. Trace and treat all partners within the last 60 days

SYPHILIS

- **PATHOPHYSIOLOGY**—*Treponema 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

SEXUALLY TRANSMITTED INFECTIONS (STIs) (CONT'D)

- **SECONDARY SYPHILIS**—develops within 2 weeks to 6 months, with symptoms such as 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 (general paresis, a 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)
- **DIAGNOSIS**—first-line diagnostic test of choice for a primary syphilitic chancre should be either 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 treponematosis
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 (STIs) (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

JAMA 2003 290:11

PELVIC INFLAMMATORY DISEASE

- **PATHOPHYSIOLOGY**—includes endometritis, tubo-ovarian abscess, salpingitis, and pelvic peritonitis. Most commonly due to *N. gonorrhoeae, C. trachomatis, M. hominis, U. urealyticum;* may involve endogenous (gut) organisms including anaerobes. Complications include infertility, ectopic pregnancy, and chronic pelvic pain

SEXUALLY TRANSMITTED INFECTIONS (STIs) (CONT'D)

- **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. Ultrasound. Pregnancy test
- **TREATMENTS**—**outpatients** (*ceftriaxone* 250 mg IM ×1 and *doxycycline* 100 mg PO 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 q6h ×14 days, or *clindamycin* 900 mg IV q8h and *gentamicin* 1.5 mg/kg IV q8h ×14 days)

Soft Tissue Infections

NEJM 2004 350:9; NEJM 2007 357:4; CID 2005 41:10

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, *S. 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, venectomy, radiation, prior cellulitis

CELLULITIS—acute spreading infection involving the dermis and subcutaneous tissue, mostly caused by Staphylococci and group A *Streptococcus*. It usually presents as a swollen, erythematous plaque with ill-defined border

ERYSIPELAS—superficial cellulitis involving the upper dermis and lymphatics, mostly caused by group A *Streptococcus*. It 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 or household contacts of known MRSA; street involved/shelters/incarceration, injection drug use, athletes, children/day care

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**—*Borrelia burgdorferi*, Tularemia
- **FRESHWATER**—*Aeromonas hydrophila*
- **SEAWATER**—*Vibrio vulnificus*
- **FISH EXPOSURE**—*Erysipelothrix rhusiopathiae, Streptococcus iniae*
- **HOT TUB**—*Pseudomonas aeruginosa* folliculitis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, lactate (if suspicion of necrotizing fasciitis)
- **MICROBIOLOGY**—swab of portal of entry or any open wound for Gram stain and C&S, blood C&S

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 q4–6h ×7–14 days). For MRSA-associated skin infections, consider *vancomycin* 1–2 g IV q12h, *clindamycin* 600 mg IV TID or 300 mg PO QID, *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 or *quinupristin–dalfopristin* 7.5 mg/kg IV q8–12h. **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

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's gangrene of perineum in diabetics), **type 2** (monomicrobial *Streptococcus pyogenes* "Group A strep"; 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 surrounding tissue → late signs include fever, crepitus, shock → complications include compartment syndrome, acute renal failure, sepsis. May be limb or life-threatening. May happen over a few hours
- **ASSOCIATIONS**—host (age >50, cancer, alcoholism, immunocompromised state, malnutrition, obesity), compromised skin (burns, trauma, postoperative infection), compromised blood vessels (peripheral vascular disease, diabetes)

SPECIFIC ENTITIES (CONT'D)

- **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 X-ray to check for gas with type 1 necrotizing fasciitis. CT or MRI maybe useful. Early deep incisional biopsy is gold standard

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—urgent **surgical debridement** of all necrotic tissue. Consider **IVIG** if significant hypotension in Group A *Streptococcus* necrotizing fasciitis. **Polymicrobial** (*cefotaxime* 2 g IV q8h plus *clindamycin* 600–900 mg IV q8h [note: clindamycin inhibits toxic protein production], *Piperacillin–tazobactam* 4.5 g IV q8h, or ampicillin/penicillin G plus ciprofloxacin plus metronidazole). **Streptococcus** (*penicillin G* 4 MU IV q4h plus *clindamycin* 600–900 mg IV q8h)

Osteomyelitis

DIFFERENTIAL DIAGNOSIS

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 cm^2 is associated with ~90% chance of having underlying osteomyelitis (sens 66%, spc 85%, PPV 89%, NPV 56%). Further noninvasive testing is unlikely to improve accuracy of diagnosis

CLINICAL FEATURES (CONT'D)

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 cm^2, 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. No single historical feature or physical examination reliably excludes osteomyelitis. The diagnostic utility of a combination of findings is unknown. The gold standard for diagnosis is bone biopsy"

JAMA 2008 299:7

CLINICAL FEATURES (CONT'D)

SYMPTOMS

- **ACUTE OSTEOMYELITIS** (<2 weeks)—typically associated with bone pain, tenderness, warmth, swelling, febrile, and chills. Hip, vertebrae, and pelvis tend to manifest few 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**—CBCD, 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), U/S, 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, foreign bodies, deformities, fractures, and soft tissue gas. Usually the first imaging to investigate for osteomyelitis. However, may not detect 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, but cannot make the diagnosis

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 areas with red marrow (vertebrae, pelvis). Excellent for fracture nonunion osteomyelitis (sens 91%, spc 97%)

MRI—provides great anatomic details, more sensitive and specific than bone scan. Imaging of choice for specific body sites (vertebrae, diabetic foot) (sens 72%)

DIAGNOSTIC ISSUES (CONT'D)

ULTRASOUND—fluid collection adjacent to the bone without intervening soft tissue, elevation of the periosteum by >2 mm, and thickening of the periosteum. Sensitivity and specificity uncertain

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 skin swabs have little correlation with the actual organisms growing inside the bone, except for *S. aureus*

Related Topic
Diabetes Mellitus (p. 337)

MANAGEMENT

HEMATOGENOUS—for vertebral osteomyelitis, need blood and bone cultures, then start empiric antibiotics with *cloxacillin* 2 g IV q4–6h 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 ± *ceftazidime* 2 g IV q8h. 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 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

SPECIFIC ENTITIES (CONT'D)

- **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 q4–6h 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

NEJM 2009 361:8

Septic Arthritis

See SEPTIC ARTHRITIS (p. 273)

Tuberculosis: Pulmonary

NEJM 1999 340:5; NEJM 2001 345:3; NEJM 2004 350:20

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 organs can become infected during the bacteremia that follows initial lung infection

LATENT TB INFECTION (LTBI)—follows initial infection; asymptomatic; detected by tuberculin skin test. 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 aboriginal 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; hilar lymphadenopathy in the presence of *RML collapse* is the most common radiologic finding (2/3) with pleural effusion in 1/3. Lung infiltrates 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**—cough, yellow-green sputum (increases over time), 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 (more likely than cavitation in AIDS patients)
- **ELDERLY WITH REACTIVATION TB**—presents with fever, night sweats, or hemoptysis less often. Lesions less often cavitary and less often TST positive

CLINICAL FEATURES (CONT'D)

COMPLICATIONS OF PULMONARY TB—hemoptysis (rarely massive), pneumothorax (more common in endemic countries), bronchiectasis, and pulmonary destruction (rare)

Related Topic
Tuberculosis in Pregnancy (p. 412)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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

- **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:

- **≥5 MM**—HIV positive, recent TB contact, CXR signs, prior TB
- **≥10 MM**—other risk factors for infection (endemic, immigrant, aboriginal, homeless, injection drug user, healthcare worker, silicosis, kidney or liver disease, gastrectomy, ileal bypass)
- **≥15 MM**—no risk factors

SPUTUM SMEAR

- **UTILITY**—morning sputum ×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

DIAGNOSTIC ISSUES (CONT'D)

SPUTUM CULTURE—2–8 weeks in egg media, 4–14 days if radiometric (sens 80–85%, spc 98–99%)

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%)

INTERFERON GAMMA RELEASE ASSAYS—sensitivity >95%; not affected by prior BCG vaccination. Most useful for evaluation of latent TB in those with positive TST and previously vaccinated with BCG

MANAGEMENT

LATENT TB INFECTION—***isoniazid*** 300 mg PO daily ×6–12 months or ***rifampin*** 600 mg PO daily ×4 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—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 ×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. Alternatives include isoniazid, rifampin, pyrazinamide, plus ethambutol or streptomycin three times weekly for 24 weeks, or isoniazid, rifampin, pyrazinamide, plus ethambutol for 2 weeks, then twice weekly for 6 weeks, followed by isoniazid and rifampin twice weekly for 16 weeks (see guidelines for exceptions and alternate regimens when faced with resistance or drug intolerance)

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

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 → ↑ clearance and ↓ effects of many drugs), flu-like symptoms, red-orange urine, sweat, tears
- **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

TREATMENT ISSUES (CONT'D)

DRUG MONITORING

- **BASELINE**—platelet, Cr, AST, ALP, bilirubin, uric acid (pyrazinamide), visual acuity, and red-green color discrimination (ethambutol)
- **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)

CANADIAN TUBERCULOSIS STANDARDS—see http://www.phac-aspc.gc.ca/tbpc-latb/index-eng.php for more information

Approach to Gram Stain, Culture, and Sensitivity

GRAM-POSITIVE COCCI

CLUSTERS (catalase positive) (Staphylococci)

- **COAGULASE POSITIVE**—*S. aureus*
- **COAGULASE NEGATIVE**—*S. epidermidis, S. saprophyticus, S. hominis, S. lugdunesis, S. schleiferi*

PAIRS/CHAINS (catalase negative)

- **α-HEMOLYTIC STREPTOCOCCI**—*S. pneumoniae,* viridians group streptococci, enterococcus (Group D strep)
- **β-HEMOLYTIC STREPTOCOCCI**—*S. pyogenes* (Group A strep), *S. agalactiae* (Group B strep), group C, F, G strep
- **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

GRAM-POSITIVE BACILLI (CONT'D)

SPORE FORMING

- **AEROBIC**—*Bacillus anthrax, Bacillus cereus*
- **ANAEROBIC**—*Clostridium perfringens, C. difficile, C. botulinum*

NON-SPORE FORMING

- **AEROBIC, FACULTATIVE, AEROTOLERANT**—*Corynebacterium*/diphtheroids, *Lactobacillus, Listeria, Gardenerella, Nocardia*
- **ANAEROBIC**—*Actinomyces, Propionibacterium, Eubacterium*

BRANCHING BACILLI—★**ABCD-LMN**★ ***A****ctinomyces* (acid fast negative), ***B****acillus,* ***C****lostridium*, **D**iphtheroids, ***L****isteria,* ***L****actobacillus,* ***M****ycobacterium* (Modified and Ziehl–Neelsen acid fast), ***N****ocardia* (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*

GRAM-NEGATIVE BACILLI (CONT'D)

- **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**
  - **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—cellulitis, erysipelas, necrotizing fasciitis, pharyngitis, bacteremia, Streptococcal toxic shock syndrome, scarlet fever, acute rheumatic fever (post-streptococcal glomerulonephritis)

STREPTOCOCCUS PNEUMONIAE—may develop resistance to penicillin by altered penicillin-binding protein

ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE (CONT'D)

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

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*, ***S****erratia*†*, ***P****rovidencia*†, ***P****seudomonas*, **I**ndole-positive *Proteus*†*, ***C****itrobacter*†*, ***E****nterobacter*†*, ***M****organella*†*)

†★**SPICE-M**★ organisms with inducible, chromosomally mediated cephalosporinases (AmpC type β-lactamases) 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 q4–6h	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 q4–6h		++*S. aureus*				No
Amino-Penicillins						
Ampicillin 1–2 g IV q4–6h	Bactericidal, cell wall synthesis inhibition and lysis	+++Strep/Entero	+/−H. flu, +/−*E. coli*		*Listeria*	Yes (interval)
Amoxicillin 250–1000 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 q4–6h	Bactericidal, cell wall synthesis inhibition and lysis	++	++Pseudo	++		Yes (dose + interval)
Pip/tazo 3.375 g q6h–4.5 g IV q8h		++Staph	++Pseudo/H. flu	+++		Yes (dose + interval)
Ticarcillin 3–4 g IV q4–6h		++	++Pseudo	++		Yes (dose + interval)
Tcarcillin/clavulanate 3.1 g IV q4–6h		++	++Pseudo	+++		Yes (dose + interval)
Monobactam and Carbapenems						
Aztreonam 1–2 g IV q6–8h	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)
Third/Fourth Generation Cephal.						
Cefoxitin 1–2 g IV q6–8h	Bactericidal, cell wall synthesis inhibition and lysis	+++	+++	++		Yes (interval)
Cefotaxime 1–2 g IV q6–8h		+++	+++			Yes (interval)
Ceftriaxone 1–2 g IV q24h		+++	+++			No
Ceftazidime 1 g IV q8–12h		+++	+++Pseudo			Yes (interval)
Cefepime 1–2 g IV q12h		+	+++Pseudo			Yes (interval)
Cefixime 400 mg PO daily		+	++			Yes (interval)
Ceftobiprole 500 mg IV q8–12h		+++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)

Antibiotics (cont'd)

Antibiotics	Mechanism	Gram positive	Gram negative	Anaerobes	Others	Renal adjustments
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		++*Mycoplasma* and *Chlamydia* for all macrolides	No
Clarithromycin 250–500 mg PO BID		+	+H. flu/legion			Yes (dose)
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 SS/DS tab PO BID (also available IV)	Bactericidal, blocks DNA synthesis	+	++Steno, +PJP			Yes (interval)
Clindamycin						
Clindamycin 150–450 mg PO QID or 300–600 mg IV q6–12 h	Bacteriostatic, binds to tRNA complex	++		+++		No
Metronidazole			*H. pylori*,			
Metronidazole 500 mg PO/IV q12h	Bactericidal, DNA breakage		*G. vaginalis*	+++C. diff	++protozoa	No
Glycopeptides						
Vancomycin 15 mg/kg IV q12h	Bactericidal, interferes with peptidoglycan and RNA synthesis	+++				
		S. epidermidis, MRSA, Entero		++C. diff		Yes (interval)
Oxazolidinones						
Linezolid 600 mg PO/IV q12h	Bactericidal (Strep) and bacteriostatic (Staph, entero), 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 *E. faecalis*)		+		No
Lipopeptides						
Daptomycin 4–6 mg/kg q24h	Bactericidal, disrupts cell membrane	++MRSA, VRE		+		Yes (interval)

GENTAMICIN AND TOBRAMYCIN DOSING

TOXICITY—nephrotoxicity, ototoxicity, neuromuscular blockade (rare). Serum aminoglycoside levels correlate with nephrotoxicity

LOADING DOSE (TRADITIONAL DOSING: Q8H)—dependent on indication. For mild infection, uncomplicated UTI, synergy with β-lactams for Gram positive infections, give 0.6–1.2 mg/kg IV q8h. For serious Gram-positive infection or sepsis, give 2.5 mg/kg IV. For life-threatening infections, give 3.0 mg/kg IV

MAINTENANCE DOSE (TRADITIONAL DOSING: Q8H)

- **START**—1.7 mg/kg IV q8h. Monitor serum levels after steady state reached; i.e. 3–5 half-lives (after third dose). Monitor renal function and ototoxicity every 3 days
- **PEAK LEVELS**—obtain 30–45 min after end of infusion. Should be 4.2–8.4 μmol/L [2–4 μg/mL] when drug is being given for synergy or uncomplicated infections, 12.6–16.8 μmol/L [6–8 μg/mL] for serious Gram-negative infection or sepsis, and 14.7–18.9 μmol/L [7–9 μg/mL] for life-threatening infections
- **TROUGH LEVELS**—obtain 0–30 min prior to scheduled dose. Should be <4.2 μmol/L [<2 μg/mL] to prevent toxicity
- **ADJUSTMENTS**—dosing interval is dependent on renal function (CrCl >60 mL/min, q8h; 40–60 mL/min, q12h; 20–40 mL/min, q24h; <20 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, but particularly trough level

ONCE-DAILY GENTAMICIN AND TOBRAMYCIN DOSING

RATIONALE—optimize treatment of Gram-negative infections with less nephrotoxicity than q8h dosing. Similar ototoxicity and neuromuscular toxicity

NOT RECOMMENDED—monotherapy for infections outside urinary tract, pregnant patients, dialysis patients, endocarditis, CNS infections, osteomyelitis, ophthalmologic infections, surgical prophylaxis, patients with rapid drug clearance (e.g. burns >20% BSA), Gram-positive infections, patients receiving concurrent ototoxins (e.g. furosemide) neonates, pediatric patients with significant renal dysfunction, duration of therapy >14 days

LOADING DOSE—5–7 mg/kg IV

MAINTENANCE DOSE (5–7 mg/kg IV q24–48h)

- **START**—monitor serum level 6–14h after first dose. Monitor renal function and ototoxicity q3d

ONCE-DAILY GENTAMICIN AND TOBRAMYCIN DOSING (CONT'D)

- **ADJUSTMENTS**—dosing interval (q24–48h) is based on 6–14 h serum level (Hartford nomogram, **Antimicrob Agents Chemother 1995 39:3**). Pharmacy consult to assist with dosing (Once-daily dosing provides peak levels of 15–31–46 μmol/L [22 μg/mL] and trough levels <2.1 μmol/L [<1 μg/mL] to prevent toxicity. Peak and trough levels do not need to be monitored)

DOSING WEIGHT FOR AMINOGLYCOSIDES—for obese patient (i.e. actual body weight (BW) >125% of ideal body weight (IBW)), use adjusted body weight (ABW) for dose determination:

- **ABW** (kg)=IBW +0.4(BW-IBW)

Note: 1 kg=2.2 lbs. See p. 406 for IBW calculation

Related Topic
Drug Eruptions (p. 372)

VANCOMYCIN TOXICITY AND DOSING

TOXICITY—rash, infusion-related red man syndrome, rarely nephrotoxicity (especially 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)

- **START**—monitoring after steady state, i.e. after third dose normally, or after second dose if dosing interval >48 hour. Monitor only if >14 days in patients with stable renal function and mild/moderate infection, or >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**—there is no 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

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%. Carbapenems and first/second-generation cephalosporins have higher cross-reactivity in the penicillin allergic than third-generation cephalosporins and aztreonam. 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

NEJM 2006 354:6

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT ALLERGIC TO PENICILLIN?

HISTORY—history of penicillin allergy (LR+ 1.9, LR− 0.5)

TYPES OF ALLERGIC REACTIONS

★ACID★ **A**ntibody-mediated (IgE), **C**ytotoxic (antibody-dependent), **I**mmune-complex-mediated, **D**elayed hypersensitivity reaction

PENICILLIN ALLERGY (CONT'D)

- **TYPE I**—immediate <1 h, IgE antibodies 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—"only 10–20% of patients reporting a history of penicillin allergy are truly allergic when assessed by skin testing. Taking a detailed history of a patient's reaction to penicillin may allow clinicians to exclude true penicillin allergy, allowing these patients to receive penicillin. Patients with a concerning history of type I penicillin allergy who have a compelling need for a drug containing penicillin should undergo skin testing. Virtually all patients with a negative skin test result can take penicillin without serious sequelae"

JAMA 2001 285:19

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—depending on the suspected source. For pulmonary source, respiratory fluoroquinolone plus ceftriaxone ± vancomycin if community setting, anti-pseudomonal plus ciprofloxacin if hospital setting. For urinary source, ceftriaxone or

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

carbapenem or fluoroquinolone or aminoglycoside. For intra-abdominal source, pipericillin–tazobactam plus aminoglycoside. Duration of treatment is at least 10–14 days with rationalization of antibiotics when susceptibility results available. See p. 97 for details

MENINGITIS (*S. pneumoniae, N. meningitidis, Listeria*, HSV)—ceftriaxone/cefotaxime ± ampicillin ± vancomycin. Add acyclovir if CSF suggests viral picture. Duration of treatment is 7–21 days. See p. 241 for details

COMMUNITY–ACQUIRED PNEUMONIA (*S. pneumoniae, Klebsiella, Mycoplasma*)—macrolides ± cefotaxime or respiratory fluoroquinolones. Duration of treatment is usually 7 days. See p. 6 for details

ASPIRATION PNEUMONIA (anaerobes, Staph, GNB)—cefotaxime ± clindamycin or metronidazole. Duration of treatment is usually at least 7 days. See p. 6 for details

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

ICU/VENTILATOR-ASSOCIATED PNEUMONIA (GNB, *Pseudomonas*)—ciprofloxacin plus ceftazidime or pipericillin–tazobactam or carbapenem. Duration of treatment is usually 8 days (p. 94)

ENDOCARDITIS (*S. aureus*, *S. viridans, Enterococcus*). Duration of treatment is highly variable. See AHA guidelines and p. 52 for details

- **NATIVE VALVE DISEASE**—ampicillin + cloxacillin/nafcillin or vancomycin plus gentamicin
- **INJECTION DRUG USE**—cloxacillin or vancomycin plus gentamicin
- **PROSTHETIC VALVE DISEASE**—vancomycin plus gentamicin

ACUTE BLOODY DIARRHEA (*Salmonella, Shigella, Campylobacter*)—ciprofloxacin. Duration of treatment is 3 days. See p. 122 for details

ANTIBIOTIC-ASSOCIATED DIARRHEA (*C. difficile*)—oral metronidazole. Duration of treatment is 10 days. See p. 123 for details

PERITONITIS/INTRA-ABDOMINAL SEPSIS (coliforms, anaerobes)—pipericillin–tazobactam, imipenem, or ampicillin plus ciprofloxacin 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. 148 for further information

URINARY TRACT INFECTION (*E. coli, Klebsiella, Enterococcus, Proteus, S. saprophyticus*)—nitrofurantoin, trimethoprim–sulfamethoxazole, ciprofloxacin. Duration of treatment is 3 days if uncomplicated UTI, otherwise 14–21 days. See p. 244 for details

SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

CELLULITIS (*Staphylococcus, Streptococcus*)—cefazolin, cloxacillin, or cephalexin. Duration of treatment is usually 7–10 days. See p. 247 for details

HUMAN BITE (Gram positive, *Eikenella*, anaerobes)—amoxicillin–clavulanate, or clindamycin plus Ciprofloxacin

DIABETIC FOOT (polymicrobial)—amoxicillin–clavulanate or ciprofloxacin plus clindamycin, or trimethoprim–sulfamethoxazole plus metronidazole. Treat until resolution. May require IV antibiotics with *Pseudomonas* coverage (e.g. pipericillin–tazobactam; carbapenem). Osteomyelitis likely if ulcer >2 cm^2 or probe touches bone. See p. 248 for details

NECROTIZING FASCIITIS—surgical treatment is mandatory. For polymicrobial infection, cefotaxime plus clindamycin, pipericillin–tazobactam, or ampicillin/penicillin G plus ciprofloxacin/gentamicin plus metronidazole. For *Streptococcus*, penicillin G plus clindamycin. See p. 247 for details

OSTEOMYELITIS (Gram positive, Gram negative, anaerobes)—for Gram-positive coverage, clindamycin, cefazolin, or vancomycin. For Gram-negative coverage, cefotaxime or ciprofloxacin. For *Pseudomonas*, piperacillin or carbapenem or ceftazidime, plus ciprofloxacin or aminoglycoside. Duration of therapy usually at least 6 weeks. See p. 248 for details

SEPTIC ARTHRITIS—vancomycin, cloxacillin, or cefazolin for Gram-positive coverage, ciprofloxacin or ceftriaxone for Gram-negative coverage. Usual duration 4 weeks. See p. 273 for details

Hepatitis B

See HEPATITIS B (p. 130)

Hepatitis C

See HEPATITIS C (p. 131)

Herpes Simplex Virus Infection

See HERPES SIMPLEX VIRUS (p. 366)

Human Immunodeficiency Virus

NEJM 2005 353:16; MMWR 2009 58:RR-4;
www.aidsinfo.nih.gov/Guidelines/

RISK FACTORS FOR HIV

SEXUAL CONTACT—homosexual, heterosexual
PARENTERAL—IDU, transfusion, or unsafe needle use in 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 → if indeterminate, repeat Western blot 4–6 weeks, 3 months, and 6 months later. If worrying about window period (2–6 weeks post-exposure), may perform viral load testing
BASIC WORKUP FOR THE NEWLY DIAGNOSED

- **HIV STATUS**—viral load, CD4 count, genotype antiretroviral drug resistance testing
- **BASELINE**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, fasting lipid profile, amylase, lipase, CK, HLA B5701, βhCG, CXR, ECG
- **CO-EXISTING/OPPORTUNISTIC INFECTIONS**—HAV serology, HBV testing (HBsAg, HBsAb, HBcAb. If HBsAg or HBcAb positive, check HBV DNA as well), HCV testing (HCV antibodies, if negative but CD4 <200/mm^3 and liver enzymes abnormal, consider HCV RNA testing. If HCV positive, assess genotype ± liver biopsy), Pap smear, anal screening for HPV in gay men (no consensus yet), *Chlamydia* and gonorrhea screen, RPR (syphilis), TB skin test, 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 complication
FOLLOW-UP—viral load and CD4 count (usually 3–4-month intervals, or q2–8weeks if change of HAART)
AIDS—CD4 <200/mm^3 or any AIDS-defining diseases

- **BACTERIAL**—MAC, TB, recurrent *Salmonella* sepsis
- **VIRAL**—CMV retinitis, chronic HSV, PML

NATURAL HISTORY OF HIV (CONT'D)

- **FUNGAL**—esophageal candidiasis, extrapulmonary coccidioidomycosis, histoplasmosis or cryptococcosis
- **PARASITIC**—*Pneumocystis jiroveci* pneumonia (PJP), toxoplasmosis, chronic Cryptosporidiosis or isosporiasis
- **HIV**—HIV encephalopathy, wasting syndrome
- **NEOPLASMS**—Kaposi's sarcoma, CNS lymphoma, non-Hodgkin's lymphoma, cervical carcinoma

MAJOR CAUSES OF DEATH IN HIV PATIENTS ON HAART—AIDS (30%), liver disease (14%), 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	+	+	+	+
Candida		+	+	+
Coccidioides		+	+	+
Histoplasma		+	+	+
PJP			+	+
Cryptococcus				+
Toxoplasma				+
CMV				+
MAC				+
CNS lymphoma				+

CNS LESIONS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **BRAIN ABSCESS**—toxoplasma (CD4 <100/mm^3, usually multiple ring-enhancing lesions), tuberculosis (any CD4), Cryptococcus (CD4 <100/mm^3), Histoplasma (CD4 <500/mm^3), aspergillosis
- **CNS LYMPHOMA** (CD4 <100/mm^3)
- **PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY** (PML, CD4 <100/mm^3)—reactivation of JC virus, hypodense white matter lesion

DIAGNOSIS—CBCD, 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/mm^3 has 90% PPV for diagnosing toxoplasma
TREATMENT OF TOXOPLASMOSIS—pyrimethamine plus either sulfadiazine or clindamycin

CHRONIC MENINGITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **CRYPTOCOCCUS** (CD4 $<100/mm^3$)—ubiquitous fungus. High opening pressure (>200 cmH_2O)
- **BACTERIAL MENINGITIS** (any CD4)—*N. meningitis*, *S. pneumoniae, Listeria*, Gram-negative bacilli
- **VIRAL MENINGITIS** (any CD4)—HSV encephalitis

DIAGNOSIS—CBCD, lytes, urea, Cr, blood C&S, serum CRAG (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 $\times 2$ months for consolidation, followed by *fluconazole* 200 mg PO daily as maintenance. Management of increased intracranial pressure may be needed

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$\times$ increased risk in HIV patients. May be extrapulmonary
- **NON-TB MYCOBACTERIUM**—MAC (CD4 $<100/mm^3$, pulmonary involvement alone is rare, usually disseminated)
- **FUNGAL** (CD4 $<500/mm^3$)—*Histoplasma*, *Coccidioides*, *Cryptococcus*
- ***PNEUMOCYSTIS JIROVECII* PNEUMONIA** (PJP, CD4 $<200/mm^3$)

DIAGNOSIS—CBCD, lytes, urea, Cr, LDH ($\uparrow$ in PJP but non-specific), blood C&S and mycobacterial culture, sputum C&S and AFB, ABG, urine C&S, CXR, bronchoscopy (lavage, biopsy)

TREATMENT OF PJP—*trimethoprim–sulfamethoxazole* 15 mg of TMP/kg PO/IV divided q8h daily $\times 21$ days. If severe disease (PaO_2 <70 mmHg), add *prednisone* 40 mg PO BID $\times 5$ days, then 40 mg PO daily $\times 5$ days, then 20 mg PO daily $\times 11$ days. Alternatives to *trimethoprim–sulfamethoxazole* include dapsone plus trimethoprim, or clindamycin plus primaquine, pentamidine IV. Use atovaquone if G6PD deficiency

ESOPHAGITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
  - **CANDIDA** (CD4 $<500/mm^3$)—50–70%
  - **HSV** (any CD4)—5–10%
  - **CMV** (CD4 $<100/mm^3$)—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

HEPATITIS/CHOLANGITIS/PANCREATITIS IN HIV PATIENTS

DIFFERENTIAL DIAGNOSIS

- **INFECTIONS**
  - **TB** (any CD4)
  - **MYCOBACTERIUM AVIUM COMPLEX** (MAC, CD4 $<100/mm^3$)—*M. avium, M. intracellulare*
  - **VIRUSES**—HBV, HCV, CMV
  - **PARASITES**—Cryptosporidium, Microsporidium, Cyclospora
- **ALCOHOL**
- **DRUGS**—antiretrovirals, antibiotics (sulfa, isoniazid, rifampin, ketoconazole, fluconazole)

DIAGNOSIS—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, lipase, INR, cultures and serologies, U/S 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 $<100/mm^3$)—*M. avium*, *M. intracellulare*
  - **CMV** (CD4 $<100/mm^3$)
  - **PARASITIC ★MAGIC★**—**M**icrosporidium, Ent**A**moeba, **G**iardia, **I**sospora, **C**ryptosporidium
- **MEDICATIONS**—antiretrovirals, antibiotics
- **AIDS ENTEROPATHY**—diagnosis of exclusion

DIAGNOSIS—CBCD, lytes, urea, Cr, stool C&S, stool O&P with acid fast staining, stool MAC, C. diff toxin, fecal WBC, Cryptosporidium

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–$200/mm^3$)

AIDS-ASSOCIATED MALIGNANCIES

AIDS-DEFINING MALIGNANCIES

- **KAPOSI'S SARCOMA** (any CD4)—strongly associated with HHV8. Lesions may involve skin, oral mucosa, lungs, and GI tract. Treat with liposomal doxorubicin
- **NON-HODGKIN'S LYMPHOMA** (CD4 $<100/mm^3$)—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 $<100/mm^3$)—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's 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 and other supportive individuals. Advise regarding condom use and safer sex practices. Risk reduction strategies should be explored for substance abuse (e.g. avoid alcohol use that may cause disinhibition), tobacco use, and other social issues. HIV is a chronic disease that can be successfully treated

PJP PROPHYLAXIS—for patients with CD4 $<200/mm^3$. *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

TOXOPLASMOSIS PROPHYLAXIS—for patients with positive *Toxoplasma* serology and CD4 $<100/mm^3$. *Trimethoprim–sulfamethoxazole* DS 1 tab PO daily. If allergic, dapsone plus pyrimethamine plus folinic acid are alternatives

MAC PROPHYLAXIS—for patients with CD4 $<50/mm^3$. *Azithromycin* 1200 mg PO once weekly

HISTOPLASMOSIS PROPHYLAXIS—for patients with CD4 $<150/mm^3$ and living in endemic area. *Itraconazole* 200 mg PO daily

TB PROPHYLAXIS—for patients with positive tuberculin skin test reaction (induration $\geq$5 mm) and not treated for TB previously. *Isoniazid* 5 mg/kg/day PO daily to max 300 mg/day, or 900 mg TIW $\times$9 months. *Rifampin* 600 mg PO daily $\times$4 month restricted to exposures to INH-resistant, RIF-susceptible isolates. Should be followed by a TB specialist

VACCINATIONS

- **GIVE**—pneumococcal vaccine every 5 years, hepatitis B vaccine (if non-immune), hepatitis A vaccine (if non-immune and especially if homosexual), influenza vaccine annually
- **GENERALLY AVOID**—live vaccines (oral polio, varicella, measles-mumps-rubella, or yellow fever immunizations)

Related Topics
Hepatitis B (p. 130)
Hepatitis C (p. 131)
HIV in Pregnancy (p. 413)
Needle Stick Injury (p. 269)
Tuberculosis (p. 250)

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). 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

FUSION INHIBITOR (FI)—enfuvirtide (T-20)

CCR5 ANTAGONIST—maraviroc

EXAMPLES OF PREFERRED HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) REGIMENS

- NRTI (tenofovir plus emtricitabine) plus NNRTI (efavirenz)
- NRTI (tenofovir plus emtricitabine) plus PI (atazanavir/ritonavir or darunavir/ritonavir)
- NRTI (tenofovir plus emtricitabine) plus integrase inhibitor (raltegravir)

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 symptomatic patients and in asymptomatic patients if CD4 $<350/mm^3$. Treatment should be considered for CD4 between 350 and $500/mm^3$ and is optional for those $>500/mm^3$. Rapidly declining CD4 counts ($>100/mm^3$/year) or baseline viral loads >100,000 copies/mL increase the urgency of treatment. Initiate HIV treatment regardless of CD4 in pregnancy, HIV nephropathy, and in those with HBV when therapy for HBV is indicated. A commitment to lifelong treatment and adherence is essential prior to initiating therapy. HIV therapy is increasingly complex and should only be undertaken by those with expertise in HIV management

RESPONSE—successful if viral load $\downarrow$ by 2 logs after 8 weeks and $\downarrow$ to <50 copies/mL after 6 months of therapy. Need to continue therapy or may develop viral load rebound/drug resistance. If failure, consider

THERAPEUTIC DECISIONS IN HIV (CONT'D)

non-adherence and/or resistance. Resistance testing should be performed, and the regimen should be changed based on resistance profile

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 disseminated MAC or worsening CXR and fever in patients with TB). In general, treat opportunistic infections for 2 weeks prior to initiating antiretroviral therapy

TREATMENTS—supportive, continue antiretrovirals, give 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 is associated with increased risk of progression to end-stage liver disease

VIRAL HEPATITIS IN HIV CO-INFECTED PATIENTS (CONT'D)

- **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
- **TREATMENT**—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

HEPATITIS C

- **PATHOPHYSIOLOGY**—HIV/HCV co-infection rate up to 70–95% for patients with IDU and hemophilia and 1–12% for men who have sex with men. Co-infection results in more aggressive HCV, with more rapid progression to liver failure and hepatocellular carcinoma, particularly if concurrent alcohol use
- **DIAGNOSIS**—rarely may be HCV seronegative requiring PCR testing. Histologic injury as defined by liver biopsy is a much better predictor of clinical outcomes than liver enzymes or HCV viral load and may be useful in selected patients to guide therapy
- **PREVENTION**—risk reduction and safer needle use
- **TREATMENT**—pegylated interferon α plus ribavirin at standard doses. Response rate is about 50% lower than for HCV monoinfection. ddI is contraindicated and AZT use is discouraged in those on ribavirin

NEJM 2007 356:14

Influenza

NEJM 2008 359:24

DIFFERENTIAL DIAGNOSIS

VIRAL—influenza A, B, C, parainfluenza, RSV, metapneumovirus, adenovirus, rhinovirus
BACTERIAL PNEUMONIA—*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus*, *Moraxella*
ATYPICAL—*Mycoplasma*, *Chlamydia*, *Legionella*, TB, community-acquired MRSA

PATHOPHYSIOLOGY

CLASSIFICATION—the three types of influenza are A, B, and C. Influenza A can be classified into various 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 can be further classified into various strains that arise due to antigenic drift

PATHOPHYSIOLOGY (CONT'D)

HOSTS—influenza B and influenza C viruses mainly affect humans. In contrast, 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. The process whereby at least two different viral strains combine to form a new subtype with a mixture of surface antigens of the original strains is termed antigenic shift and is the source of pandemic influenza virus

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.

PATHOPHYSIOLOGY (CONT'D)

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 in 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 human influenza A subtype through a process called 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 have 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

DISTINGUISHING FEATURES BETWEEN INFLUENZA A, B, AND C

	Influenza A	Influenza B	Influenza C
Hosts	Humans, Birds, Mammals	Humans only	Humans, Swine
Antigenic shift	Yes, creating new subtypes	No	No
Antigenic drift	Yes, creating new strains	Yes	Yes
Epidemics	Yes	Yes	No
Pandemics	Yes	No	No

CLINICAL FEATURES

SYMPTOMS—acute onset of systemic symptoms, such as fever, headache, myalgia, arthralgia, fatigue, and respiratory symptoms such as cough, dyspnea, and sore throat

CLINICAL FEATURES (CONT'D)

COMPLICATIONS—**respiratory** (bacterial pneumonia), **muscular** (rhabdomyolysis, myositis), **neurologic** (encephalitis, aseptic meningitis, transverse myelitis, Guillain–Barre syndrome)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE INFLUENZA?

	Sens	Spc	LR+	LR–
All age groups				
Fever	–	–	1.8	0.4
Feverishness	–	–	1.0	0.7
Cough	–	–	1.1	0.42
Myalgia	–	–	0.93	1.2
Malaise	73%	26%	0.98	1.1
Headache	–	–	1.0	0.75
Sore throat	–	–	1.0	0.96
Sneezing	–	–	1.2	0.87
Nasal congestion	–	–	1.1	0.49
Chills	83%	25%	1.1	0.68
Vaccine history	–	–	0.63	1.1
Fever and cough	64%	67%	1.9	0.54
Fever, cough, and acute onset	63%	68%	2.0	0.54
Age $\geq$60				
Fever	34%	91%	3.8	0.72
Feverishness	47%	78%	2.1	0.68
Cough	–	–	2.0	0.57
Myalgia	–	–	2.4	0.68
Malaise	57%	78%	2.6	0.55
Headache	–	–	1.9	0.70
Sore throat	–	–	1.4	0.77
Sneezing	32%	33%	0.47	2.1
Nasal congestion	47%	50%	0.95	1.0

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE INFLUENZA?

	Sens	Spc	LR+	LR–
Chills	46%	82%	2.6	0.66
Vaccine history	–	–	0.63	1.1
Fever and cough	30%	94%	5.0	0.75
Fever, cough, and acute onset	27%	95%	5.4	0.77

APPROACH—"clinical findings identify patients with influenza-like illness but are not particularly useful for confirming or excluding the diagnosis of influenza. Clinicians should use timely epidemiologic data to ascertain if influenza is circulating in their communities, then either treat patients with influenza-like illness empirically or obtain a rapid influenza test to assist with management decisions"

JAMA 2005 293:8

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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 for the following individuals: 50 or older, children 6–24 months or taking long-term salicylates, any chronic medical condition, pregnant women, healthcare workers, household contacts of those at risk, and residents of chronic care facilities. In some jurisdictions, universal vaccination for influenza is recommended. Depending on the match between vaccine and circulating virus, the efficacy can range from 70 to 90% for a good match and 0 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

MANAGEMENT (CONT'D)

the duration of symptoms by 1 day, reduces viral shedding, and may reduce complications in those at risk. Inhaled zanamivir is relatively contraindicated in patients with asthma or chronic respiratory conditions. Household contacts of infected individuals should be vaccinated and may be given prophylaxis with *oseltamivir* 75 mg PO daily or *zanamivir* 10 mg inhaled daily ×10 days. Resistance to oseltamivir is a problem in some strains of influenza A, and amantadine or rimantidine may have a role. Treatment of 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 C and resistance is now widspread in influenza A

VACCINE PRODUCTION—every February/March, the World Health Organization makes recommendations regarding the three strains (two A and one 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

Antiviral Agents

Antiviral agents	Mechanism	HSV, VZV	CMV	Influenza A	Influenza B
Acyclovir 200–800 mg PO BID 5x/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 x4 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		++	+++		
Foscarnet 90 mg/kg IV q12–24h	Pyrophosphate analogue that inhibits viral DNA polymerase	++	+++		
Cidofovir 5 mg/kg IV qweek	Nucleoside analogue that inhibits viral DNA polymerase	++	+++		
Amantadine 100 mg PO BID	Inhibit 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 q12–24h	Neuraminidase Inhibitors. Block release of influenza virus from infected cells			++	++
Oseltamivir 75 mg PO daily–BID				++	++

Fungal Infections

GENERAL APPROACH

CLASSIFICATION—fungal infections can be classified into three main categories: yeasts, molds ("filamentous fungi"), and dimorphic fungi

- **YEASTS**—grow as single cells (via budding) and include *Candida, Malassezia, Rodotorula, Trichosporon*
- **MOLDS**—these filamentous fungi grow as hyphae (via sexual and asexual reproduction) and include *Aspergillus*, 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—*Candida albicans* ("Germ-tube positive" with pseudohyphae) or non-albicans species ("Germ-tube negative," e.g. *C. glabrata, C. tropicalis, C. parapsilosis, C. krusei*), mostly in patients with hematological malignancy, neutropenia, on immunosuppressants, IDU, or those in the intensive care unit with hemodialysis, broad-spectrum antibiotics, surgery, central venous catheters, and 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 represents colonization only unless patient is symptomatic

TREATMENTS

- **OROPHARYNGEAL**—*clotrimazole troche* 10 mg 5× daily, *nystatin* suspension (500,000 U) or *nystatin pastilles* (200,000 U) 4× daily, *fluconazole* 100 mg PO/IV daily ×1–2 weeks
- **ESOPHAGITIS**—*fluconazole* 200 mg PO/IV daily ×2–3 weeks
- **CANDIDURIA**—remove catheter, indications for treatment include kidney transplant recipients,

CANDIDIASIS (CONT'D)

prior to cystoscopy or invasive GU procedure, neonates, severe illness, and possibly neutropenia (controversial). *Fluconazole* 200 mg PO/IV daily ×2 weeks

- **ACUTE DISSEMINATED CANDIDEMIA**—remove all intravascular devices. *Fluconazole* 800 mg 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 then 100 mg IV daily ×2 weeks (minimum) after last positive culture for *C. albicans*. Echinocandin and lipid formulation of amphotericin B are 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 *albicans* and *dubliniensis*. This is of no clinical significance because *albicans* and *dubliniensis* have same susceptibility patterns. Susceptibility patterns for other non-albicans infections may significantly differ. Consider echinocandin for non-albicans

CID 2009 48:5

ASPERGILLOSIS

MICROBIOLOGY—genus contains >185 species including *A. fumigatus* (80% of clinical infections), *A. flavus, A. niger, and A. terreus*

PATHOPHYSIOLOGY—mostly in patients with neutropenia, organ or stem cell transplants, advanced AIDS, or on 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 lesions (halo sign=nodule with surrounding hemorrhage, air-crescent sign=necrosis and cavitation). Sputum fungal culture and eosinophils, bronchoalveolar lavage, or lung biopsy

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

ASPERGILLOSIS (CONT'D)

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

CID 2008 46:3

ZYGOMYCETES (MUCORMYCOSIS)

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 pozaconazole. Note that susceptibility testing of Zygomycetes is not always reliable, and that caspofungin and "azoles" (apart from pozaconazole) are not generally effective

HISTOPLASMOSIS

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 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)

CID 2007 45:7

CRYPTOCOCCOSIS

MICROBIOLOGY—formerly believed to be unicellular yeast, although now confirmed to be dimorphic. Unlike other dimorphic fungi (e.g. *Histoplasma, Blastomyces, and Coccidioides*), *Cryptococcus* is ubiquitous and not geographically isolated. *Cryptococcus neoformans* has two varieties: *C. neoformans* var. *neoformans* and var. *gattii*

PATHOPHYSIOLOGY

- ***C. NEOFORMANS***—almost invariably in immunocompromised patients including HIV with CD4 $<100/mm^3$, 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 $\pm$ focal parenchymal brain infection

CLINICAL FEATURES—CNS, 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)

CID 2010 50:3

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 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 *Cocciodioides* is a level 3 pathogen. Therefore, cultures should be processed in high-level isolation unit and labeled carefully. There have been numerous reports of iatrogenic infection of laboratory personnel when adequate precautions not taken

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

CID 2005 41:9

BLASTOMYCES

PATHOPHYSIOLOGY—mostly found in northwest 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

CID 2008 46:12

Antifungal Agents

	Mechanism	Candida	Cryptococcus	Aspergillus	Other molds[a]	Dimorphic[b]	Zygomycota[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
Posaconazole 200 mg PO QID		+++	+++	+++	+++Fusa	++	+++	No
Amphotericin B[g]								
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[h]								
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	Inhibits synthesis of DNA (thymidylate synthetase)							
5 Flucytosine		+++	+++				++	Yes (dose)

[a] other than *Aspergillus*, *Fusarium*, *Scedosporium,* and *Pseudallescheria boydii* are all examples of molds
[b] dimorphic fungi include *Histoplasma capsulatum*, *Coccidioides immitis*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, and *Sporothrix schenckii*
[c] zygomycota fungi include *Rhizopus*, *Mucor,* and *Absidia*
[d] fluconazole is ineffective against some *Candida*, *Molds*, and *Zygomycetes*
[e] itraconazole is ineffective against some *Candida*, *Scedosporium*, and *Zygomycetes*. It has activity against *Cryptococcus,* but has less CSF penetration than fluconazole
[f] voriconazole is ineffective against some *Candida*, *Scedosporium*, and *Zygomycetes*. It has activity against *Cryptococcus*, but has less CSF penetration than fluconazole
[g] amphotericin B is ineffective against molds (*Fusarium*, *Scedosporium*, *Trichosporum*, *Aspergillus terreus*), *C. guilliermondii* and *C. lusitaniae*
[h] caspofungin is ineffective against *Zygomycetes*, *Cryptococcus,* and *Fusarium* but probably has activity against other molds

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) or amphotericin B (first line for others)

INDICATIONS FOR VORICONAZOLE (CONT'D)

FUNGEMIA—empiric treatment for fungi not yet speciated where neither amphotericin B nor fluconazole can be used

FEBRILE NEUTROPENIA—empiric antifungal treatment for patients intolerant of amphotericin B

INDICATIONS FOR CASPOFUNGIN

INVASIVE ASPERGILLOSIS—third line treatment for patients who are refractory or intolerant of voriconazole (first line) or amphotericin B (second line)

INVASIVE CANDIDIASIS—second or third line treatment for patients who are refractory or intolerant of fluconazole (first line for some) or amphotericin B (first line for others)

FUNGEMIA—empiric treatment for fungi not yet speciated where neither amphotericin B nor fluconazole can be used

FEBRILE NEUTROPENIA—empiric antifungal treatment for patients intolerant of amphotericin B

TREATMENT DEFINITIONS

REFRACTORY—persistence of positive cultures OR lack of clinical response despite ≥5 days of therapy and removal of catheter if applicable

INTOLERANCE—doubling from baseline and serum Cr ≥450 μmol/L [≥5.1 mg/dL], creatinine clearance ≤40 mL/min or concomitant administration of nephrotoxins, tripling of serum creatinine from baseline, documented allergy, or intolerable infusion reactions

Infection Control

NOSOCOMIAL INFECTIONS

DEFINITION—infections acquired in hospital that occur between 72 h after admission and 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 endotracheal tube insertion (>48 h, p. 94)

BACTEREMIA—secondary to central venous catheters. Infection rates are 3–7%

SURGICAL SITE INFECTIONS—secondary to incisions

PREVENTION STRATEGIES—hand washing, hand washing, and hand washing. 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 erect if intubated

ISOLATION

- **AIRBORNE** (negative pressure room with high-efficiency particulate aerator filter, certified N95 respirator for personal protection)—varicella, tuberculosis. Negative pressure room required
- **DROPLET** (mask within 3–6 feet; eye protection)—*H. influenzae*, *N. meningitidis*, influenza, RSV, pertussis
- **CONTACT** (glove, gown, wash hands)—*C. difficile*, VRE, MRSA

***N. MENINGITIDIS* PROPHYLAXIS**

- **CHEMOPROPHYLAXIS**—for exposures in last 7 days with *ciprofloxacin* 500 mg PO ×1 dose or *rifampin* 600 mg PO BID ×2 days can be used to reduce the risk of *N. meningitidis* in "close contacts." Vaccines are not recommended for primary prophylaxis post-exposure, but may be useful for epidemic control on a population basis

NOSOCOMIAL INFECTIONS (CONT'D)

- **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

PRE-EXPOSURE PROPHYLAXIS—immunization (hepatitis B vaccine at 0, 1, 6 months, influenza)

RISK OF TRANSMISSION—depends on the mechanism of exposure, source patient characteristics, pre- and post-exposure prophylaxis

- **HBV**—6–30% if source positive. Transmission via urine, feces, and saliva unlikely
- **HCV**—1.8% if source positive. Transmission via urine and feces unlikely
- **HIV**—0.3% if source positive. Transmission via urine, feces, and saliva unlikely

POST-EXPOSURE PROCEDURE

- **SOURCE PATIENT TESTING**—HBV, HCV, HIV
- **EXPOSED PERSON BASELINE TESTING**—HBV, HCV, HIV (ELISA, Western), CBCD, 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 (if source patient HIV positive). Therapy may include zidovudine and lamivudine ± protease inhibitor such as lopinavir/

NEEDLE STICK INJURY (CONT'D)

ritonavir (if source patient had been treated and drug resistance possible). Treatment should be started within 4 h

- **COUNSELING**—protective sexual intercourse, hold blood donation and breastfeeding, side effects of prophylactic medication(s), follow-up in 2 weeks

MMWR 2005 54:RR-9

NEEDLE STICK INJURY (CONT'D)

PROPHYLAXIS FOR OTHER INFECTIOUS AGENTS—diphtheria (penicillin or erythromycin), meningococcal (rifampin, ciprofloxacin, ceftriaxone), pertussis (trimethoprim–sulfa, erythromycin), rabies (rabies immune globulin, vaccine), varicella zoster (varicella-zoster immune globulin, vaccine), hepatitis A (immune globulin, vaccine)

Immunization for Adults — Ann Intern Med 2009 150:1

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 moths (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, men who have sex with men, 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), men who have sex with men, ?food handlers	–
Influenza IM	Inactivated	Annually (Oct)	Adults >50year, >6 month-50years with chronic disease, pregnancy, healthcare workers	
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 >60years. 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 9–26years (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	–
Td (tetanus, diphtheria) IM	Toxoid, inactivated	0, +2 months, +6–12 months, q10year	All adults *not* previously immunized in childhood (see Tdap under Pertussis)	–
Pneumococcal IM/SC	Polysaccharide	0, +5year	Adults >65years, >6 months-50years 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, *HAEMOPHILUS INFLUENZAE***—splenectomy

CONTRAINDICATIONS

- **ALL VACCINES**—anaphylaxis, severe illness
- **LIVE VACCINES**—pregnancy, immunocompromised (steroids, AIDS but not HIV, malignancies)

SIDE EFFECTS—local erythema, fever

Notes

9
RHEUMATOLOGY

Section Editor: Dr. Elaine Yacyshyn

Septic Arthritis

DIFFERENTIAL DIAGNOSIS OF MONOARTHRITIS

★ICU RN★

INFECTIONS

- **BACTERIAL**—Gonococci, *Staphylococcus aureus, Streptococcus*, Enterobacteriaceae, *Borrelia burgdorferi*, Syphilis, TB
- **VIRAL**—HIV, HBV, Parvovirus, rubella, mumps, enterovirus, adenovirus
- **FUNGAL**—*Cryptococcus, Blastococcus*
- **OSTEOMYELITIS/OSTEONECROSIS EXTENDING TO JOINT**

CRYSTAL—gout, pseudogout, hydroxyapatite, basic calcium phosphate

UNCLASSIFIED

- **TRAUMA**
- **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★**—**P**olymyositis, **P**alindromic rheumatism, **S**LE, **S**cleroderma, **R**heumatoid arthritis
- **SERONEGATIVE★PEAR★**—**P**soriatic arthritis, **E**nteric arthritis, **A**nkylosing spondylitis, **R**eactive 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, while most patients with risk factors for septic arthritis listed below are due to non-gonococcal infections (*S. aureus*, Streptococci, Gram-negative bacilli)

- **COMORBIDITIES**—diabetes, chronic kidney disease, rheumatologic disease, cancer, advanced disability
- **TREATMENT RELATED**—immunosuppressive therapy (glucocorticoids, cytotoxic agents), prosthetic joint

PATHOPHYSIOLOGY (CONT'D)

- **SPECIFICS**—IDU (more axial joints with MRSA, Gram negative especially *Pseudomonas*), endocarditis (sterile fluid as autoimmune process)

GONOCOCCAL ARTHRITIS—more common in women. Less destructive and has better outcome than non-gonococcal arthritis. The synovial fluid Gram stain is only positive in $<10\%$, and culture is often negative in gonococcal arthritis

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's, 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. Examine all joints and pay particular attention to the affected one. 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

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS ADULT PATIENT HAVE SEPTIC ARTHRITIS?

	Sens	Spc	LR+	LR−
History				
Age >80	19%	95%	3.5	0.86
Diabetes	12%	96%	2.7	0.93
Rheumatoid arthritis	68%	73%	2.5	0.45

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_9,

CLINICAL FEATURES (CONT'D)

	Sens	Spc	LR+	LR−
Recent joint surgery	24%	96%	6.9	0.78
Hip/knee prosthesis	35%	89%	3.1	
Skin infection	32%	88%	2.8	0.73
HIV infection	79%	50%	1.7	0.47
Joint pain	85%			
Joint edema	78%			
Fever	57%			
Sweats	27%			
Rigors	19%			
Physical				
Fever	46%	31%	0.67	1.7
Investigations				
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 ≥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"

JAMA 2007 297:13

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, uric acid, ANA, RF, ESR, CRP, INR, PTT
- **IMAGING**—joint XR (chondrocalcinosis in pseudogout (the presence of crystals does not rule out sepsis)
- **ARTHROCENTESIS**—★**3C**★ (**C**ell count with diff, **C**ulture and Gram stain, **C**rystal)

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

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. Absolute contraindication is infection overlying site of injection. Relative contraindications include *significant hemostasis* defects and bacteremia (**NEJM 2006 354:e19**)

- **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

MANAGEMENT

REMEMBER TO ALWAYS ASPIRATE BEFORE PROCEEDING TO TREATMENT

SYMPTOM CONTROL—NSAIDs/opioids for pain

TREAT UNDERLYING CAUSE—**empiric** (if not at risk for sexually transmitted disease, *nafcillin* 2 g IV q4h or *vancomycin* 1 g IV q12h, plus *ceftriaxone* 2 g IV q24h or *cefotaxime* 2 g IV q8h. If at risk of sexually transmitted disease, *nafcillin* 2 g IV q4h for Gram-positive organisms on Gram stain; otherwise, give *ceftriaxone* 2 g IV q24h or *cefotaxime* 2 g IV q8h if organisms not identifiable yet). **Gonococcal** (*ceftriaxone* 1 g IV q24h). **Lyme arthritis** (*amoxicillin* 500 mg PO QID, *doxycycline* 100 mg PO BID, *ceftriaxone* 2 g IV daily, *cefotaxime* 3 g IV BID ×4–6 weeks). **Therapeutic arthrocentesis**. **Arthroscopic or surgical drainage** (if joint inaccessible to needle drainage, organism resistant to antibiotics, or no clinical response in 3–4 days)

Gout

NEJM 2003 349:17

CAUSES

DECREASED URATE EXCRETION (90%)

- **RENAL DISEASE**
- **DRUGS ★CAN'T LEAP★**—**C**yclosporine, **A**lcohol, **N**icotinic Acid, **T**hiazides, **L**oop diuretics, **E**thambutol, **A**SA (low dose), **P**yrazinamide

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

PRECIPITANTS—surgery, dehydration, fasting, binge eating, binge 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**—CBCD, 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 XR

INVESTIGATIONS (CONT'D)

- **ARTHROCENTESIS**—**★3C★** (**C**ell count with diff, **C**ulture and Gram stain, **C**rystal, for gout, sens 85%, spc 100%)

SPECIAL

- **TOPHI 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 FLUID—ALWAYS confirm diagnosis with a synovial fluid tap 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; *sulindac* 150–200 mg PO BID ×7–10 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* 100–150 mg intra-articularly once). ***Colchicine*** 0.6 mg PO daily-BID during acute attack (avoid the approach of giving colchicine q1h until development of diarrhea)

LONG-TERM MANAGEMENT—purine-restricted diet (↓ red meats, ↓ seafood, ↑ low-fat dairy products, ↑ fruit and veges). ***Allopurinol*** 50–300 mg PO daily (first line, xanthine oxidase inhibitor, renal correction required, do not give in acute attack; however, continue allopurinol if already on it prior to acute attack). ***Probenecid*** 250–1000 mg PO BID (first line, ↓ renal urate reabsorption. Ensure normal renal function). ***Sulfinpyrazone*** 50–200 mg PO BID. ***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 (≥3/year, tophaceous deposits,

TREATMENT ISSUES (CONT'D)

overproduction of uric acid, or continued cyclosporine treatment)

ALLOPURINOL TREATMENT—remember to start colchicine or NSAIDs prior to allopurinol and to overlap therapy to prevent precipitating flare. Allopurinol alone can cause an abrupt decrease in serum uric acid → breakdown and release of synovial urate crystal deposits → inflammation. Aim to decrease serum uric acid level below 300 μmol/L [5.1 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 are visible radiographically. Crystals appear rhomboid and

SPECIFIC ENTITIES (CONT'D)

have positive birefringence (blue when parallel to polarized light, yellow when perpendicular). Risk factors include old age, advanced osteoarthritis, neuropathic joint, gout, hyperparathyroidism, hemochromatosis, diabetes, hypothyroidism, hypomagnesemia, trauma, and symptoms

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

NEJM 1994 330:11

DIFFERENTIAL DIAGNOSIS

★RICE★

RHEUMATOLOGIC

- **SEROPOSITIVE**—SLE, rheumatoid arthritis
- **SERONEGATIVE—**psoriatic arthritis, enteric arthritis, reactive arthritis
- **VASCULITIS**—polymyalgia rheumatica, Wegener's granulomatosis, Behcet's disease, Still's disease

INFECTIONS

- **BACTERIAL**—septic (Gonococci), meningococci, endocarditis, Lyme disease, Whipple's disease, mycobacteria
- **VIRAL**—Parvovirus, rubella, HBV, HCV, HIV, EBV
- **FUNGAL**
- **POST-INFECTIOUS/REACTIVE**—enteric infections, genitourinary infections, rheumatic fever, inflammatory bowel disease

CRYSTAL-INDUCED—gout, pseudogout

ETC

- **MALIGNANCIES**—acute leukemia
- **SARCOIDOSIS**—Lofgren's syndrome
- **FAMILIAL MEDITERRANEAN FEVER**
- **POLYMYALGIA RHEUMATICA**
- **MUCOCUTANEOUS DISORDERS**—dermatomyositis, erythema nodosum, erythema multiforme, pyoderma gangrenosum, pustular psoriasis

CLINICAL FEATURES

DISTINGUISHING FEATURES

- **TEMPERATURE >40°C [>104°F]**—Still's disease, bacterial arthritis, SLE

CLINICAL FEATURES (CONT'D)

- **FEVER PRECEDING ARTHRITIS**—viral arthritis, Lyme disease, reactive arthritis, Still's disease, bacterial endocarditis
- **MORNING STIFFNESS**—RA, polymyalgia rheumatica, Still's disease, some viral/reactive arthritis
- **MIGRATORY ARTHRITIS**—rheumatic fever, gonococcemia, meningococcemia, viral arthritis, SLE, acute leukemia, Whipple's disease
- **EPISODIC RECURRENCE**—palindromic rheumatism, Lyme disease, crystal-induced arthritis, IBD, Whipple's disease, Familial Mediterranean fever, Still's 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** ($>15x10^9$/L)—bacterial arthritis, bacterial endocarditis, Still's disease, systemic vasculitis, acute leukemia
- **LEUKOPENIA**—SLE, viral arthritis
- **POSITIVE RHEUMATOID FACTOR**—RA, viral arthritis, tuberculoses arthritis, bacterial endocarditis, SLE, sarcoidosis, systemic vasculitis

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, uric acid, TSH, ESR, CRP, RF, anti-CCP,

INVESTIGATIONS (CONT'D)

ANA, serologies (*Borrelia burgdorferi*, Streptococci, Parvovirus, HBV, HCV, HIV), c-ANCA, urinalysis

- **IMAGING**—CXR, X-rays of affected joints

SPECIAL

- **ARTHROCENTESIS**—**★3C★** (**C**ell count with diff [>2000 WBC/mm^3], **C**ulture and Gram stain, **C**rystal)

MANAGEMENT

TREAT UNDERLYING CAUSE
SYMPTOM CONTROL

SPECIFIC ENTITIES

STILL'S DISEASE

- **PATHOPHYSIOLOGY**—unknown. Most consider this as a diagnosis of exclusion
- **DIAGNOSIS**—major criteria include fever ≥39°C [≥102.2°F] (quotidian vs. diquotidian), salmon color maculopapular rash, arthralgia/arthritis ≥2 weeks, leukocytosis. Minor criteria include pharyngitis, lymphadenopathy, abnormal liver enzymes, hepatomegaly/splenomegaly, negative ANA, and 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)

Rheumatoid Arthritis

DIFFERENTIAL DIAGNOSIS OF POLYARTHRITIS

★RICE★

RHEUMATOLOGIC (>6 weeks)

- **SEROPOSITIVE ★PSSR★**—**P**olymyositis, **P**alindromic rheumatism, **S**LE, **S**cleroderma, **S**jogren's syndrome, **R**heumatoid arthritis
- **SERONEGATIVE ★PEAR★**—**P**soriatic arthritis, **E**nteric arthritis, **A**nkylosing spondylitis, **R**eactive arthritis, undifferentiated
- **VASCULITIS**—polymyalgia rheumatica, Wegener's granulomatosis, Behcet's disease, Still's disease

INFECTIONS (<6 weeks)

- **BACTERIAL**—sepsis, endocarditis, Lyme disease, Whipple's disease, mycobacteria
- **VIRAL**—Parvovirus, rubella, HBV, HCV, HIV
- **FUNGAL**
- **POST-INFECTIOUS/REACTIVE**—enteric infections, genitourinary infections, rheumatic fever, inflammatory bowel disease

CRYSTAL—gout, pseudogout, hydroxyapatite, basic calcium phosphate

ETC

- **MALIGNANCIES**—leukemia
- **SARCOIDOSIS**—Lofgren's syndrome
- **FAMILIAL MEDITERRANEAN FEVER**
- **MUCOCUTANEOUS DISORDERS**—dermatomyositis, erythema nodosum, erythema multiforme, pyoderma gangrenosum, pustular psoriasis polymyalgia rheumatica

PATHOPHYSIOLOGY

CLASSIFICATION OF ARTHRITIS

- **MONOARTHRITIS**—1 joint involved
- **OLIGOARTHRITIS**—2–4 joints involved
- **POLYARTHRITIS**—≥5 joints involved

DESTRUCTION OF CARTILAGE—T-helper 1 mediated process → proteases produced by synovial cells destroy proteoglycans in the articular cartilage → 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 level of education

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 Boutonniere, 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 joint 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 (cervical myelopathy with hand weakness/numbness)
- **TEMPOROMANDIBULAR** (30%)

CLINICAL FEATURES (CONT'D)

- **OTHERS**—related disorders include Baker cyst, tenosynovitis, carpal tunnel syndrome

Related Topics
Gout (p. 275)
Inflammatory Myositis (p. 281)
Lupus (p. 280)
Scleroderma (p. 281)

EXTRA-ARTICULAR MANIFESTATIONS—only in rheumatoid factor seropositive patients

- **RHEUMATOID NODULES** (20%)
- **PULMONARY**—pleural effusion (exudates, low glucose), pulmonary nodules (Caplan's syndrome), acute interstitial pneumonitis, bronchiolitis obliterans
- **CARDIAC**—valvular abnormalities, myocarditis, pericardial effusion, constrictive pericarditis
- **GI**—elevated transaminases (especially ALP), nodular hyperplasia (portal hypertension, hypersplenism)
- **HEMATOLOGIC**—anemia of chronic disease, Felty syndrome (triad of seropositive rheumatoid arthritis, neutropenia often associated with anemia and thrombocytopenia and splenomegaly. Patients at risk of life-threatening bacterial infections). Large granular lymphocyte leukemia, lymphoma
- **NEUROLOGIC**—peripheral sensory neuropathy (not motor), myelopathy from cervical vertebral subluxation
- **OPHTHALMIC**—keratoconjunctivitis sicca (Sjogren's 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	Worsens	Improves
Activity	Improves	Worsens
Synovitis, redness	+	–
Fever, weight loss	+	–
ESR, CRP, platelets	↑	No change

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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)

SPECIAL

- **INFECTIOUS WORKUP**—serologies (Parvovirus, HBV, HCV, EBV, CMV, *Borrelia burgdorferi*)
- **ARTHROCENTESIS**—★**3C**★ (**C**ell count with diff [>2000 WBC/mm^3], **C**ulture and Gram stain, **C**rystal. Cannot make definite diagnosis of rheumatoid arthritis from arthrocentesis)

DIAGNOSTIC AND PROGNOSTIC ISSUES

ACR DIAGNOSTIC CRITERIA FOR RHEUMATOID ARTHRITIS—morning stiffness (>1 h), arthritis of ≥3 joint areas (either side of PIP, MCP, wrist, elbow, knee, ankle, and MTP), arthritis of hand joints (PIP, MCP), symmetric arthritis by area, subcutaneous rheumatoid nodules, positive rheumatoid factor, radiographic changes (hand and wrist X-ray with erosion of joints or unequivocal demineralization around joints). Need 4 of 7 criteria to make diagnosis, with first 4 criteria for at least 6 weeks

PROGNOSIS—increased number of joints involved, presence of rheumatoid nodules and seropositivity all suggest more severe disease

MANAGEMENT

SYMPTOM CONTROL—**physical therapy**, **diet** (Ω-3 and Ω-6 fatty acids). **Joint protection** (range of motion exercises, orthotics, splints). **NSAIDs** (anti-inflammatory dose). **Intraarticular steroid injections** (if severe pain). **Patient education**

DISEASE-MODIFYING AGENTS OF RHEUMATOID DISEASE (DMARDs)—**single agent** (methotrexate with folic acid, sulfasalazine, hydroxychloroquine, minocycline, cyclosporine, azathioprine, gold). **Combination triple therapy** (methotrexate plus sulfasalazine plus hydroxychloroquine). **Selective pyrimidine synthesis inhibitor** (leflunomide). **TNFα inhibitors** (infliximab, etanercept, adalimumab). **B-cell inhibitor** (rituximab, an anti-CD20 monoclonal antibody). **T-lymphocyte activation inhibitor** (abatacept). **Surgical intervention**

SPECIFIC ENTITIES

PALINDROMIC RHEUMATISM—episodic arthritis with one or more joints being affected sequentially for hours to days, and symptom-free periods in

SPECIFIC ENTITIES (CONT'D)

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

SJOGREN'S SYNDROME (KERATOCONJUNCTIVITIS SICCA)

- **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, along with impaired taste, parotid gland enlargement, dental caries), dyspareunia, arthralgia, arthritis, and constitutional symptoms. May be associated with Raynaud's phenomenon, cutaneous vasculitis, cerebritis, CNS vasculitis, stroke, and peripheral neuropathy
- **INVESTIGATIONS**—quantitative Ig (polyclonal IgG), RF, ANA, ENA (SS-A, SS-B). Check for secondary causes
- **TREATMENTS**—symptomatic (artificial tears, *pilocarpine* 5 mg PO QID), hydroxychloroquine

LOFGREN'S SYNDROME—a benign self-limited form of sarcoidosis. Tetrad of erythema nodosum, hilar lymphadenopathy, arthritis (ankles and sometimes knees), and uveitis

SPECIFIC ENTITIES (CONT'D)

RESPIRATORY DISEASES IN RHEUMATOID ARTHRITIS

- **AIRWAY**—cricoarytenoid arthritis with central airway obstruction, bronchiectasis, obliterative bronchiolitis, chronic small airway obstruction
- **PARENCHYMA**—pneumonia (particularly with immunosuppression), 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

UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE—overlap syndrome with clinical features of two or more rheumatologic disorders (RA, SLE, Sjogren's syndrome, scleroderma, inflammatory myopathies) but does not fit the diagnostic criteria for any specific disorder

MIXED CONNECTIVE TISSUE DISEASE—a specific overlap syndrome with clinical features of SLE, scleroderma, polymyositis, and antibodies to RNP. Characteristically, Raynaud's phenomenon, myositis, and synovitis are present

Systemic Lupus Erythematosus

PATHOPHYSIOLOGY

POPULATION—typically affects women aged 15–45

AUTOIMMUNE REACTION—antibody-immune complex deposition in kidneys (glomerulonephritis), autoantibodies against cell surface antigens on hematopoietic progenitor cells (anemia, neutropenia, thrombocytopenia), antiphospholipid antibodies (thrombosis)

ACR DIAGNOSTIC CRITERIA ★4-RASHES★

- **4** rashes—malar rash, discoid rash, oral ulcers, photosensitivity
- **R**enal—proteinuria >0.5 g/day or $\geq 3+$, or cellular casts)
- **A**rthritis ≥ 2 peripheral joints, non-erosive
- **S**erositis—pleuritis, pericarditis
- **H**ematologic—hemolytic anemia, leukopenia $<4.0 \times 10^9$/L, lymphopenia $<1.5 \times 10^9$/L, thrombocytopenia $<100 \times 10^9$/L
- **E**xcitation—seizures, psychosis
- **S**erology—ANA, anti-dsDNA, anti-Smith, antiphospholipid antibodies, false-positive VDRL

PATHOPHYSIOLOGY (CONT'D)

Need ≥ 4 of 11 criteria (each rash counts as one criterion and ANA as a separate criterium) to make diagnosis. Note that many patients may not ever fulfill four criteria until several years into their disease course

CLINICAL FEATURES

JOINT SYMPTOMS—symmetric non-erosive polyarthritis with joint pain, swelling, redness, morning stiffness (>1 h), and dysfunction. Sens 88%

- **HANDS**—Jaccoud's arthritis (joint deformities are unusual). Fingers and wrists may be involved
- **LEGS**—knees more commonly affected
- **AVASCULAR NECROSIS**—hip, shoulder, and knee may be affected

EXTRA-ARTICULAR MANIFESTATIONS

- **PULMONARY**—pleuritis (sens 50%), pulmonary hypertension, PE, shrinking lung syndrome (dyspnea, pleuritic chest pain, progressive reduction in lung volume, elevated diaphragms)
- **CARDIAC**—pericarditis (sens 30%), myocarditis, Libman–Sacks endocarditis

CLINICAL FEATURES (CONT'D)

- **RENAL**—proteinuria or active sediment (sens 50%), glomerulonephritis
  - **WHO CLASSIFICATION OF LUPUS NEPHRITIS**
    - **NORMAL** (class I)—asymptomatic
    - **MESANGIAL PROLIFERATIVE** (class II)—mild hematuria or proteinuria
    - **FOCAL PROLIFERATIVE** (class III)—nephritic syndrome, proteinuria
    - **DIFFUSE PROLIFERATIVE** (class IV)—nephritic syndrome, nephrotic syndrome
    - **MEMBRANOUS GLOMERULONEPHRITIS** (class V)—nephrotic syndrome
    - **GLOMERULOSCLEROSIS** (class VI)—uremia
    - **SEVERITY**—VI >IV >III >V >II >I, consider aggressive treatment for class III, IV
- **GI**—mesenteric thrombosis and vasculitis, transaminitis/hepatitis. Corticosteroids could increase risk of peptic ulcer disease
- **HEMATOLOGIC**—anemia of chronic disease, autoimmune hemolytic anemia, lymphopenia, thrombocytopenia
- **NEUROLOGIC**—aseptic meningitis, transverse myelitis, stroke, seizures, organic brain syndrome, psychosis, depression, peripheral neuropathy
- **DERMATOLOGIC**—photosensitivity (sens 50%), malar rash (nasolabial folds spared, sens 50%), discoid lupus (erythematous papules/plaques with central hypopigmentation, atrophic scarring involving scalp and exposed skin, sens 25%), mucosal ulcers (oral, vaginal, nasal septal), alopecia, livedo reticularis, palpable purpura, Raynaud's

SEROLOGIC—ANA (sens >99%), anti-dsDNA (sens 40%), anti-Smith (sens 25%), 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 embolisms

INVESTIGATIONS

BASIC

- **BLOOD TESTS**—CBCD, 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, spc), anti-Ro/La (especially in pregnancy, associated with neonatal lupus and congenital complete heart block), antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant), cryoglobulin
- **INFECTIOUS WORKUP**—serologies (Parvovirus, HBV, HCV, EBV, CMV)
- **ARTHROCENTESIS**—★**3C**★ (**C**ell count with diff [>2000 WBC/mm^3], **C**ulture and Gram stain, **C**rystal. Cannot make definite diagnosis of systemic lupus erythematosus from arthrocentesis)

MANAGEMENT

SYMPTOM CONTROL—**cutaneous lupus** (sunscreen, hydroxychloroquine). **Arthritis** (NSAIDs, hydroxychloroquine, steroids, methotrexate). **Nephritis and neuritis** (steroids, cyclophosphamide, mycophenolate mofetil). **Serositis** (NSAIDs, steroids). **Thrombocytopenia** (steroids, IVIG, splenectomy). **Avoid exogenous estrogen**

TREAT UNDERLYING CAUSE—**rituximab**

SPECIFIC ENTITIES

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, atenolol, anti-TNFα (infliximab, etanercept), captopril, carbamazepine, chlorpromazine, enalapril, ethosuximide, hydrochlorothiazide, isoniazid, lithium, methyldopa, 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, no "blacks," 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

RAYNAUD'S PHENOMENON

- **PATHOPHYSIOLOGY**—exaggerated vasoconstriction to cold, emotional stress, or exercise. Triphasic changes from white to blue to red
- **CAUSES**—**primary** (isolated Raynaud's), **secondary** (trauma [Jack hammer, vibrations], rheumatologic [SLE, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis, mixed connective tissue disease], drugs [ergots, cocaine, β-blockers, bleomycin, vinblastine, interferon], tumors [lymphoma,

SPECIFIC ENTITIES (CONT'D)

carcinoid syndrome, pheochromocytoma], occlusive arterial disease, hyperviscosity, hypothyroidism, Parvovirus B19, PBC)

- **CLINICAL FEATURES**—usually symmetric episodes of sharply demarcated color changes of the 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**—avoidance (cold, stress, smoking, sympathomimetic drugs). Keep core temperature stable. Terminate attacks early (place hands in warm water). Calcium channel blockers (*nifedipine* 10–60 mg PO TID, *amlodipine* 5–20 mg PO daily). Topical nitrates. ASA. Anticoagulate (if antiphospholipid antibodies or surgical interventions required)

Related Topic
Cutaneous Lupus Erythematosus (p. 371)

SCLERODERMA

- **PATHOPHYSIOLOGY**—extensive fibrosis and some degree of inflammation of skin, blood vessels, and internal organs (GI, lungs, renal, cardiac). There are four subtypes, including diffuse systemic sclerosis (progressive systemic sclerosis), limited systemic sclerosis ★**CREST**★ syndrome (**C**alcinosis, **R**aynaud's phenomenon, **E**sophageal dysmotility, **S**clerodactyly, **T**elangiectasias), localized scleroderma (morphea, linear), and scleroderma sine scleroderma
- **CLINICAL FEATURES**—Raynaud's phenomenon may precede skin changes for years. Usually involves the skin (starts from extremities extending proximally, progressing from edematous to fibrotic to atrophic stage. Common signs include dilated capillary loops, sclerodactyly, flexion contractures, hypopigmentation, hyperpigmentation, "coup de sabre deformity", purse lip, telangiectasia), and GI hypomotility (dry mouth, dysphagia, dyspepsia, N&V, abdominal pain, constipation, diarrhea, weight loss). The lungs (pleural effusion, pulmonary fibrosis, pulmonary hypertension), kidneys (renal crisis), and heart (pericarditis) may also be involved

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—major criterion is sclerodermatous skin changes proximal to the MCP joints. Minor criteria include sclerodactyly, digital pitting scars, and bilateral pulmonary fibrosis. Tests include antibodies to topoisomerase I (anti-SCl 70) seen more in diffuse systemic sclerosis and antibody to centromere seen more in CREST
- **TREATMENTS**—Raynaud's (calcium channel blockers). GERD (proton pump inhibitor). Renal crisis (ACE inhibitors). Interstitial pneumonitis (steroids, azathioprine, cyclophosphamide). Pulmonary hypertension (endothelin antagonists [Bosentan])

INFLAMMATORY MYOPATHIES

- **PATHOPHYSIOLOGY**—classified as polymyositis, dermatomyositis, and inclusion body myositis
- **ASSOCIATIONS**—dermatomyositis is associated with malignancy (GI, lung, ovarian, breast, lymphoma) in 6–45% of patients
- **CLINICAL FEATURES**—proximal, symmetric, progressive muscle weakness developing over weeks to months, may be associated with morning stiffness. Muscle pain is not common. Extramuscular manifestations include **arthralgias**, **cardiac** (conduction abnormalities, cardiomyopathy), **respiratory** (muscle weakness, aspiration, interstitial lung disease), **skin** (Gottron's 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 are usually normal
- **DIAGNOSIS**—symmetric proximal weakness, elevation of muscle enzymes, EMG findings consistent with inflammatory myositis, muscle biopsy consistent with inflammatory myositis. Need all four criteria for definite polymyositis, and three criteria plus skin findings for definite dermatomyositis. Important to exclude other causes of myopathies. Anti-Jo1, anti-Mi2, anti-SRP
- **TREATMENTS**—prednisone, methotrexate, azathioprine, leflunomide, IVIG

DISTINGUISHING FEATURES BETWEEN STEROID MYOPATHY AND INFLAMMATORY MYOPATHIES

	Steroidmyopathy	**Inflammatory myopathies**
History	Steroid use Other steroid-related symptoms	Other inflammatory myopathy symptoms
Physical	Neck flexor normal	Neck flexor weaker
Tests	CK less often ↑	CK often ↑, anti-Jo1/anti-Mi2 Ab
EMG	Normal	Abnormal activity
Stop steroid	Improves	Worsens

Seronegative Spondyloarthropathies

DIFFERENTIAL DIAGNOSIS OF OLIGOARTHRITIS

★RICE★

RHEUMATOLOGIC (>6 weeks)

- **SEROPOSITIVE ★PSSR★**—**P**olymyositis, **P**alindromic rheumatism, **S**LE, **S**cleroderma, **R**heumatoid arthritis
- **SERONEGATIVE ★PEAR★**—**P**soriatic arthritis, **E**nteric arthritis, **A**nkylosing spondylitis, **R**eactive arthritis, undifferentiated
- **VASCULITIS**—polymyalgia rheumatica, Wegener's granulomatosis, Behcet's disease, Still's disease

INFECTIONS (<6 weeks)

- **BACTERIAL**—sepsis, endocarditis, Lyme disease, Whipple's 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's syndrome
- **FAMILIAL MEDITERRANEAN FEVER**
- **MUCOCUTANEOUS DISORDERS**—dermatomyositis, erythema nodosum, erythema multiforme, pyoderma gangrenosum, pustular psoriasis 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, morning stiffness >30 min
- **ENTHESOPATHY**—inflammation at the sites of insertion of ligaments, tendons, joint capsule, and fascia to bone, with both destruction and new bone formation. This results in Achilles tendonitis, plantar fasciitis, tenosynovitis, and dactylitis/sausage fingers
- **SEROLOGY**—HLA-B27 positive, rheumatoid factor negative

BACK EXAMINATION

- **INSPECTION**—swelling, erythema, atrophy, scars, and loss of thoracic kyphosis and cervical/lumbar lordosis
- **RANGE OF MOTION**—check gait and flexion, extension, lateral bending, rotation
- **PALPATION**—tenderness over spinous processes and sacroiliac joints

CLINICAL FEATURES (CONT'D)

- **SPECIAL TESTS**—Schober's test (place mark 5 cm below and mark 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. Perform 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, cauda equine compression, and enthesitis (costochondritis, patellar and Achilles tendonitis, plantar fasciitis). May also assess for extraintestinal manifestations of inflammatory bowel disease

DISTINGUISHING FEATURES BETWEEN VARIOUS SERONEGATIVE SPONDYLOARTHROPATHIES

- **PSORIATIC ARTHRITIS**—history of psoriasis, DIP involvement
- **ENTERIC ARTHRITIS**—history of IBD
- **ANKYLOSING SPONDYLITIS**—back involvement, ankylosis (stiffness)
- **REACTIVE ARTHRITIS**—history of urethritis/cervicitis/diarrhea, eye involvement
- **UNDIFFERENTIATED**—does not fit any of the above

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, ESR, CRP, urinalysis
- **IMAGING**—X-rays of affected joints (lumbosacral spine, peripheral)

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 (only order once)
- **ARTHROCENTESIS**—**★3C★** (**C**ell count with diff, **C**ulture and Gram stain, **C**rystal)

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%)

MANAGEMENT

SYMPTOM CONTROL—physical therapy, NSAIDs, glucocorticoid injections

TREAT UNDERLYING CAUSE—sulfasalazine, methotrexate, pamidronate, and anti-TNF agents. Surgery

SPECIFIC ENTITIES

ANKYLOSING SPONDYLITIS (AS)

- **CLINICAL FEATURES**—spondylitis, sacroiliitis, morning stiffness, and arthritis of the hips, knees, shoulders, and occasionally peripheral joints. Loss of lumbar lordosis and thoracic kyphosis with significant decreased range of motion and chest expansion, positive Schober's test and occiput-to-wall test. Extraarticular manifestations include anterior uveitis, C1–2 subluxation, restrictive lung disease, aortic regurgitation, conduction abnormalities, and secondary amyloidosis. Imaging reveals bamboo spine (syndesmophytes), shiny corners (squaring and increased density anteriorly of vertebral bodies), and whiskering (new bone and osteitis at tendon and ligament insertions)
- **NEW YORK DIAGNOSTIC CRITERIA**
  - **CLINICAL CRITERIA**—low back pain and morning stiffness of >3 months, limitation of motion of the lumbar spine in both the sagittal and frontal planes, and limitation of chest expansion (<2.5 cm [1 in.])
  - **RADIOLOGIC CRITERIA**—sacroiliitis with more than minimum abnormality bilaterally or unequivocal abnormality unilaterally
  - **DIAGNOSIS**—one clinical plus one radiologic criterion = definite AS; three clinical criteria or one radiologic criterion only = probable AS

ENTEROPATHIC ARTHRITIS

- **PATHOPHYSIOLOGY**—10–20% of IBD patients (more common in Crohn's 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 colitis. Other extraintestinal manifestations of IBD include fever, clubbing, uveitis, iritis, anemia, jaundice (primary sclerosing cholangitis), aphthous ulcers (Crohn's mainly), arthritis, erythema nodosum, pyoderma gangrenosum, DVT, and amyloidosis
- **TREATMENTS**
  - **TYPE I ARTHROPATHY**—acute, pauciarticular peripheral arthritis ± spondylitis and sacroiliitis, associated with flares. Usually self-limited and resolves with treatment of IBD (but not axial arthritis)
  - **TYPE II ARTHROPATHY**—polyarticular peripheral arthritis that does not parallel bowel disease. Consider sulfasalazine, methotrexate, azathioprine, and glucocorticosteroids. Avoid NSAIDs if possible (which may worsen bowel symptoms)

SPECIFIC ENTITIES (CONT'D)

PSORIATIC ARTHRITIS

- **PATHOPHYSIOLOGY**—psoriatic arthritis is ALWAYS associated with psoriasis. Arthritis may appear after (70%), before (15%), or at the same time (15%) as skin lesions
- **CLINICAL FEATURES**—spondylitis, sacroiliitis, morning stiffness, arthritis (distal DIP joints, asymmetric oligoarthritis of lower limbs, symmetric polyarthritis, arthritis mutilans), enthesitis (Achilles tendonitis, plantar fasciitis, tenosynovitis, dactylitis), nail changes (pits, onycholysis), pitting edema, and uveitis. 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%
- **DIAGNOSIS**—requires one major and three minor criteria
  - **MAJOR**—presence of musculoskeletal inflammation (inflammatory arthritis, enthesitis, back pain)
  - **MINOR**—skin psoriasis, nail lesions, dactylitis, negative rheumatoid factor, and juxtaarticular bone formation on X-ray
- **TREATMENTS**—methotrexate, sulfasalazine, leflunomide, anti-TNF agents

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**—spondylitis, sacroiliitis, morning stiffness, lower limb arthritis (asymmetric oligoarthritis of lower limbs), 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). Plain film reveals fluffy erosions, periosteal spurs, and asymmetric syndesmophytes

SPECIFIC ENTITIES (CONT'D)

- **ACR DIAGNOSTIC CRITERIA**—episode of arthritis of more than 1 month with urethritis and/or cervicitis (sens 84.3%, spc 98.2%), episode of arthritis of more than 1 month and either urethritis or cervicitis, or bilateral conjunctivitis (sens 85.5%, spc 96.4%), episode of arthritis, conjunctivitis, and urethritis (sens 51%, spc 99%), episode of arthritis of more than 1 month, conjunctivitis, and urethritis (sens 48%, spc 99%)

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—NSAIDs (pain control), sulfasalazine, anti-TNF agents, methotrexate, azathioprine, leflunomide

Related Topics
Inflammatory Bowel Disease (p. 120)
Psoriasis (p. 362)

Back Pain NEJM 2005 353:4

DIFFERENTIAL DIAGNOSIS

MECHANICAL

- **TRAUMA**—sprain, strain, fracture
- **FRACTURE**—compression, traumatic
- **SPONDYLOSIS**—disc, annulus, facet
- **SPONDYLOLISTHESIS**

INFLAMMATORY

- **RHEUMATOLOGIC**—psoriatic arthritis, enteric arthritis, ankylosing spondylitis, reactive arthritis
- **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"

JAMA 1992 268:6

CLINICAL FEATURES (CONT'D)

INVESTIGATIONS

BASIC

- **IMAGING**—spine XR

SPECIAL

- **IMAGING**—CT spine, MRI spine (if surgery), myelogram (gold standard but seldom used)
- **MYELOMA WORKUP**—CBCD, lytes, urea, Cr, ESR, serum protein electrophoresis, urinary protein electrophoresis

Related Topics
Ankylosing Spondylitis (p. 283)
Radiculopathy (p. 323)
Spinal Cord Compression (p. 228)

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

SPECIFIC ENTITIES

SPINAL CORD COMPRESSION—compression of spinal cord (upper motor neuron, usually above L1 level). Symptoms include lower limb weakness, increased tendon reflexes in legs, sensory loss usually 1–5 levels below cord lesion with sacral sparing (see p. 228 for more details)

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)—defined as 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

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 the 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**—common causes include degenerative disc disease, osteoarthritis of facet joints with osteophyte and cyst formation, ligamentum flavum hypertrophy, and spondylolisthesis. Laminectomy, spinal fusion, trauma, Cushing's syndrome, Paget's 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 the lower extremities. The Romberg test may show wide-based gait and unsteadiness
- **DIAGNOSIS**—CT/MRI spine, lumbar myelogram
- **TREATMENTS**—pain control (acetaminophen, NSAIDs, opioids, lumbar epidural corticosteroid injections), decompression surgery with laminectomy and partial facetectomy. Physiotherapy consultation

Osteoarthritis

NEJM 2007 357:14

DIFFERENTIAL DIAGNOSIS

PRIMARY OSTEOARTHRITIS

- **GENERALIZED**—primary generalized, diffuse idiopathic skeletal hyperostosis
- **ISOLATED**—nodal, hips, erosive

SECONDARY OSTEOARTHRITIS

- **MECHANICAL**—post-traumatic, post-surgical
- **NEUROPATHIC JOINTS**—diabetes, syphilis, spinal cord injury
- **INFLAMMATORY**—RA, crystal arthropathies, infectious
- **METABOLIC**—hemochromatosis, Wilson's disease, acromegaly, Paget's disease, Cushing's 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). Important to try to distinguish from periarticular structures (tendonitis, bursitis)

PATHOPHYSIOLOGY

ARTICULAR CARTILAGE—not due to 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 and subsequent degeneration of surrounding soft tissues

RISK FACTORS FOR PRIMARY OSTEOARTHRITIS—age, female, obesity, high bone mass, mechanical factors (previous joint injury, excessive varus, or valgus), smoking, genetics

CLINICAL FEATURES

SUBTYPES OF PRIMARY OSTEOARTHRITIS

- **GENERALIZED**—affects DIP (Heberden's nodes), PIP (Bouchard's nodes) and first CMC joints, hips, knees, and spine. More common in women
- **ISOLATED NODAL**—affects DIP joints only. More common in women
- **ISOLATED HIP**—affects hips only. More common in men
- **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)—affects spine mainly but peripheral joints may also be involved, with osteophytes connecting $\geq$4 vertebrae. Also known as Forestier disease. X-rays are diagnostic. May mimic ankylosing spondylitis

INVESTIGATIONS

IMAGING—X-ray of affected joints (joint space narrowing, marginal osteophytes, subchondral sclerosis, and cysts)

DIAGNOSTIC ISSUES

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY OSTEOARTHRITIS—primary osteoarthritis almost never involves the shoulders, elbows, ankles, MCP joints, or ulnar side of wrist. Should consider secondary osteoarthritis if unusual sites for primary osteoarthritis or widespread chondrocalcinosis

ACR DIAGNOSTIC CRITERIA FOR HAND OSTEOARTHRITIS—hand pain, aching, or stiffness and three or four of the following features (hard tissue enlargement of 2 or more of 10 selected joints [second and third DIP and PIP, first CMC], hard tissue enlargement of 2 or more DIP joints, fewer than 3 swollen MCP joints, deformity of at least 1 of 10 selected joints). Sens 94%, spc 87%

ACR DIAGNOSTIC CRITERIA FOR HIP OSTEOARTHRITIS—hip pain and at least two of the following three features: ESR $<$20 mm/h, radiographic femoral or acetabular osteophytes, radiographic joint space narrowing. Sens 89%, spc 91%

MANAGEMENT

CONSERVATIVE MEASURES—patient education, weight reduction, exercise, physiotherapy, assistive devices

SYMPTOM CONTROL—*acetaminophen* 325–650 mg PO q4–6 h, NSAIDs (use lowest effective dose and add proton pump inhibitor for gastric protection. *Naproxen* 200–500 mg BID, *ibuprofen* 200–800 mg QID, *diclofenac gel* 5% apply to affected area QID), capsaicin cream, intra-articular glucocorticoids, acupuncture, glucosamine, and chondroitin sulfate. No medical treatment shown to slow progression. Splints and braces may also be useful sometimes

JOINT REPLACEMENT—indicated if uncontrollable pain or joint instability

SPECIFIC ENTITIES

POST-TRAUMATIC SECONDARY OSTEOARTHRITIS—usually isolated large joints. Knee OA may develop after meniscal tear, and shoulder OA may develop with long-standing rotator cuff injury

HEMOCHROMATOSIS—affects second and third MCP and shoulders mainly (see p. 420 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 femur head, tibial plateau, humeral head, and vertebrae more commonly
- **ASSOCIATIONS**—★**ASEPTIC**★ **A**lcohol, **S**teroids, **S**epsis, **S**torage disease (Gaucher), **S**ickle cell disease, **E**mboli (fat, cholesterol), **P**ost-radiation, **T**rauma, **I**diopathic, **C**onnective tissue disease (SLE, rheumatoid arthritis, vasculitis), **C**ancer, hyper**C**oagulable states

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—joint pain. Have high index of suspicion, especially if prior use of high-dose steroids
- **DIAGNOSIS**—plain radiograph (initially appears normal), CT, bone scan. MRI is the most sensitive test

SPECIFIC ENTITIES (CONT'D)

- **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 (more localized)

NEUROLOGIC—multiple sclerosis

PSYCHIATRIC—depression

PATHOPHYSIOLOGY

INCREASED PAIN PERCEPTION ASSOCIATIONS—irritable bowel syndrome, irritable bladder syndrome, chronic headaches, mood disorders (depression, anxiety), sleep disorders

CLINICAL FEATURES

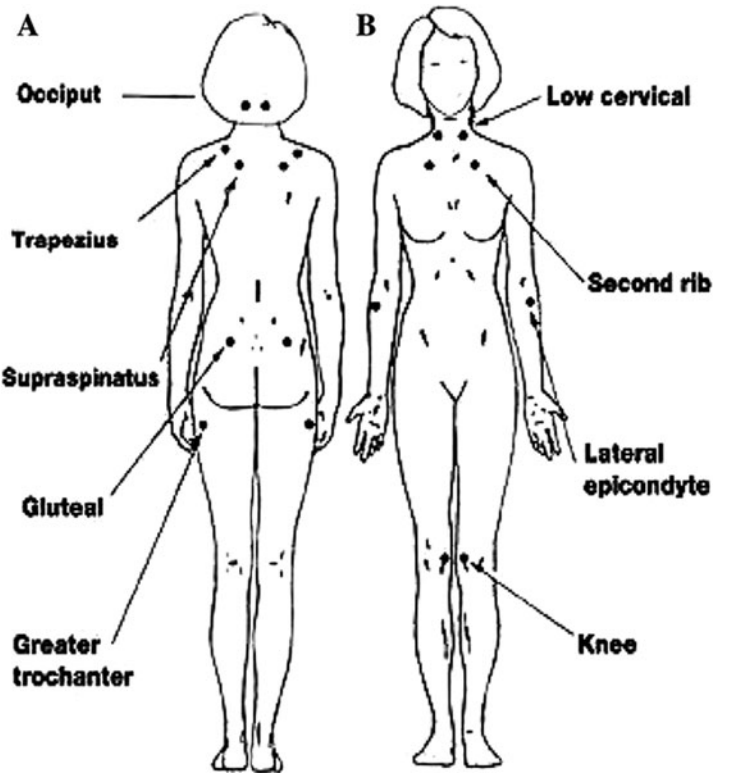
GENERALIZED SYMPTOMS—diffuse soft tissue pain,sleep disturbances, fatigue

SPECIFIC TENDER POINTS—$\geq$11/18 (occiput, sternocleidomastoid, second rib, trapezius, supraspinatus, lateral epicondyle, gluteal, greater trochanter, medial fat pad of knees)

INVESTIGATIONS

BASIC

- **LABS** (usually normal)—CBCD, lytes, urea, Cr, Ca, Mg, PO_4, ESR, TSH, CK



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MANAGEMENT

REASSURANCE AND PATIENT EDUCATION PROGRAMS

LIFESTYLE—physical therapy/activity, sleep hygiene

MEDICATIONS—amitriptyline, muscle relaxants (cyclobenzaprine), SSRI, pregabalin

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 four 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 NEJM 2003 349:2

DIFFERENTIAL DIAGNOSIS

PRIMARY VASCULITIDES—Takayasu aortitis, giant cell/temporal arteritis, polyarteritis nodosa (PAN), microscopic polyangiitis (MPA), Churg–Strauss syndrome, Wegener's granulomatosis

SECONDARY VASCULITIDES (hypersensitivity)

★VASCULITIS★

- **VARIOUS DRUGS**
- **AUTOIMMUNE**—SLE, rheumatoid arthritis, Behcet's disease, relapsing polychondritis
- **SERUM SICKNESS**—penicillin
- **CRYOGLOBULINEMIA**
- **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's 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 (L=large, M=medium, S=small vessels)

- **LARGE VESSEL VASCULITIS**—Takayasu aortitis (L), temporal arteritis (L, M)
- **MEDIUM VESSEL (PLUS SMALL VESSEL) VASCULITIS**—Kawasaki disease (L, M, S), polyarteritis nodosa (M, S), Wegener's granulomatosis (M, S), Churg–Strauss (M, S)
- **SMALL VESSELS VASCULITIS** (leukocytoclastic, hypersensitivity vasculitis)—secondary vasculitides (S)

CLINICAL FEATURES

SYMPTOMS

- **CONSTITUTIONAL**—fever, arthralgias, fatigue, anorexia
- **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

CLINICAL FEATURES (CONT'D)

- **CAUSES**—inflammatory (polyarteritis nodosa, Wegener's granulomatosis, Henoch–Schonlein purpura, SLE, cryoglobulinemia), infectious (sepsis, infective endocarditis, disseminated meningococcemia), 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. Greater likelihood of vasculitis if combination

INVESTIGATIONS

BASIC

- **BLOOD TESTS**—CBCD, 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, *Borrelia burgdorferi*)
- **FURTHER IMAGING GUIDED BY SYMPTOMS**—MR head, CT chest, abd, pelvis, angiogram
- **BIOPSY OF AFFECTED ORGAN**—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	+						Cardiovas.
Giant cell arteritis	+						ESR++, PMR
Polyarteritis nodosa		+			+	+	GI++
Microscopic polyangiitis			+	+	+		p-ANCA
Wegener's granulomatosis	±	+	+	+			Sinus, c-ANCA
Churg–Strauss syndrome			+	+		+	Asthma, eosinophilia
Henoch–Schonlein purpura					+	+	IgA
Behcet's disease	+					+	Oral ulcers
Cryoglobulinemia		+		+		+	Cryoglobulin

++ = particularly important involvements, + = important involvements

MANAGEMENT

PRIMARY VASCULITIDES—***prednisone*** 1 mg/kg/day PO daily. ***Cyclophosphamide*** 2 mg/kg/day IV daily or 500–1000 mg/m^2 IV monthly

SECONDARY VASCULITIDES—treat underlying cause

SPECIFIC ENTITIES

TAKAYASU AORTITIS (PULSELESS DISEASE)

- **PATHOPHYSIOLOGY**—systemic vasculitis of the large arteries, typically the aorta and its branches with vessel occlusion causing MI, TIA, strokes, visual disturbances, and claudication
- **ASSOCIATIONS**—young women of Asian or Mexican descent
- **ACR DIAGNOSTIC CRITERIA**—age at disease onset <40 years, claudication of extremities, decreased brachial artery pulse, systolic blood pressure difference >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 three of six criteria for diagnosis (sens 91%, spc 98%)
- **TREATMENTS**—steroids, methotrexate, vascular surgery, anti-platelet and anticoagulation therapy

SPECIFIC ENTITIES (CONT'D)

POLYMYALGIA RHEUMATICA

- **ASSOCIATIONS**—temporal arteritis in 15%
- **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), ↑ 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

SPECIFIC ENTITIES (CONT'D)

1 mg/month) every 4 weeks until tapered off. Use of prednisone greater than 15 mg decreases the diagnostic specificity. Relapse is frequent

GIANT CELL ARTERITIS/TEMPORAL ARTERITIS

- **ASSOCIATIONS**—older age, polymyalgia rheumatica in 30–50%
- **CLINICAL FEATURES**—systemic vasculitis of the large and medium arteries. This causes headache, amaurosis fugax, diplopia, jaw claudication, painful scalp nodules, and tender temporal artery. Extracranial GCA involves aorta in 10–15% of cases
- **ACR DIAGNOSTIC CRITERIA**—age >50, new-onset headache, abnormal temporal artery, ESR >50 mm/h, abnormal temporal artery biopsy. Need three of five criteria (sens 94%, spc 91%)
- **TREATMENTS**—if no ocular symptoms, *prednisone* 40–60 mg PO daily ×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, start *methylprednisolone* 1 g IV daily ×3 days, then *prednisone* 80 mg PO daily and taper over time. Initiate therapy before biopsy if high index of suspicion. Consider methotrexate if steroid-sparing therapy required. *ASA* 81 mg PO daily is recommended to reduce vascular complications

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE TEMPORAL ARTERITIS?

	LR+	LR−
History		
Jaw claudication	4.2	0.72
Diplopia	3.4	0.95
Temporal headache	1.5	0.82
Any headache	1.2	0.7
Unilateral visual loss	0.85	1.2
Any visual symptom	1.1	0.97
Vertigo	0.71	1.1
Anorexia	1.2	0.87
Weight loss	1.3	0.89
Arthralgia	1.1	1
Fatigue	1.2	0.94
Fever	1.2	0.92
Myalgia	0.93	1.1
Polymyalgia rheumatica	0.97	0.99
Physical		
Beaded temporal artery	4.6	0.93
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	1.6	0.93
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	1.2	0.35
ESR >100 mm/h	1.9	0.8

APPROACH—"when taking a history in a patient with possible temporal arteritis, jaw claudication and diplopia substantially increase the probability of positive biopsy results. No historical findings help rule out the diagnosis by their absence. Among physical examination findings, synovitis makes the diagnosis of temporal arteritis less likely, while beaded, prominent, enlarged, and tender temporal arteries each increase the likelihood of positive biopsy results. While these findings increase the chance of having temporal arteritis, they are variably sensitive from 16% (beaded temporal artery) to 65% (any temporal artery abnormality). The results of tests of ESR alter the likelihood of positive biopsy results. A normal ESR or ESR <50 mm/hr each make positive biopsy results unlikely. Among patients clinically suspected of disease, those with an ESR >100 mm/hr have a modestly increased likelihood of biopsy proven temporal arteritis. The prevalence of temporal arteritis in the general population is <1%, while it is 39% for those referred for temporal artery biopsy, suggesting that clinicians are fairly good at identifying high risk patients"

JAMA 2002 287:1

SPECIFIC ENTITIES (CONT'D)

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 DIAGNOSTIC 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 medium-sized artery containing PMN. Need 3 of 10 criteria (sens 82%, spc 87%)
- **TREATMENTS**—steroids, cyclophosphamide

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**—steroids, cyclophosphamide

WEGENER'S GRANULOMATOSIS

- **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, and **S**kin involvement
- **ACR DIAGNOSTIC 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 two of four criteria for diagnosis (sens 88%, spc 92%)
- **TREATMENTS**—steroids, cyclophosphamide, methotrexate, rituximab

SPECIFIC ENTITIES (CONT'D)

CHURG–STRAUSS SYNDROME

- **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
- **CLINICAL FEATURES**—pneumonic infiltrate, skin rash, myocarditis, peripheral neuropathy, and nephropathy
- **ACR DIAGNOSTIC CRITERIA**—asthma, eosinophilia >10%, mono or polyneuropathy, pulmonary infiltrates (non-fixed), paranasal sinus abnormality, extravascular eosinophils. Need four of six criteria for diagnosis (sens 85%, spc 99.7%)
- **TREATMENTS**—steroids, cyclophosphamide

HENOCH–SCHONLEIN PURPURA

- **PATHOPHYSIOLOGY**—systemic vasculitis of small vessels characterized by IgA-containing immune complex deposition in tissues
- **ACR DIAGNOSTIC CRITERIA**—palpable purpura, age <20 at disease onset, intestinal angina, granulocytes in walls of arterioles or venules on biopsy. Need two of four criteria (sens 87%, spc 88%)
- **TREATMENTS**—usually resolves spontaneously. Consider steroids (*prednisone* 85 mg PO daily, taper by 5 mg/week) for symptom control. Consider cyclophosphamide plus high-dose steroids if crescentic glomerulonephritis

BEHCET'S 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 (iritis, anterior uveitis), 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), and CNS (aseptic meningitis, meningoencephalitis, focal neurological deficits)
- **DIAGNOSTIC CRITERIA**—oral aphthous ulcers recurring ≥3x over 1 year, plus two of the following: recurrent genital aphthous ulcers, eyes features, skin features, and positive pathergy testing at 24–48 h
- **TREATMENTS**—steroids and others (lesion dependent)

Approach to Serologies

INFLAMMATORY MARKERS

ERYTHROCYTE SEDIMENTATION RATE (ESR) (non-specific)

- **DISORDERS**—elevated in vasculitis such as temporal arteritis and polymyalgia rheumatica and almost all inflammatory disorders (rheumatologic, infectious, malignancy), anemia, renal disease, pregnancy, birth control pills, thyroid disease, and old age
- **UTILITY**—associated with disease activity in temporal arteritis and polymyalgia rheumatica. Normal value corrected for age and is usually less than [age in years + 10 (if female)]/2

C-REACTIVE PROTEIN (CRP) (non-specific)

- **DISORDERS**—elevated in vasculitis such as temporal arteritis and polymyalgia rheumatica and almost all inflammatory disorders (rheumatologic, infectious, malignancy), obesity, diabetes, CAD, and smoking
- **UTILITY**—associated with disease activity in temporal arteritis and polymyalgia rheumatica

RHEUMATOID ARTHRITIS

RHEUMATOID FACTOR—polyclonal IgM against Fc portion of IgG (non-specific)

- **DISORDERS**—significantly elevated in rheumatoid arthritis (sens 80%), Sjogren's syndrome, mixed cryoglobulinemia, and subacute bacterial endocarditis. Somewhat elevated in other rheumatologic diseases (SLE, MCTD, polymyositis, sarcoidosis), pulmonary and hepatic diseases, infections, and malignancy. May also be positive in the normal elderly
- **UTILITY**—seronegative rheumatoid arthritis does not have extraarticular findings. Does not correlate with disease activity

ANTICYCLIC CITRULLINATED PEPTIDES (CCP) (very specific)

- **UTILITY**—very useful for diagnosis of rheumatoid arthritis (sens 85%, spc 95%). For patients with elevated rheumatoid factor of >50 U/mL and fulfilling other criteria, rheumatoid arthritis is diagnosed without need for anti-CCP. However, if rheumatoid factor <50 U/mL, consider anti-CCP testing (suggests rheumatoid arthritis if positive)

LUPUS

ANTINUCLEAR ANTIBODIES (ANA) (non-specific but most sensitive test for SLE)

- **DISORDERS**—SLE (sens >99%), mixed connective tissue disease (sens >95%), Sjogren's syndrome (sens 75%), inflammatory myopathies (sens >75%), scleroderma (sens >60–90%), rheumatoid arthritis (sens 15–35%), and normal elderly

LUPUS (CONT'D)

- **STAINING PATTERNS**
  - **RIM**—most specific, SLE
  - **HOMOGENOUS**—SLE
  - **NUCLEOLAR**—scleroderma, CREST
  - **DIFFUSE**—non-specific
  - **SPECKLED**—most common, least specific, consider SLE, MCTD, scleroderma, Sjogren's
- **UTILITY**—negative ANA can help to exclude SLE, but ANA testing is not useful in known SLE patients

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-RNP

- **DISORDERS**—SLE, mixed connective tissue disease
- **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–Schonlein 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's (sens 25%)

SJOGREN'S SYNDROME

ANTI-RO (SS-A)

- **DISORDERS**—Sjogren's syndrome (sens 75%), SLE (sens 25%)
- **UTILITY**—associated with sicca in other connective tissue disorders, extraglandular disease in Sjogren's syndrome, heart block in neonates with anti-Ro positive mothers, cutaneous lupus rash, photosensitivity, and thrombocytopenia in SLE

SJOGREN'S SYNDROME (CONT'D)

ANTI-LA (SS-B)

- **DISORDERS**—Sjogren's 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's, 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

INFLAMMATORY MYOPATHIES (CONT'D)

ANTI-SRP—antibodies against antisignal recognition protein

- **DISORDERS**—dermatomyositis and polymyositis

VASCULITIS

C-ANCA—autoantibodies against proteinase-3. Confirm by testing for antiproteinase-3

- **DISORDERS**—Wegener's granulomatosis (sens >80%) is the most common disorder

P-ANCA—autoantibodies against myeloperoxidase (non-specific). May need to confirm with testing for anti-myeloperoxidase (MPO)

- **DISORDERS**—Churg–Strauss (sens 65%), idiopathic crescentic glomerulonephritis (sens 65%), microscopic polyangiitis (sens 45%), polyarteritis nodosa (sens 15%), Wegener's granulomatosis (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** Also examine C-spine and upper limb (neurological testing)
Hand and wrist	Boutonniere, Swan neck, subluxation @ MCP and wrist, ulnar deviation @ MCP, radial deviation @ carpus, rheumatoid nodules, Heberden's and Bouchard's nodes	Thumb flexion, extension, abduction, and adduction Finger flexion/extension Opposition Wrists flexion/extension	Wrist Carpal joints MCP joints PIP joints DIP joints	**Tinel's test, Phalen's test** (carpel tunnel syndrome) **Finkelstein's test** (de Quervain's tenosynovitis) Hand grip strength and function (write) Neurological testing of hand
Hip	Lumbar lordosis Gait[c]	Abduction (50°) Adduction (20°) Internal rotation (35°) External rotation (45°) Flexion (120°) Extension (20–30°)	ASIS Iliac crest SI joint Greater trochanter Ischial tuberosity	**FABER test** (groin pain=hip joint, buttock pain=SI joint) **Thomas test** (hip flexion contracture) **Trendelenburg test** (weakness of gluteus medius on standing side) **Leg length discrepancy** (true and false)
Knee	Varus Valgus Genu recurvatum Baker cyst Gait[3]	Flexion (135°) Extension (10°) Eversion (10°) Inversion (10°)	Patella, tibial tuberosity Head of tibia/fibula Joint line tenderness Femoral condyles Bursas (suprapatellar, subpatellar, infrapatellar, anserine) Bulge test, balloon test, patella tap	**Anterior drawer test, Lachman test, pivot shift** (anterior cruciate ligament) **Posterior drawer test** (posterior cruciate ligament) **Collateral ligaments** **McMurray test, medial–lateral grind test** (meniscal)
Ankle and foot	Varus Valgus Achilles tendon Nails, bunion Hallux valgus Metatarsus varus Pes planus Shoes	Dorsiflexion (20°) Plantarflexion (50°) Subtalar joint—inversion and eversion (5°) Forefoot joints Joints of toes	Achilles tendon Malleolus Anterior talofibular ligament Deltoid ligament Calcaneus Base of MTP Calcaneus Navicular	**Anterior drawer test** **Lateral/medial stability** **Subtalar complex stability** **Achilles tendon rupture**

[a] SEADS—**S**ymmetry/swelling, **E**rythema, **A**trophy, **D**eformity, and **S**urgeries/scars
[b] SWAT—**S**welling/synovitis, **W**armth, **A**natomic landmarks, **T**enderness
[c] Gait—heel strike, foot flat (mid-stance), heel off (lift off), toes off (swing)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN INSTABILITY OF THE SHOULDER OR A LABRUM LESION?

POSITION FOR TESTING—shoulder 90° abducted and 90° externally rotated, elbow 90° flexed for all tests described below, with the exception of biceps load for which the shoulder is 120° abducted and maximally externally rotated and the elbow is 90° flexed

	Sens	Spc	LR+	LR−
Clinical tests for shoulder instability				
Relocation test—applying pressure to shoulder anteriorly causes relief	85%	87%	6.5	0.18
Anterior release—releasing anterior pressure causes pain	92%	89%	8.3	0.09
Apprehension test—applying pressure to shoulder posteriorly causes pain	88%	50%	1.8	0.23
Clinical tests for labral tears				
Biceps load I and II tests—flexion of elbow against resistance causes pain	83%	98%	29	0.09
	90%	96%	26	0.11
Pain provocation of Mimori—passive movement from maximally supinated to pronated causes pain	100%	90%	7.2	0.03
Internal rotation resistance strength—internal rotation against resistance causes pain	88%	96%	25	0.12

APPROACH—"best evidence supports the value of the relocation and anterior release tests for diagnosis of shoulder instability. Symptoms related to labral tears remain unclear. Most promising for establishing labral tears are currently the biceps load I and II, pain provocation of Mimori, and the internal rotation resistance strength tests"

JAMA 2004 292:16

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A TORN MENISCUS OR LIGAMENT OF THE KNEE?

	LR+	LR−
Clinical tests for anterior cruciate ligament tear		
Anterior drawer test	3.8	0.30
Lachman test	42	0.1
Lateral pivot shift test	–	–
Composite assessment	25	0.04
Clinical tests for posterior ligament tear		
Composite assessment	21	0.05
Clinical tests for meniscal tear		
McMurray test	1.3	0.8
Joint line tenderness	0.9	1.1
Joint effusion	5.7	0.7
Medial–lateral grind	4.8	0.4
Apley apprehension test	–	–
Composite assessment	2.7	0.4

APPROACH—"the complete examination for specific meniscal or ligamentous injuries of the knee performed much better than specific maneuvers, suggesting that synthesis of a group of examination maneuvers and historical items may be required for adequate diagnosis"

JAMA 2001 286:13

Notes

10
NEUROLOGY

Section Editor: Dr. Brian Thiessen

Brain Tumors

PATHOPHYSIOLOGY

CLASSIFICATION BY HISTOLOGY

- **NEUROEPITHELIAL**
  - **GLIOMAS**
    - **ASTROCYTOMA** (30%)—pilocytic (grade 1), fibrillary (grade 2), anaplastic (grade 3), glioblastoma multiforme (grade 4, 20% of all brain tumors)
    - **OLIGODENDROGLIOMA** (4%)—well differentiated, anaplastic, mixed; 50% have 1p19q co-deletion
    - **EPENDYMOMA** (2%)
  - **CHOROID PLEXUS TUMORS**
  - **NEURONAL AND MIXED NEURONAL-GLIAL TUMORS**
  - **PINEAL PARENCHYMAL TUMORS**
  - **EMBRYONAL TUMORS** (1.7%)—medulloblastoma, pineoblastoma, neuroblastoma, ependymoblastoma
- **CRANIAL/SPINAL NERVES**—schwannoma, neuro-fibroma, malignant peripheral nerve sheath tumor (malignant schwannoma, 8%)
- **MENINGES**
  - **MENINGIOMA** (30%)
  - **ATYPICAL MENINGIOMA**
  - **ANAPLASTIC MENINGIOMA**
  - **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
- **GERM CELL**—germinoma, embryonal carcinoma, choriocarcinoma, teratoma
- **CYSTS AND TUMOR LIKE**—Rathke cleft cyst, epidermoid cyst, dermoid cyst
- **SELLAR REGION**—pituitary adenoma (6%), pituitary carcinoma, craniopharyngioma (<1%)
- **LOCAL EXTENSION FROM REGIONAL TUMORS**—paraganglioma, chordoma, chondrosarcoma
- **METASTATIC TUMORS**

PATHOPHYSIOLOGY (CONT'D)

RISK FACTORS

- **FAMILY HISTORY**
- **ENVIRONMENTAL**—radiation (meningioma, glioma), vinyl chloride (glioma)
- **DISEASES**—HIV (CNS lymphoma), familial adenomatous polyposis (medulloblastoma), Li–Fraumeni syndrome, Turcot's syndrome, neurofibromatosis

GLIOBLASTOMA MULTIFORME DEVELOPMENT—in elderly patients, more likely de nova (primary GBM). In younger patients, more likely evolved from low-grade glioma (secondary GBM) with stepwise mutation

MGMT IN GLIOBLASTOMA MULTIFORME—epigenetic silencing with methylation of MGMT (O^6-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. Also increases intracranial pressure causing headache, nausea and vomiting, papilledema, and third nerve 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. 176)
Seizures (p. 309)
Headaches (p. 313)

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

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_10,

CLINICAL FEATURES (CONT'D)

SIGNS—cranial nerve examination, with particular attention to fundoscopy and visual fields (driving), cognitive assessment with MMSE (driving, should be ≥24), speech, motor, sensory, gait, cerebellum, pronator drift, Romberg sign

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- **IMAGING**—MRI head, CT head
- **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 64%; median time to recurrence 4.5 years, median survival from recurrence 12 months

PROGNOSIS FOR GLIOBLASTOMA MULTIFORME—median survival 14 weeks with observation only, 20 weeks with resection, 36 weeks with radiation added, and 40–50 weeks with chemotherapy added

PROGNOSTIC FACTORS FOR ANAPLASTIC ASTROCYTOMA AND GLIOBLASTOMA MULTIFORME—older age, poor Karnofsky performance status, degree of excision, neurologic deficits

MEDIAN SURVIVALS FOR OLIGODRENDROGLIOMAS

Oligodrendroglioma	1p19q deletion	No 1p19q deletion
Low grade	15 years	5 years
High grade	5–10 years	2 years

MANAGEMENT

SYMPTOM CONTROL—seizure control (phenytoin, levetiracetam, carbamazepine, lamotrigine, clobazam, valproate, topiramate), steroids may be used short term for cerebral edema with symptoms such as headaches, neurological deficits

TUMOR CONTROL

- **ASTROCYTOMA**
  - **LOW GRADE (GRADE 2)**—maximal surgical debulking. Upfront radiation improves progressive-free survival but not overall survival. Thus, it may be delayed in patients who are asymptomatic
  - **ANAPLASTIC (GRADE 3)**—maximal surgical debulking, followed by radiation ± chemotherapy (PCV, temozolomide)
  - **GLIOBLASTOMA MULTIFORME (GRADE 4)**—maximal surgical debulking, concurrent chemoradiation with temozolomide ×6 weeks, followed by 4-week break and then adjuvant temozolomide d1–5 q28d ×6

MANAGEMENT (CONT'D)

- **LOW-GRADE OLIGODENDROGLIOMA**
  - **WITH 1P19Q DELETION**—resection. Chemotherapy at progression to delay radiation is an option
  - **WITHOUT 1P19Q DELETION**—resection. Radiation may be delayed until progression or symptoms.
- **HIGH-GRADE OLIGODENDROGLIOMA**
  - **WITH 1P19Q DELETION**—resection ± chemotherapy ± radiation
  - **WITHOUT 1P19Q DELETION**—resection, RT alone or concurrent chemoradiation with temozolomide ×6 weeks, followed by 4-week break and then adjuvant temozolomide d1–5 q28d ×6
  - **SALVAGE CHEMOTHERAPY FOR GLIOMAS**—nitrosoureas, bevacizumab, etoposide, carboplatin, procarbazine
  - **EPENDYMOMA**—resection ± radiation. Palliative chemotherapy may be provided with recurrence
  - **PRIMARY NEUROECTODERMAL TUMORS** (medulloblastoma, supratentorial, pineoblastoma)—resection plus craniosoinal 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

DRIVING—the key factors that affect driving include seizures, visual fields, motor deficits, and cognition (MMSE ≥ 24)

TREATMENT ISSUES

SIDE EFFECTS OF BRAIN IRRADIATION

- **RADIONECROSIS**—contrast-enhanced 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's sign, paresthesias (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

SPECIFIC ENTITIES (CONT'D)

- **UNCAL**—temporal lobe and uncus shift medially into the tentorial notch, causing compression of third nerve and contralateral cerebral peduncle (ipsilateral hemiparesis, false localizing sign)
- **TONSILLAR**—cerebellar tonsils downward into the foramen magnum compresses the medulla and upper spinal cord, resulting in rapid failure of vital functions

BRAIN METASTASIS

- **PATHOPHYSIOLOGY**—occurs in 20–30% of patients, most commonly from lung, breast, melanoma, and primary unknown cancers. About 10× more frequent than primary brain tumors. Found in cerebral hemispheres, cerebellum, and brain stem 80%, 15% and 5% of the time
- **TREATMENT**—surgery plus radiation offers survival advantage over radiation alone, although <50% of brain metastases are resectable. Radiation reduces recurrence but does not improve survival

SPECIFIC ENTITIES (CONT'D)

LEPTOMENINGEAL CARCINOMATOSIS

- **PATHOPHYSIOLOGY**—occurs in 5% of patients, most commonly from 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, thiotepa). Necrotizing leukoencephalopathy may develop months after in those who survived, particularly after combined methotrexate and radiation administration

Acute Stroke Syndromes

NEJM 2007 357:6
NEJM 2008 359:13
AHA/ASA Stroke Guidelines 2009

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
- **GLOBAL ISCHEMIA**—MI, VT

HEMORRHAGIC STROKE

- **INTRACEREBRAL VESSEL RUPTURE**—hypertension, trauma, bleeding diatheses, amyloid angiopathy, illicit drug use, vascular malformation
- **SUBARACHNOID VESSEL RUPTURE**—aneurysm rupture, vascular malformation, bleeding diatheses, trauma, amyloid angiopathy, illicit drug use (cocaine)

STROKE MIMICS (usually global rather than focal neurological symptoms) ★**DIMS**★

- **DRUG INTOXICATION**
- **INFECTIONS**
- **INSANITY**—conversion disorder
- **METABOLIC**—hypoglycemia, renal failure, hepatic failure
- **MIGRAINES**
- **SYNCOPE**
- **SEIZURES**—Todd's paralysis
- **STRUCTURAL**—trauma, tumors, subdural hemorrhage

PATHOPHYSIOLOGY

FIVE QUESTIONS

1. Is the patient stable?
2. Is this a stroke?
3. Where is the stroke? Symptoms/signs, CT head
4. What kind of stroke? Ischemic (thrombotic, embolic, global ischemic), hemorrhagic (intracerebral, subarachnoid)
5. How to manage the patient? Thrombolytics?

PATHOPHYSIOLOGY (CONT'D)

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 vessels. Found at penetrating branches of the anterior, middle, and posterior cerebral and basilar arteries
- **CARDIOAORTIC EMBOLIC STROKE**
  1. **CARDIAC SOURCES DEFINITE** (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

PATHOPHYSIOLOGY (CONT'D)

4. **UNKNOWN SOURCE EMBOLIC STROKE**
5. **OTHERS**—dissection, moyamoya, primary thrombosis, cerebral mass

RISK FACTORS FOR STROKE

- **THROMBOTIC**—age, smoking, diabetes, dyslipidemia, hypertension, family history, male, history of TIA
- **EMBOLIC**—smoking, diabetes, dyslipidemia, hypertension, family history, male, history of heart disease (valvular, AF, endocarditis)
- **ICH**—hypertension, trauma, bleeding diatheses, illicit drugs, vascular malformations, blacks, Asians

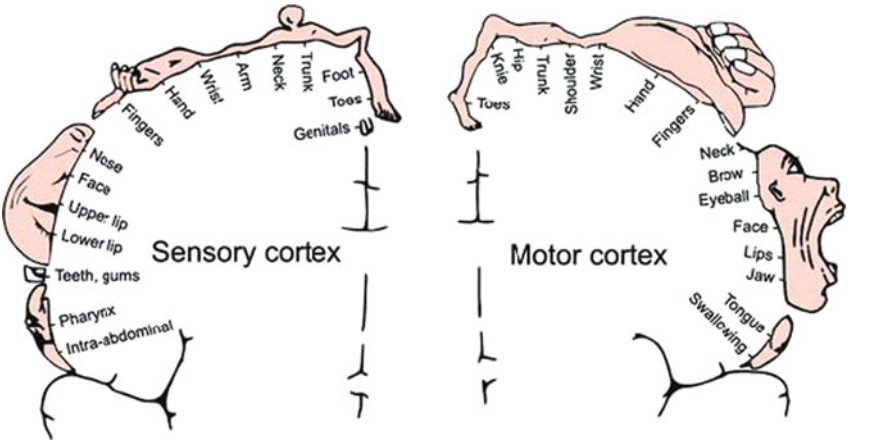
PATHOPHYSIOLOGY (CONT'D)

- **SAH**—illicit drugs, bleeding diatheses

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
- **NON-NEUROLOGIC**—myocardial infarction, arrhythmia, aspiration, pneumonia, DVT, pulmonary embolism, malnutrition, pressure sores, orthopedic complications, contractures

MAP OF MOTOR/SENSORY CORTEX



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CLINICAL FEATURES

TRANSIENT ISCHEMIC ATTACK—defined as an ischemic episode with full recovery within 24 h. Most TIAs last <5 min, while most ischemic attacks >1 h are associated with infarction. Risk of stroke in patients with TIA is 5% within 2 days and 10% within 90 days

PREDICTION OF STROKE RISK AFTER TIA

- **★ABCD2★ CRITERIA**
  - **A**ge—1=age >60 years,
  - **B**lood pressure—1=hypertension at the acute evaluation >140/90 mmHg)
  - **C**linical features—2=unilateral weakness, 1 = speech disturbance without weakness
  - **D**uration of symptom—1=10–59 min, 2=>60 min
  - **D**iabetes—1=present
- **INTERPRETATION**
  - **LOW RISK** (scores 0–3)=risk of stroke 1.0% at 2 days. Hospital observation may not be necessary without another indication such as new-onset atrial fibrillation

CLINICAL FEATURES (CONT'D)

  - **MODERATE RISK** (scores 4–5)=risk of stroke 4.1% at 2 days. Hospital observation justified in most situations
  - **HIGH RISK** (scores 6–7)=risk of stroke 8.1% at 2 days. Hospital observation recommended

CLINICAL STROKE CLASSIFICATION

- **ANTERIOR CEREBRAL ARTERY** (embolic >thrombotic)—motor and sensory deficit (leg >face, arm), frontal release signs (grasp, snout, root, and suckling reflexes), abulia, paratonic rigidity, gait apraxia, personality Δ
- **MIDDLE CEREBRAL ARTERY** (left dominant hemispheric, 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
- **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

CLINICAL FEATURES (CONT'D)

- **DEEP (SUBCORTICAL/LACUNAR) HEMISPHERE OR BRAIN STEM** (small artery infarct)—hemiparesis (pure motor stroke); sensory loss (pure sensory stroke); dysarthria and clumsy hand; 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** (brain stem, 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
In-hospital clinical assessment	**LR+**	**Prob. stroke**
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%

NIH STROKE SCALE—**level of consciousness** (0=alert, 1=not alert, 2=obtunded, 3=unresponsive, **level of consciousness questions** (0=answers both correctly, 1=answers one correctly, 2=answers neither correctly), **level of consciousness commands** (0=performs both tasks correctly, 1=performs one task correctly, 2=performs neither task), **gaze** (0=normal, 1=partial gaze palsy, 2=total gaze palsy), **visual fields** (0=no visual loss, 1=partial hemianopsia, 2=complete hemianopsia, 3=bilateral hemianopsia), **facial palsy** (0=normal, 1=minor paralysis, 2=partial paralysis, 3=complete paralysis), **left motor arm** (0=no drift, 1=drift before 5 s, 2=falls before 10 s, 3=no effort against gravity, 4=no movement), **right motor arm** (0=no drift, 1=drift before 5 s, 2=falls before 10 s, 3=no effort against gravity, 4=no movement), **left motor leg** (0=no drift, 1=drift before 5 s, 2=falls before 5 s, 3=no effort against gravity, 4=no movement), **right motor leg** (0=no drift, 1=drift before 5 s, 2=falls before 5 s, 3=no effort against gravity, 4=no movement), **ataxia** (0=absent, 1=one limb, 2=two limbs), **sensory** (0=normal, 1=mild loss, 2=severe loss), **language** (0=normal, 1=mild aphasia, 2=severe aphasia, 3=mute or global aphasia), **dysarthria** (0=normal, 1=mild, 2=severe), **extinction/inattention** (0=normal, 1=mild, 2=severe)

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)"

JAMA 2005 293:19

Related Topics
CT Head (p. 333)
Dysphagia (p. 112)

CLINICAL FEATURES (CONT'D)

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

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"

JAMA 1993 270:23

CLINICAL FEATURES (CONT'D)

CLINICAL CLUES TO DIAGNOSIS

- **THROMBOTIC**—stuttering progression with periods of improvement. Lacunes develop over hours or at most a few days; large artery ischemia 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, severe headache, focal brain dysfunction less common. May be precipitated by sex or other physical activity

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, troponin, CK, PTT, INR, AST, ALT, ALP, bilirubin, total chol, 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
- **EEG**—if seizures
- **TOXICITY 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. Early signs (within 6 h) of MCA infarction include **hyperdense middle cerebral artery sign** (thrombus or embolus in

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

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 overtime

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—**ABC**, O_2, IV, **do not treat blood pressure unless extreme** (hypertensive encephalopathy or >220/120 mmHg, then *labetalol* 40–80 mg IV q10min or 200–400 mg PO BID until BP <185/110 mmHg). **Thrombolytics** (if within 4.5 h of onset of ischemic stroke, see below; *alteplase* 0.9 mg/kg IV). **Anticoagulation is not indicated** unless embolic stroke with obvious cardiac source (e.g. atrial fibrillation) or dissection (to be initiated 7–10 days after stroke). ***ASA*** 160–325 mg PO daily (if thrombolytics given, may start ASA after first 24 h. For long-term secondary prophylaxis, consider clopidogrel, ASA/persantine, or dipyridamole if cannot tolerate or failed ASA). If SAH, consider nimodipine. **Neurology or neurosurgery consult.** Early mobilization/rehabilitation with multi-disciplinary team management (e.g. swallowing assessment, physiotherapy, occupational therapy). Monitor complications and treat other cardiovascular risk factors

TREATMENT ISSUES

THROMBOLYSIS

- **INCLUSION**—clinical diagnosis of ischemic stroke, age 18–80 years, onset of symptoms within 4.5 h, measurable neurological deficit, stroke symptoms present for at least 30 min with no significant improvement before treatment

TREATMENT ISSUES (CONT'D)

- **EXCLUSION**—**historical** (time of symptom onset unknown, prior history of ICH, stroke/head trauma <3 months, MI <3 months, major surgery/trauma <14 days, GI/GU bleed <21 days, arterial puncture in non-compressible site <7 days, combination of previous stroke and DM, oral anticoagulant treatment, coagulopathy), **clinical** (rapidly improving stroke symptoms, minor/isolated symptoms, seizure at onset of stroke with residual impairment secondary to postictal phenomenon, suspicion of SAH, acute MI/post-MI pericarditis, persistent hypertension ≥185/110), **labs** (platelet $<100\times10^9$/L, glucose <2.8 mM [50 mg/dL], or >22.2 mM [400 mg/dL], ↑ PTT), **CT head** (hemorrhage, major early infarct signs), **severe stroke** as assessed clinically (NIH score >25) or radiographically (stroke involving >1/3 of cerebral hemisphere)
- **OUTCOME**—among patients receiving thrombolysis within 3 h of onset, favorable outcomes in 31–50% of treated patients compared to 20–38% of non-treated 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	No needed if no previous stroke	ASA 30% Clopidogrel 43% ASA/persantine 43%

The percentages in this table represent relative risk reduction

CRITERIA FOR CAROTID ENDARTERECTOMY

Carotid stenosis	Symptomatic	Asymptomatic
≥70%	Yes (NNT 6.3)	Yes for men with stenosis ≥60% only (NNT 33)
50–69%	Yes for men only (NNT 22)	
<50%	No	No

NNT=number needed to treat. Medical management (ASA) for those not eligible for carotid endarterectomy

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	Flaccidity
Strength	Upper limbs flexors >extensors pronation >supination Lower limbs extensors >flexors	Nerve root/peripheral nerve distribution
Reflex	Increased with clonus Babinski upgoing	Decreased Babinski downgoing
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"

SPECIFIC ENTITIES (CONT'D)

- **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)

DISTINGUISHING FEATURES BETWEEN DIFFERENT TYPES OF APHASIA

	Wernicke	Broca's	Global
Comprehension	No	Normal	No
Fluency	Normal	No	No
Naming	No	No	No
Repetition	No	no	No
Others		Contralat. sensory/ motor Δ	

DYSARTHRIA (SPEECH IMPAIRMENT)

- **DYSARTHRIA**—speech disorder resulting from disturbances in muscular control that affect respiration, articulation, phonation, resonance, or prosody
- **DYSPHONIA**—voice disturbance in parameters of vocal quality, pitch, or intensity

Types of dysarthria	Quality
Spastic (hemispheric stroke cranial nerves-LMN)	Harsh, strained voice Low pitch voice

SPECIFIC ENTITIES (CONT'D)

Types of dysarthria	Quality
Hyperkinetic (basal ganglia lesion)	Harsh, strained voice Low pitch voice Voice stoppages
Hypokinetic (Parkinson's)	Hoarseness Low volume
Ataxic (cerebellar lesion)	Explosive, scanning speech
Flaccid (cranial nerves VII, IX, X)	Breathy, nasal, low volume Wheezing

PRIMITIVE REFLEXES

- **GRASPING REFLEX**—deep pressure over palmar surface results in grasp response
- **SUCKLING REFLEX**—insertion of an object into mouth results in sucking motion
- **ROOTING 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 foramen	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—Medulla Mesencephalic—Pons/ 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] Motor—wasting of temporal and masseter muscles, weakness of jaw movement Reflex—corneal reflex (afferent) and jaw jerk (afferent and efferent)
VI	Pons	Superior orbital fissure[b]	Motor—crossed eyes, impaired lateral gaze
VII[a]	Motor, solitary, superior salivatory—Pons	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]

Cranial Nerve Examination (Cont'd)

CN	Nucleus location	Skull exit	Abnormalities
VIII	Vestibular, cochlear—medulla	Internal acoustic meatus[c]	Sensory—whispering, Rinne's test, Weber's test. Dix—Hallpike maneuver (if vertigo). Check for nystagmus
IX	Nucleus ambiguous, inferior salivatory, solitary—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 ambiguous, 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
XI	Nucleus ambiguous—medulla Spinal accessory—cervical cord	Jugular foramen	Motor—weakness with shrugging shoulders and rotating head against resistance
XII[a]	Medulla	Hypoglossal canal	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 CA stroke can cause right lower facial droop and tongue deviation to the right

[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 brain stem. Peripheral lesions include aneurysm, tumor, meningitis, nasopharyngeal carcinoma, orbital lesions, and ischemic lesions (diabetes, hypertension). "Pupil-sparing" suggests ischemic lesions as they tend to involve the central portion of the nerve. 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 brain stem or upper cord lesion (syringobulbia, 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. 307

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. An adenoma may compress the optic chiasm inferiorly, causing superior bitemporal quadranopsia and eventually complete bitemporal hemianopia
- **HOMONYMOUS HEMIANOPIA**—lesion is located post-optic chiasm
- **FORMAL VISUAL FIELD TESTING**—Goldman perimeter

SPECIFIC ENTITIES (CONT'D)

OCULAR FINDINGS IN HYPERTENSION AND DIABETES

- **HYPERTENSION**—see p. 57
- **DIABETES**—see p. 337

Related Topics
Diplopia (p. 306)
Dysarthria (p. 304)
Facial Droop (p. 307)
Ptosis (p. 318)

SPECIFIC ENTITIES (CONT'D)

DISTINGUISHING FEATURES BETWEEN PAPILLEDEMA, OPTIC ATROPHY, AND OPTIC NEURITIS

	Papilledema	**Optic atrophy**	**Optic neuritis**
Etiology	↑ ICP Tumors Hypertension	Neuritis Glaucoma Congenital	Multiple sclerosis
Symp	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	Anterior spinal artery	Posterior inferior cerebellar artery
Cranial nerve (ipsilateral)	XII	V—↓ facial sens. VIII—nystagmus, vertigo, nausea IX, X—dysphagia, hoarseness, altered taste Sympathetic—Horner's
Motor (contralateral)	UMN weakness	None
Sensory (contralateral)	↓ vibration, proprioception	↓ pain and temperature
Cerebellum (ipsilateral)	Normal	Affected

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	Upward
Inferior rectus	III	Downward
Lateral rectus	VI	Lateral
Medial rectus	III	Medial
Superior oblique	IV	Downward medial
Inferior oblique	III	Upward medial

CLINICAL FEATURES

HISTORY—determine whether diplopia resolves with one eye closed, which direction diplopia is worse, whether separation of images occur vertically, horizontally, or obliquely, whether any head position makes diplopia better, and whether diplopia is worse at distance (typically VI 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 (III nerve 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

SPECIAL

- **TENSILON TEST**—if suspect 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), brain stem 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's Palsy 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's palsy, Ramsay Hunt syndrome (VZV), acoustic or facial neuroma
- **DISTAL TO INTERNAL AUDITORY CANAL AND GENICULATE GANGLION**—Bell's palsy, temporal bone fracture, cholesteatoma, glomus tumor, middle-ear infection

CAUSES OF FACIAL DROOP (CONT'D)

- **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 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's palsy)
Lesion	Contralateral cortex or corticobulbar fibers	Ipsilateral facial nerve nucleus or facial nerve
Upper facial muscles	Furrows present Can close eyes	No furrows 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]
Other findings	Hemiplegia (same side as palsy)	Hyperacusis

[a] 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, cerebellopontine angle, or at stylomastoid foreman

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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'S PALSY

INVESTIGATIONS—consider if other cranial nerve deficits develop, no recovery in 3–6 weeks, facial twitch or spasm precedes Bell's palsy (suggestive of tumor)

PROGNOSIS—71% of untreated patients recover spontaneously

MANAGEMENT OF BELL'S PALSY

TREAT UNDERLYING CAUSE—*prednisone* 1 mg/kg PO ×7 days (given within 3 days of onset). For severe facial weakness, consider *valacyclovir* 1 g PO TID ×7 days. Surgical decompression (only if documented 90% nerve degeneration by electroneurography)

SPECIFIC ENTITIES

RECURRENT OR BILATERAL FACIAL PALSY—Guillain–Barre syndrome, myasthenia gravis, lesions at skull base (lymphoma, sarcoidosis, Lyme disease)

RAMSAY HUNT SYNDROME—reactivation of herpes zoster virus in geniculate ganglion. Facial palsy, ear pain, and vesicles in external auditory meatus may be present. Taste often affected

Multiple Sclerosis

DIFFERENTIAL DIAGNOSIS

INFLAMMATORY DISEASES—Devic's neuromyelitis (neuromyelitis optica, combination of optic neuritis and cervical myelopathy), acute disseminated encephalomyelitis, SLE, PAN, Sjogren's, Behcet's disease, granulomatosis angiitis, paraneoplastic encephalomyelopathies

INFECTIONS—Lyme neuroborreliosis, neurosyphilis, HIV, HTLV-1, PML (JC virus)

GRANULOMATOUS DISEASES—sarcoidosis, Wegener granulomatosis, 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/year
- **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 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

CLINICAL FEATURES (CONT'D)

SENSORY (most common)—paresthesia, dysesthesia, hyperesthesia. Pain syndromes include trigeminal neuralgia, Lhermitte's sign (lightening 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**—CBCD, lytes, urea, Cr, Ca, Mg, PO_4, CK, quantitative Ig, ANA, ENA
- **IMAGING**—MRI head/spine (sens 90%)
- **LUMBAR PUNCTURE**—with CSF IgG index and oligoclonal bands (mild lymphocytosis $<50/mm^3$, mild ↑ protein with ≥2 oligoclonal bands)

SPECIAL

- **EVOKED POTENTIAL STUDIES**

DIAGNOSTIC AND PROGNOSTIC ISSUES

DIAGNOSTIC CRITERIA—the Poser criteria require a history of ≥2 attacks, with clinical or laboratory evidence of ≥2 CNS lesions. The newer McDonald criteria incorporate MRI evidence of multiple sclerosis for diagnosis (lesions disseminated by time and space)

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

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 ("benign MS")

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 lesion of MRI

GOOD PROGNOSTIC FACTORS IN RELAPSING–REMITTING MULTIPLE SCLEROSIS—initial presentation optic neuritis, purely sensory disorder, normal MRI

MANAGEMENT

EXACERBATIONS—***methylprednisolone*** 500–1000 mg IV daily ×3–5 days. **Plasma exchange**

IMMUNOTHERAPY—**★ABCR★** drugs **A**vonex (*interferon β-1a* 30 μg IM weekly), **B**etaseron (*interferon β-1b* 250 μg SC q2days), **C**opaxone (*glatiramer acetate* 20 mg SC daily), **R**ebif (*interferon β-1a* 22–44 μg SC three times a week). **Natalizumab** (monoclonal antibody against leukocyte α4 integrin for relapsing–remitting multiple sclerosis. See **NEJM 2007 356:25** for more details). **Mitoxantrone** may also be useful

- **RELAPSING–REMITTING**—early treatment shown to have favorable outcomes. Reasonable to start newly diagnosed patients with any of the four ABCR drugs
- **PRIMARY AND SECONDARY PROGRESSIVE**—evidence does not support benefit from interferon β in primary progressive disease, and limited in secondary progressive disease

SYMPTOM CONTROL—**fatigue** (*amantadine* 100 mg PO BID), **spasticity** (physiotherapy, baclofen, tizanidine, benzodiazepines), **hyperreflexic bladder** (fluid restriction, timed voiding, oxybutynin, propantheline, imipramine, intermittent catheterization)

Related Topics
Cranial Nerve Lesions (p. 304)
Orthostatic Hypotension (p. 312)

Dementia

See DEMENTIA (p. 378)

Delirium

See DELIRIUM (p. 380)

Seizures NEJM 2008 359:2

DIFFERENTIAL DIAGNOSIS

UNPROVOKED EPILEPTIC SEIZURES

- **PRIMARY EPILEPSIES**—absence, generalized tonic clonic, juvenile myoclonic
- **STRUCTURAL**—stroke (infarction), head trauma, brain tumors, neuro-degenerative disorders
- **INFECTIONS**—encephalitis
- **CONGENITAL**—neuronal migration errors and cortical dysgenesis, vascular malformations

PROVOKED EPILEPTIC SEIZURES

- **DRUGS**—**withdrawal** (benzodiazepine, alcohol), **overdoses** (methanol, ethylene glycol, TCAs), **illicit drug use** (cocaine, amphetamines, LSD)

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **METABOLIC**—hypoglycemia, non-ketotic hyperglycemia, hyponatremia, hypocalcemia, uremia, hypoxia (cerebral anoxia), hyperthyroidism
- **INFECTIONS**—meningitis, febrile seizures
- **OTHERS**—arrhythmia, acute intermittent porphyria

PSYCHOGENIC NON-EPILEPTIC (PSEUDOSEIZURES)—stressful psychological conflicts, major emotional trauma

SEIZURE MIMICS—syncope, TIA, migraine, benign positional vertigo, hypoglycemia, sleep disorders (sleep apnea, narcolepsy/cataplexy, night terrors, nightmares, nocturnal myoclonus), periodic paralysis, breath-holding spells

PATHOPHYSIOLOGY

TERMS

- **SIMPLE**—conscious
- **COMPLEX**—impaired consciousness
- **PARTIAL**—part of cortex
- **GENERALIZED**—bilateral cortex, unconscious
- **CLONIC**—jerky contractions, rhythmic
- **TONIC**—muscle stiffening
- **EPILEPSY**—$\geq$ 2 unprovoked seizures
- **STATUS EPILEPTICUS**—>30 min of seizures

TYPES OF SEIZURES

- **SIMPLE PARTIAL SEIZURES** (awareness not lost)—sensory, motor, autonomic, experiential
- **COMPLEX PARTIAL SEIZURES** (impaired consciousness)—temporal, e.g. automatisms
- **GENERALIZED SEIZURES** (loss of consciousness)—tonic–clonic, clonic, tonic, myoclonic, absence, or atonic

PATHOPHYSIOLOGY (CONT'D)

TYPES OF EPILEPSIES

- **LOCALIZATION RELATED**—frontal lobe, temporal lobe, parietal lobe, occipital lobe
- **GENERALIZED**—juvenile absence epilepsy, juvenile myoclonic epilepsy, infantile spasms

COMPLICATIONS OF SEIZURES—aspiration pneumonia, neurogenic pulmonary edema, hypoxic brain injury, cardiac injury, rhabdomyolysis (acute renal failure, hyperkalemia), lactic acidosis

CLINICAL FEATURES

HISTORY—when was first seizure, prodrome, aura, ictal symptoms, postictal period, diurnal variation, precipitants, maximum seizure-free period, seizure types, related injuries, driving, 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	Usually upright
	No warning	Usually warning
	Aura	Lightheaded
Event	Vocalization at onset	No vocalization
	Tonic–clonic convulsions	Occasional clonic movements, hypotonia
		Pale
	Cyanotic/gray	Incontinence occasionally
	Incontinence frequent	Tongue biting rare (tip)
	Tongue biting (side)	Less commonly injured
	Frequent injuries (fall on face, #, dislocations)	Short ↓ level of consciousness
	Longer ↓ level of consciousness	
Post-event	Confused, tired, sleepy	Alert
	Muscle ache	Diaphoretic

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, Ca, Mg, PO_4, AST, ALT, ALP, bilirubin, albumin, CK, troponin, TSH, INR, PTT, prolactin
- **IMAGING**—CT head, MRI head
- **EEG**—for unprovoked or recurrent seizures

SPECIAL

- **CXR**—if suspect aspiration
- **LUMBAR PUNCTURE**—if suspect meningitis/encephalitis

DIAGNOSTIC ISSUES

AURA—warning symptoms before seizure. Aura is actually a simple partial seizure, indicating that the seizure is focal in origin

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)

DIAGNOSTIC ISSUES (CONT'D)

TODD'S PARALYSIS—hemiparesis or hemiplegia following a seizure is suggestive of 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**, O_2, IV, **stat investigations** (ABG, CBCD, lytes, Cr, glucose, Mg, Ca, PO_4, toxic screen, antiepileptic drug level), *glucose* if hypoglycemia (*thiamine* 100 mg IV, 50% *glucose* 50 mL IV), **first line** (*lorazepam* 2 mg q1–3min IV push, consider rectal diazepam if no IV access), **second line** (*phenytoin* 20 mg/kg IV, no faster than 50 mg/min, start

MANAGEMENT (CONT'D)

continuous monitor), **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 for intubation). Note: phenytoin and benzodiazepines are incompatible in IV tubing and will precipitate if infused in same line. Use separate IV sites. See p. 101 for treatment of rhabdomyolysis

ACUTE SEIZURE CONTROL—**benzodiazepines** (*lorazepam* 1 mg IV/SL PRN, up to a total dose of 0.1 mg/kg. *Diazepam* 10 mg PO q6h and 5 mg PO q2h PRN). **Antiepileptic** (*fosphenytoin* 20 mg/kg IV, *phenytoin* 300 mg IV over 10 min, phenobarbital, carbamazepine, valproate). *If* **alcohol withdrawal** (add *thiamine* 100 mg IV/PO daily, *multi-vitamin* 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 daily, 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; *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

DRIVING ISSUES—recommendations vary from region to region. Check with driving authority for specific restrictions and legal requirements. If single unprovoked seizure, usually no driving restrictions are needed as long as EEG and imaging are normal. If >1 unprovoked seizure, consider 6–12 months of seizure-free interval before re-instating 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%

TREATMENT ISSUES (CONT'D)

ANTIEPILEPTIC CHOICES

- **BROAD-SPECTRUM ANTIEPILEPTIC DRUGS**—increasing order of efficacy, include valproic acid, lamotrigine, topiramate, levetiracetam, and zonisamide. These antiepileptic medications represent reasonable first-line therapy for most seizure types
- **NARROW-SPECTRUM ANTIEPILEPTIC DRUGS**—include carbamazepine, phenytoin, gabapentin, tiagabine, oxcarbazepine, and pregabalin. These medications are effective against partial seizures with or without secondarily generalized features, but have limited activity against primary generalized seizures

	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

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 mental retardation

DRUG- OR TOXIN-INDUCED SEIZURES—top five drug-induced etiologies include isoniazide, theophylline, oral hypoglycemic agents, carbon monoxide, and bupropion. Supportive management for theophylline-induced, carbon 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)

Related Topics
Brain Tumors (p. 297)
Seizures in Pregnancy (p. 415)
Toxicology (p. 102)

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

PHYSICAL—orthostatic hypotension, irregular or slow-rising pulse, apical-carotid delay, reduced 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 mortality up to 30% in 1 year 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**—CBCD, lytes, Cr/urea, CK, troponin
- **IMAGING**—CXR, echocardiogram, carotid dopplers, CT head
- **OTHERS**—ECG, 24 h Holter

INVESTIGATIONS (CONT'D)

SPECIAL

- **EEG**—if suspect seizures
- **STRESS TEST**
- **TILT TABLE TEST**—to confirm vasovagal syncope

MANAGEMENT

ACUTE—ABC, O_2, IV

TREAT UNDERLYING CAUSE

TREATMENT ISSUES

SAN FRANCISCO SYNCOPE RULE—prospectively validated to improve prediction of serious outcomes in patients with syncope and to guide admission decisions. If patient has any of 5 risk factors **★CHESS★ C**HF history, **H**ct <30, **E**CG abnormality, **S**BP <90 mmHg, or **S**hortness of breath, then admit for further workup. Sensitivity 96%, reduces admissions by 10%

Arch Intern Med 2009 169:14

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

SPECIFIC ENTITIES (CONT'D)

return to right atrium → decreased cardiac output. Normally, this triggers the autonomic response via baroreceptors in carotid 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**—see autonomic neuropathy for more details (p. 327)
- **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

SPECIFIC ENTITIES (CONT'D)

- **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, DDAVP, and potentially pyridostigmine

NEJM 2008 358:6

Related Topics
Arrhythmia (p. 39)
Dizziness (p. 315)
Falls (p. 382)
Stroke (p. 299)
Valvular Heart Disease (p. 47)

Migraine Headaches

NEJM 2002 346:4; NEJM 2006 354:2

DIFFERENTIAL DIAGNOSIS OF HEADACHES

VASCULAR (primary)—migraine, cluster, tension, medication overuse
INFECTIONS—meningitis, encephalitis
STRUCTURAL—**hemorrhage** (subarachnoid, epidural, subdural, intracerebral), **thrombosis** (ischemic stroke, cerebral vein), **tumor**, **trauma**

DIFFERENTIAL DIAGNOSIS OF HEADACHES (CONT'D)

OTHERS—sinusitis, temporal arteritis, pseudotumor cerebri, trigeminal neuralgia, pituitary apoplexy

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH HEADACHE HAVE A MIGRAINE OR NEED NEUROIMAGING?

★POUND★ CRITERIA—**P**ulsating, duration of 4–72 h**O**urs, **U**nilateral, **N**ausea, **D**isabling (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

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"

JAMA 2006 296:10

CLINICAL FEATURES (CONT'D)

ALARM SYMPTOMS (suggesting secondary causes)—"thunderclap headache," progressive headache over days to months, new onset after age 40, precipitated by Valsalva maneuver or exertion, nocturnal occurrence or morning awakening, systemic symptoms (myalgias, fever, weight loss, malaise, scalp tenderness, jaw claudication), neurologic signs or symptoms (confusion, decreased level of alertness, meningismus, papilledema, seizures)

HISTORY—temporal factors such as onset and duration of each episode as well as frequency are particularly important in making the diagnosis. Characterize headaches (location, nature, intensity, radiation, alleviation, and aggravation), precipitants (stress, food, physical activity), and any associated neurological symptoms. Consider temporal arteritis (jaw claudication, visual changes, temporal scalp tenderness) in the elderly, past medical history, current medications (especially headache medications)

PHYSICAL—vitals. Neurological examination including visual fields and fundoscopy. Remember to check temporal arteries in the elderly

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, ESR (temporal arteritis), INR, PTT
- **IMAGING**—CT head, MRI head

SPECIAL

- **LUMBAR PUNCTURE**

DIAGNOSTIC ISSUES

INTERNATIONAL HEADACHE SOCIETY MIGRAINE CRITERIA

1. At least 5 attacks
2. Episodic attacks lasting 4–72 h
3. Any 2 of unilateral pain, throbbing, moderate or severe intensity, pain aggravated by physical activity
4. Any 1 of N&V, photophobia, and 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** (*amitriptyline* 25–300 mg PO qhs, *desipramine* 25–200 mg PO qhs, nortriptyline), **β-blockers** (atenolol, propranolol, metoprolol, and nadolol), **anticonvulsants** (valproic acid, topirimate, gabapentin), **calcium channel blockers** (verapamil, flunarizine), **serotonin antagonists** (cyproheptadine, methysergide), **botulinum toxin**

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

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 8x 1-h attacks each day lasting 4–8 weeks each 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

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 (>5x and up to 24× per day) and are shorter (8–25 min). By definition, responsive to indomethacin

PSEUDOTUMOR CEREBRI (idiopathic intracranial hypertension)

- **PATHOPHYSIOLOGY**—idiopathic ↑ in intracranial pressure predominantly in obese women of childbearing 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 (>250 mmH_2O)
- **TREATMENTS**—weight loss, NSAIDs for pain, furosemide, *acetazolamide* 250 mg PO QID, lumboperitoneal shunting, optic nerve sheath fenestration, serial neuro-ophthalmologist follow-up

Meningitis

See MENINGITIS (p. 241)

Dizziness and Vertigo

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 neuronitis (3%), acute recurrent peripheral vestibulopathy, Meniere's disease (6%), cholesteatoma drugs (aminoglycoside, phenytoin), acoustic neuroma, herpes zoster oticus, deep sea diving

DIFFERENTIAL DIAGNOSIS (CONT'D)

SYNCOPE/PRE-SYNCOPE/ORTHOSTATIC HYPOTENSION—see SYNCOPE (p. 312)

IMBALANCE—spastic gait (infarction), apraxic gait (normal pressure hydrocephalus, frontal lobe dementia, Alzheimer's), ataxia gait (cerebellar disorder), shuffling gait (Parkinson's 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

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE 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

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 head-hanging maneuver to check for positional nystagmus. In combination with other data (including a brief neurological examination) in an emergency department setting, the absence of positional nystagmus can be useful in identifying serious causes of dizziness"

JAMA 1994 271:5

CLINICAL FEATURES (CONT'D)

HISTORY—distinguish between vertigo, 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 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. Check with Dix–Hallpike–Barany maneuver

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, 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's phenomenon (nystagmus and vertigo caused by loud noises at a particular frequency)
	Other non-auditory cranial nerve symptoms usually present	Tinnitus, hearing loss

DIAGNOSTIC ISSUES (CONT'D)

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 complete unilateral vestibular loss, or other brain stem signs or symptoms

Related Topic
Syncope (p. 312)

MANAGEMENT

SYMPTOM CONTROL—benzodiazepines (*diazepam* 2–10 mg IV), **anticholinergic** (*meclizine* 25 mg PO q8–12h, *diphenhydramine* 25–50 mg q6–8 h, *promethazine* 25 mg PO, *dimenhydrinate* 50–100 mg PO), **histamine analogue** (*betahistine* 8–16 mg PO TID for Meniere's disease)

SPECIFIC ENTITIES

BENIGN POSITIONAL VERTIGO

- **PATHOPHYSIOLOGY**—calcium debris in posterior semicircular canal (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–Barany maneuver (patient lies down with the head turned toward one shoulder quickly for 1 min, and then turned toward other direction for 1 min. May reproduce symptoms and rarely lasts >60 s)

SPECIFIC ENTITIES (CONT'D)

- **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

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
- **TREATMENTS**—betahistine, hearing aid use, intracochlear gentamicin injection

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

Hearing Impairment

DIFFERENTIAL DIAGNOSIS

SENSORINEURAL (inner ear to cortex)—**CVA**, **presbycusis**, **multiple sclerosis**, **Meniere's disease**, **trauma** (noise exposure, barotraumas, 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

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE HEARING IMPAIRMENT?

	LR+	LR−
History		
Asking patients whether they have hearing impairment	2.5	0.13
Hearing handicap inventory for the elderly (screening version) score of ≥8	3.8	0.38
Physical		
Inability to perceive whispering	6.1	0.03
Weber test	1.6–1.7	0.70–0.76
Rinne test	2.7–62	0.01–0.85
Investigations		
Not passing the audioscope test	2.4	0.07

APPROACH—"elderly individuals who acknowledge they have hearing impairment require audiometry, while those who reply no should be screened with the whispered voice test. Individuals who perceive the whispered voice require no further testing, while those unable to perceive the voice require audiometry. The Weber and Rinne tests should not be used for general screening"

JAMA 2006 295:4

CLINICAL FEATURES (CONT'D)

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. If cannot hear any more (bone conduction >air conduction), conductive hearing loss on that side

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

NOTE: 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

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's syndrome (usually unilateral), myasthenia gravis (bilateral or unilateral), botulism (usually bilateral), myotonic dystrophy (usually bilateral)

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's 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),

CLINICAL FEATURES (CONT'D)

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 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—**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	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

APPROACH—"the presence of speech becoming unintelligible after 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"

JAMA 2005 293:15

DISTINGUISHING FEATURES BETWEEN HORNER'S SYNDROME AND THIRD NERVE PALSY

	Horner's 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 ciliospinal reflex	
	Heterochromia	

INVESTIGATIONS

BASIC

- **LABS**—TSH, ANA, RF
- **IMAGING**—CT chest (thymoma, malignancy), CT/MR head (if third nerve palsy)

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 q3–6h. Thymectomy (controversial if no thymoma). Other treatments include corticosteroids, azathioprine, cyclosporine, mycophenolate, plasmapheresis, IVIG

MYASTHENIC CRISIS—ICU admission, treat any precipitating infection, discontinue any anticholinesterase agents, correct electrolyte abnormality, monitor respiratory status, and intubate if VC <15 mL/kg, 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 improve 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's Syndrome (p. 13)
Thymoma (p. 189)

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
- **FLOCCULONODULAR LOBE SYNDROME** (dysequilibrium, vertigo, and nystagmus)—brain tumors (medulloblastoma)

DIFFERENTIAL DIAGNOSIS (CONT'D)

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. 244)

	Cerebellar ataxia	Tabes dorsalis
History	Speech Δ	Sensory Δ
	Incoordination	Bowel/bladder Δ
	Gait difficulties	Impotence, pain
Inspection	Normal cognition	Dementia if neurosyphilis
	Ataxic speech	
H&N	Nystagmus	Argyll Robertson pupils
	Scanning speech	Optic atrophy
	Explosive speech	
Motor	Hypotonia, dysmetria, dysdiadochokinesia, heel-shin test, pendular reflexes	Normal tone
		Heel-shin test
		Absent reflexes (Westphal's sign)
		Extensor plantar

CLINICAL FEATURES (CONT'D)

DISTINGUISHING FEATURES BETWEEN CEREBELLAR DISORDER AND TABES DORSALIS (see p. 244)

	Cerebellar ataxia	Tabes dorsalis
Sensory	Normal	↓ 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's 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, wide-based stance, ataxic gait (wide based and staggering), rebound (outstretched arms swing easily when pushed), pronator drift (upward), truncal ataxia (Romberg's 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. 405)

Parkinson's Disease

CLASSIFICATION OF MOVEMENT DISORDERS

HYPOKINETIC

- **BRADYKINESIA**
- **RIGIDITY**
- **POSTURAL INSTABILITY**
- **PARKINSONIAN SYNDROMES**—constellation of rest tremor, rigidity, bradykinesia, and loss of postural reflexes

HYPERKINETIC

- **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's chorea
- **PSEUDOATHETOSIS**—chorea-type movements secondary to sensory loss
- **PAINFUL LEGS AND MOVING TOES**—continuous, stereotyped, flexion–extension, or adduction–abduction movements of toe

CLASSIFICATION OF MOVEMENT DISORDERS (CONT'D)

- **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 HYPEREKPLEXIA, STIFF-PERSON SYNDROME**—continuous isometric contractions of somatic muscles

PATHOPHYSIOLOGY

PARKINSONISM ★TRAP★—any 2 of **T**remor, **R**igidity, **A**kinesia/bradykinesia, and **P**ostural instability.

PATHOPHYSIOLOGY (CONT'D)

Parkinson's disease is primary or idiopathic parkinsonism. Secondary or acquired parkinsonism may be due to head trauma, cerebrovascular disease, drugs, or hydrocephalus

PARKINSONISM PLUS SYNDROMES—progressive supranuclear palsy, multiple system atrophy, Lewy body dementia, cortico-basal ganglionic degeneration

CLINICAL FEATURES

PHYSICAL EXAMINATION FOR PARKINSON'S DISEASE—resting tremor (4–6/s), rigidity, bradykinesia, micrographia, dementia, stare (reduced blink rate), mask face (hypomimia), glabellar tap, drooling, dysarthria, difficulty getting up from chair, postural instability, difficult with heel-to-toe walking, shuffling gait, and en bloc turn. Associated with disordered sleep, constipation, pain, and depression

CLINICAL FEATURES (CONT'D)

DISTINGUISHING FEATURES BETWEEN PHYSIOLOGIC AND PSYCHOGENIC MOVEMENT DISORDERS

- **HISTORY**—abrupt onset, static course, spontaneous remissions (inconsistency over time), obvious psychiatric disturbance, multiple somatizations, healthcare works, 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

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE PARKINSON'S DISEASE?

	LR+	LR−
History		
Tremor	1.3–17	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	1.3–1.5	0.47–0.61
Rigidity	0.5–2.8	0.38–1.6
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)

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's 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"

JAMA 2003 289:3

DISTINGUISHING FEATURES BETWEEN VARIOUS TREMORS

	Parkinson	Essential	Cerebellar
Tremor	Resting	Postural (action)	Intention (action)
Hertz	4–6	5–9	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

CLINICAL FEATURES (CONT'D)

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

INVESTIGATIONS FOR HYPERKINETIC MOVEMENT DISORDERS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, LDH, CK, INR, PTT, urinalysis
- **IMAGING**—CT head, MRI head

SPECIAL

- **FURTHER NEUROLOGIC WORKUP**—EMG/NCS, muscle/nerve biopsy, lumbar puncture, genetic testing (CAG repeats), and smear for acanthocytes if suspect Huntington's disease
- **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, PTH
- **METABOLIC WORKUP**—copper, 24 h urinary copper, vitamin B12, ceruloplasmin, RBC folate, lactate pyruvate

MANAGEMENT

TREAT UNDERLYING CAUSE

- **SINEMET**—*carbidopa/levodopa* 25/100–25/250 mg PO TID. Combined use with entacapone can lead to more sustained levodopa levels. See **NEJM 2008 359:23** for details
- **DOPAMINE AGONISTS**—*bromocriptine* 5–10 mg PO BID, pramipexole, ropinirole, pergolide. Ineffective in patients unresponsive to levodopa

MANAGEMENT (CONT'D)

- **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**—Sinemet 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 Sinemet. 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

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
- **FOOT MOVEMENTS**—heel strike, foot flat (midstance), 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's)
Broad based gait	Cerebellar—vermis
Ataxic gait	Cerebellar—anterior (alcohol)
Unsteady, sensory ataxia gait	Posterior column (Tabes dorsalis, B12 deficiency, Friedreich's ataxia)
Trendelenburg gait (waddling)	Hip adductor muscle weakness (gluteus medius)
Steppage gait	Foot drop (peroneal nerve palsy)

Related Topics
Dementia (p. 378)
Orthostatic Hypotension (p. 312)

Radiculopathy 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
- **LUMBOSACRAL REGION**—L5 and S1 (>90% combined) are the most commonly affected nerve roots

Related Topics
Back Pain (p. 284)
Peripheral Neuropathy (p. 327)
Spinal Cord Compression (p. 228)

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 red flags (fever, chills, unexplained weight loss, unremitting night pain, previous cancer, immunosuppression, and IDU) which may suggest tumor or infections

SPURLING'S SIGN—reproduction of symptoms (e.g. pain radiating down arm) with extension and lateral rotation of neck toward affected side followed by compressive force to the top of the head suggests cervical radiculopathy and may facilitate localization. Despite popularization in physical examination books

CLINICAL FEATURES (CONT'D)

and modest diagnostic utility (LR+ 3.6), Spurling's test should probably *not* be performed. In patients with rheumatoid arthritis, cervical malformations, or metastatic diseases, this test risks serious injury to the spine

INVESTIGATIONS

IMAGING—spine X-ray (low sens), CT spine, MR spine (especially if suspect myelopathy, red flags, progressive neurologic deficits, no improvement for 4–6 weeks)

EMG AND NERVE CONDUCTION STUDY

TREATMENT OF CERVICAL RADICULOPATHY

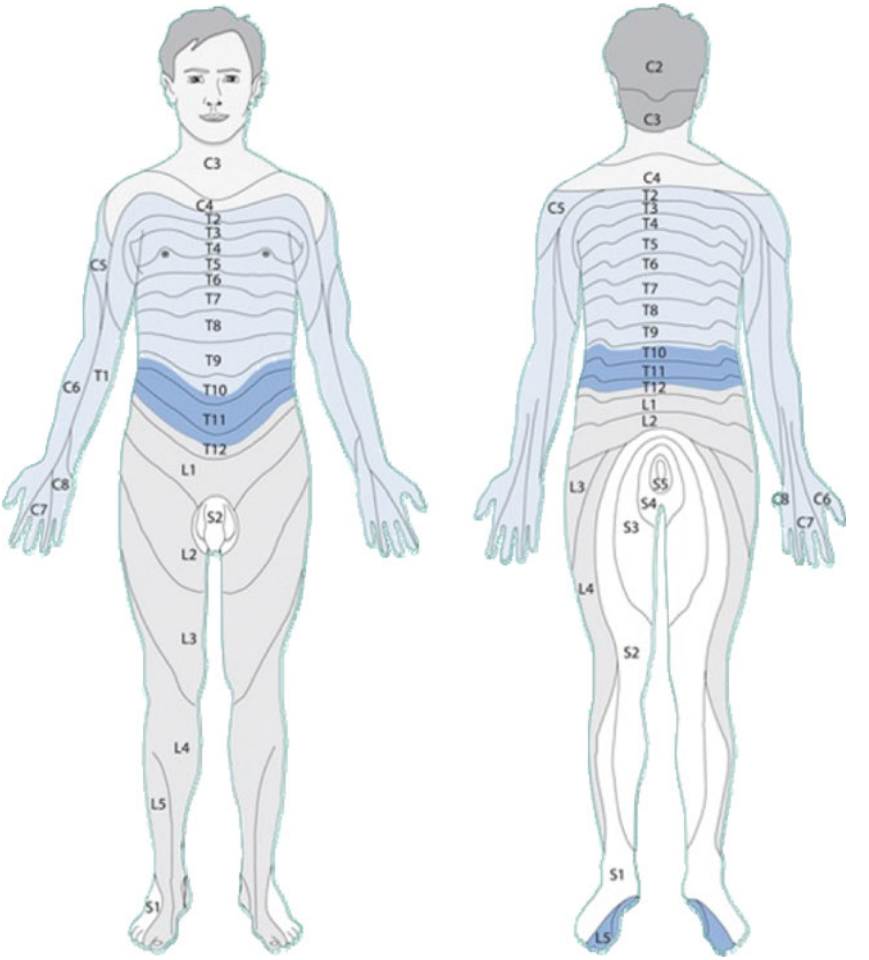
NON-SURGICAL—acetaminophen, NSAIDs, opioids, corticosteroid injections, cervical traction, exercise

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's (flexion and adduction of the thumb when the examiner flexes the terminal phalanx of the long finger), and Lhermitte's sign

DERMATOMES



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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
T1	Intrinsic muscles of hand
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**)

MYOTOMES (CONT'D)

Root	Muscles
L5	Extensor hallucis longus (**big toe extension**), tibialis posterior (planterflexion 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

BRACHIAL PLEXUS

Nerve	Root/origin	Muscle function
Dorsal scapular	C**5**/root level	Rhomboids (retracts scapula)
Long thoracic	C**5**67/root	Serratus anterior (scapula abduction)
Suprascapular	C**5**6 Upper trunk	Supraspinatus (arm abduction) Infraspinatus (arm external rotation)
Lateral anterior thoracic	C6**7** Upper, middle trunk	Pectoralis major (arm adduction, internal rotation)
Medial anterior thoracic	C**8** Lower trunk	Pectoralis major (arm adduction, int. rotation) Pectoralis minor (protracts scapula)
Subscapular	C**5**6 Posterior cord	Subscapularis (arm adduction) Teres major (arm extension, ext. rotation)
Thoracodorsal	C**7**8 Posterior cord	Latissimus dorsi (arm extension, adduction, internal rotation)
Axillary	C**5** Posterior cord	Deltoid (arm abduction) Teres minor (arm external rotation)
Musculo-cutaneous	C**5**6 Lateral cord	Biceps (forearm flexion) Brachioradialis (supination)
Median	C5**67T1** Anterior cord	See tables below
Radial	C**678** Posterior cord	See tables below
Ulnar	C**8T1** Lateral cord	See tables below

MUSCLE–NERVE FUNCTION CORRELATION

Muscle	Innervation	Function
Tibialis anterior	Deep peroneal n. (L4**L5**S1)	Inversion, **dorsiflexion**
Tibialis posterior	Tibial n. (**L4**L5)	**Inversion**, planterflexion
Peroneus longus	Superficial peroneal n. (L5**S1**)	**Eversion**, planterflexion
Peroneus brevis	Superficial peroneal n. (L5**S1**)	**Eversion**, planterflexion

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS

C6 VS. MEDIAN NERVE LESION

	C6	Median nerve (C6-T1)
Sensory	Palmer surface of **1st-2nd fingers Lateral surface of arm/forearm**	Palmer surface of **1st-lateral 4th fingers**
Motor	**Biceps, brachioradialis, forearm pronators** **Wrist extensors**	★**LOAF**★ **L**ateral 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**

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT'D)

C7 VS. RADIAL NERVE LESION

	C7	Radial nerve (C5–T1)
Sensory	Palmer surface of **3rd finger**	Dorsal surface of **1st-lateral 4st fingers**
	Dorsal surface of arm/forearm	Dorsal surface of arm/forearm
Motor	Triceps	Triceps (normal if high lesion)
	Wrist extensors and **flexors**	Wrist extensors
	Finger and thumb extensors	**Brachioradialis**
		Fingers and thumb extensors
Reflex	Triceps	Triceps (normal unless high lesion)
		Brachioradialis

C8/T1 VS. ULNAR NERVE LESION

	C8/T1	Ulnar nerve (C8T1)
Sensory	Palmar and dorsal surface of 4th and 5th fingers	Palmar and sometimes dorsal surface of 4th and 5th fingers
	Medial surface of arm and forearm	
Motor	Lumbricals (3rd, 4th), interossei	Lumbricals (3rd, 4th), interossei
	5th finger opposition, abduction, and flexion. Thumb adductor	5th finger opposition, abduction and flexion. Thumb adductor
	LOAF muscles (median n.)	
	Wrist flexion and abduction	
	Triceps (radial n.)	
Reflex	**Triceps**	None

L3 VS. OBTURATOR NERVE LESION

	L3	Obturator nerve (L34)
Sensory	Thigh/knee and **medial leg**	Medial thigh/knee
Motor	Hip adduction	Hip adduction
	Knee extension	
Reflex	**Knee**, adductor	Adductor

L4 VS. FEMORAL NERVE LESION

	L4	Femoral nerve (L234)
Sensory	Lateral leg to medial malleolus	Lateral leg to medial malleolus
Motor	Knee extension	Knee extension
	Dorsiflexion (deep peroneal n.)	**Hip flexion**
Reflex	Knee	Knee

L5 VS. PERONEAL NERVE LESION

	L5	Common peroneal n. (L45S1)
Sensory	Lateral leg, dorsal foot including first web space	Lateral leg, dorsal foot including first web space
Motor	Dorsiflexion and eversion	Dorsiflexion (deep peroneal n.) and eversion (superficial peroneal n.)
	Great toe dorsiflexion	
	Knee flexion	Great toe dorsiflexion
	Planterflexion and inversion (tibial n.)	
	Hip abduction (sup. gluteal n.)	

DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT'D)

S1 VS. SCIATIC NERVE LESION

	S1	**Sciatic nerve (L4–S3)**
Sensory	**Lateral foot including 5th toe**	**Lower leg and foot**
Motor	Planterflexion	Planterflexion and eversion, dorsiflexion and inversion
	Toe flexion	
	Hip abduction and extension	**Knee flexion**
Reflex	Ankle	Ankle

For the nerve root/peripheral nerve lesions tables above,

BOLD=highlights 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)

Lesion	**Abductor pollicis brevis**	**1st dorsal interosseous**
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

Peripheral Neuropathy

DIFFERENTIAL DIAGNOSIS

MONONEUROPATHY—compression, mononeuritis
MONONEURITIS MULTIPLEX—vasculitis, diabetes
POLYNEUROPATHY

- **AXONAL INJURY**
  - **NEOPLASTIC**—carcinoma, lymphoma, MGUS-IgA, IgG, IgM
  - **INFECTIOUS**—sepsis, HIV, Lyme
  - **METABOLIC**—diabetes, uremia
  - **VITAMIN DEFICIENCY**—malabsorption
  - **DRUGS**—cisplatin, taxanes, vincristine, isoniazid, nucleoside analogue
- **DEMYELINATING**—Guillain–Barre, neoplastic (carcinoma, lymphoma, MGUS-IgM), drugs (taxanes), chronic inflammatory demyelinating polyradiculoneuropathy

CLINICAL FEATURES

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)

CLINICAL FEATURES (CONT'D)

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**—CBCD, lytes, urea, Cr, glucose, ESR, serum protein electrophoresis, vitamin B12, ANA, TSH, urinalysis

SPECIAL

- **EMG AND NERVE CONDUCTION STUDY**
- **NERVE/MUSCLE BIOPSY**
- **LUMBAR PUNCTURE**

MANAGEMENT

TREAT UNDERLYING CAUSE—**diabetic** (glucose control), **lymphoma/myeloma** (chemotherapy)
SYMPTOM MANAGEMENT—**tricyclic antidepressants** (*desipramine* 10–50 mg qhs), ***gabapentin*** (300 mg PO daily ×1 day, then 300 mg PO BID

MANAGEMENT (CONT'D)

×1 day, then 300 mg PO TID, max 1800 mg/day), **anticonvulsants** (topiramate, carbamazepine)

SPECIFIC ENTITIES

CARPEL TUNNEL SYNDROME

- **PATHOPHYSIOLOGY**—median nerve entrapment syndrome
- **ASSOCIATIONS**—repetitive use, acromegaly, amyloidosis, hypothyroidism, rheumatoid arthritis, diabetes mellitus, pregnancy, and mucopolysaccharidosis. Bilateral disease suggests a systemic condition

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—nerve conduction studies (sens 49–84%, spc 95–99%) should be done if inadequate response to conservative therapy (changes in the workplace, nighttime neutral splints), thenar atrophy, or if the diagnosis is unclear
- **TREATMENTS**—activity modifications, wrist splinting, NSAIDs, corticosteroid injections (success 49–81%, recurrence 50–86%), carpel tunnel release (success 75–99%)

SPECIFIC ENTITIES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE CARPEL 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 palmer 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	21.4	0.1
Tinel's sign	1.4	0.8
Phalen's sign	1.3	0.7

APPROACH—"Katz hand symptom diagrams, hypalgesia, and thumb abduction strength testing are helpful in establishing diagnosis of carpel tunnel syndrome"

JAMA 2000 283:23

SPECIFIC ENTITIES (CONT'D)

AUTONOMIC NEUROPATHY

- **CAUSES**—autonomic failure may be secondary to peripheral neuropathy associated with diabetes, cancer (paraneoplastic), amyloidosis, cachexia, HIV, Guillain–Barre syndrome, Lambert–Eaton syndrome, other inflammatory/infectious conditions, or due to primary disorders such as Parkinson's 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

SPECIFIC ENTITIES (CONT'D)

	Sympathetic dysfunction	Parasympathetic dysfunction
H&N	Horner's	Dry eyes + mouth Dilated pupil
Heart	No respiratory variation	
GI/GU		Constipation Distended bladder Impotence
MSK, gait	Postural instability	

Related Topics
Diabetic neuropathy (p. 337)
Radiculopathy (p. 323)

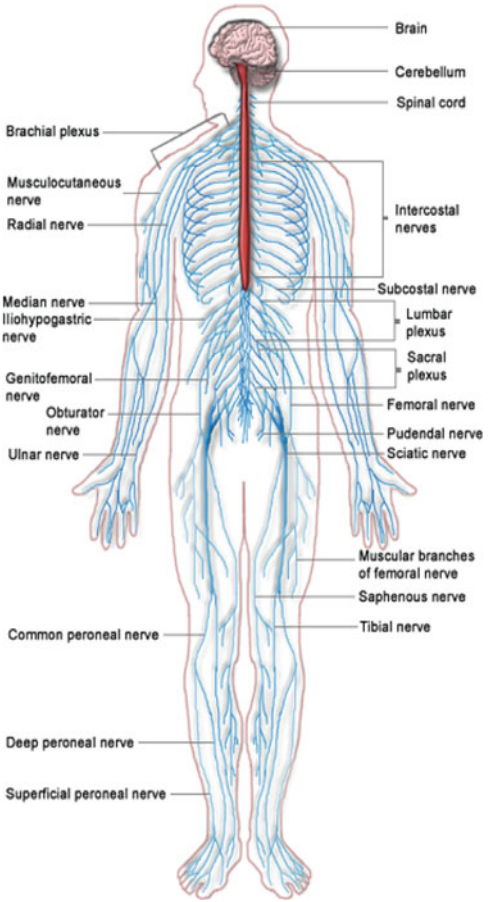
SPECIFIC ENTITIES

GUILLAIN–BARRE SYNDROME (GBS)

- **PATHOPHYSIOLOGY**—precipitants (*Campylobacter jejuni*, pper respiratory tract infections, 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 → potential autonomic dysfunction (50%), cranial nerves, respiratory muscle involvement. Areflexia. 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, ↑ protein), PFT
- **TREATMENTS**—*IVIG* 0.5–1 g/kg IV daily, plasma exchange. ICU admission with respiratory support if FVC <20 mL/kg, maximum inspiratory pressure <30 cmH_2O, maximum expiratory pressure <40 cmH_2O, rapid progression <7 days, cranial or autonomic involvement

MONONEURITIS MULTIPLEX—simultaneous/sequential involvement of noncontiguous nerve trunks (multiple nerve infarcts due to a systemic vasculitis)

PERIPHERAL NERVES



Reprinted from http://en.wikipedia.org/wiki/File:Nervous_system_diagram.png

PERIPHERAL NERVES (CONT'D)

MONONEUROPATHIES

Nerve (origin)	Pathophysiology	Signs and symptoms	Comments
Axillary nerve (C5–6)	Lesion usually near shoulder joint Affects deltoid and teres minor	Motor: weakness of shoulder abduction, shoulder atrophy Sensory: deficit similar to C5 lesion	
Subscapular nerve (C5–6)	Lesion usually at suprascapular notch of scapula Affects supraspinatus and infraspinatus	Motor: weakness of lateral rotation of arm 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 Affects brachioradialis, triceps, wrist, finger and thumb extensors	Motor: wrist drop, weakness of finger and thumb extensors Sensory: changes in dorsal surface of 1st-lateral 4th fingers, dorsal surface of arm/forearm	Saturday night palsy (acute compression) is frequent cause 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 Foshse Affects finger and thumb extensors	Motor: finger drop, wrist relatively spared Sensory: intact	
Ulnar nerve (C8–T1)	Lesion usually at cubital tunnel or ulnar groove at the elbow Affects ulnar flexor of the wrist, long flexors of 4th-5th digits and intrinsic hand muscles	Motor: weakness of finger adduction, abduction and thumb adduction (Froment's sign), claw-hand and interosseous atrophy Sensory: changes in both dorsal and palmer 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 Affects intrinsic hand muscles only	Motor: weakness of finger adduction and abduction. Interosseous atrophy Sensory: changes in palmer surface of 4th and 5th fingers only Tests: Tinel sign negative	Cyclist's palsy

PERIPHERAL NERVES (CONT'D)

MONONEUROPATHIES

Nerve (origin)	Pathophysiology	Signs and symptoms	Comments
Median nerve (C6–T1)	Lesion at carpal tunnel Affects abductor pollicis brevis, proximal muscles include forearm pronator, long finger, and thumb flexors	Motor: weakness, pain, numbness and tingling over thumb, 2nd and 3rd fingers Sensory: changes in palmer surface of 1st-lateral 4th fingers Tests: square wrist sign, closed fist sign, Flick sign, Tinel sign and Phalen sign	Carpel tunnel syndrome
Anterior interosseous branch of median nerve (C7–T1)	Lesion usually just below the elbow Affects long flexors of thumb and index and middle fingers	Motor: weakness of pinch, pain in volar forearm Sensory: intact	
Femoral nerve (L2–4)	Lesion usually proximal to inguinal ligament Affects iliopsoas (hip flexor) and quadriceps femoris (knee extensor)	Motor: buckling of knee, absent knee jerk, weak anterior thigh muscles with atrophy. Obturator nerve (hip adduction) not affected Sensory: changes in lateral leg to medial malleolus	Post-femoral catheterization or pelvic surgery with retroperitoneal hematoma, diabetes mellitus
Lateral femoral cutaneous branch of femoral nerve (L2–3)	Lesion usually at inguinal ligament	Motor: intact Sensory: dysesthetic hyperpathia of lateral thigh (burning)	Meralgia paresthetica (entrapment of lateral cutaneous femoral nerve to anterolateral aspect of thigh)
Obturator nerve (L3–4)	Lesion usually at pubis or intrapelvic Affects thigh adductors	Motor: weakness of hip adduction Sensory: deficit of medial thigh	
Sciatic nerve (L4–S3)	Lesion usually near sciatic notch Affects hamstring muscles, hip abductor and all muscles below the knee	Motor: severe lower leg and hamstring weakness, flail foot, difficulty walking Sensory: changes in lower leg and foot	Overdose victims
Tibial nerve (L5–S2)	Lesion usually at tarsal tunnel or near medial malleolus Affects calf muscles (proximally), toe flexor, and other intrinsic foot muscles	Motor: weak toe flexors Sensory: pain and numbness of sole	Tarsal tunnel syndrome
Peroneal nerve (L4–S1)	Lesion usually at neck of fibula Affects dorsiflexors of toes and foot and evertors of foot	Motor: weakness of foot eversion and foot drop Sensory: deficit similar to L5 lesion	Cross-leg palsy

Muscle Weakness

DIFFERENTIAL DIAGNOSIS

INFLAMMATORY MYOPATHY—polymyositis, dermatomyositis, inclusion body myositis, juvenile dermatomyositis, vasculitis, overlap syndromes (SLE, scleroderma, rheumatoid arthritis, Sjogren's)

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

ENDOCRINE MYOPATHY—hypothyroidism, hyperthyroidism, Cushing's, diabetes, acromegaly

METABOLIC MYOPATHY—hypokalemia, hypocalcemia, hypophosphatemia, hyponatremia, hypernatremia, disorders of carbohydrate/lipid/purine metabolism

NEOPLASTIC MYOPATHY—paraneoplastic

RHABDOMYOLYSIS

- **DRUGS**—alcohol, cocaine, statins, neuroleptic malignant syndrome, malignant hyperthermia
- **HYPERACTIVITY**—seizures, exertion
- **TRAUMA/OPERATION**
- **IMMOBILITY**

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–Barre, myeloma, amyloidosis, diabetes
- **NEUROMUSCULAR JUNCTION**—myasthenia gravis, botulism, Eaton–Lambert, organophosphate poisoning
- **MUSCLES**—myopathies (see above)

Related Topics
Critical Illness Weakness (p. 89)
Dermatomyositis (p. 279)
Eaton-Lambert Syndrome (p. 319)
Myasthenia Gravis (p. 318)

CLINICAL FEATURES

APPROACH TO CLINICAL DIAGNOSIS

1. **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
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
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
4. **DISTAL VS. PROXIMAL MUSCLE WEAKNESS?**
   - if distal, consider peripheral neuropathy, myasthenia gravis, motor neuron disease
   - if proximal, consider myopathies (see differential diagnosis), myasthenia gravis, Duchenne muscular dystrophy

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, thyroid myopathy, and inherited metabolic myopathies

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, Ca, Mg, PO_4, CK, aldolase, LDH, AST, ALT, ANA, ANCA, HBV/HBC serology, cryoglobulin, RF, TSH

INVESTIGATIONS (CONT'D)

SPECIAL

- **EMG AND NERVE CONDUCTION STUDY**
- **MUSCLE BIOPSY**
- **POLYMYOSITIS/DERMATOMYOSITIS WORKUP**—anti-Jo 1 and 2, anti-SRP (signal recognition particle), anti-Mi2

MANAGEMENT

REHABILITATION

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

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
- **DELAYED REVERSAL OF NEUROMUSCULAR BLOCKADE**—non-depolarizing neuromuscular blocking agents (pancuronium, vecuronium) in susceptible patients

SPECIFIC ENTITIES (CONT'D)

- **CRITICAL MYOPATHY**—muscle weakness and atrophy. Muscle damage second degree to sepsis and multi-system organ failure
- **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 (bulbar, cervical, and lumbosacral). No sensory deficit
- **CLINICAL FEATURES**—upper motor neuron signs (hyperactive reflexes, extensor plantar responses), lower motor neuron signs (muscle weakness, atrophy, and fasciculations) in multiple regions
- **DIAGNOSIS**—EMG/NCS
- **TREATMENTS**—antiglutamate agent (riluzole)

DROP HEAD SYNDROME—persistent head flexion. May be due to myasthenia gravis, polymyositis, or amyotrophic dystonia

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

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**, **brain stem,** and **spinal cord**. Also useful for most tumors, epilepsy, demyelinating diseases, inflammatory and infectious conditions (e.g. HSV encephalitis), degenerative diseases, and congenital abnormalities

MRI WITH GADOLINIUM—improved differentiation between pathologic and normal tissues (especially T1 relaxation). This increases the sensitivity and specificity. Contrast may also provide physiologic and functional information in addition to lesion delineation

CT/MR ANGIOGRAPHY—used for evaluation of occlusive cerebrovascular disease, dissection, and in the detection of intracerebral aneurysms as small as 5 mm in diameter. However, 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**

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 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

APPROACH TO CT HEAD (CONT'D)

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

HEAD CT FINDINGS IN STROKE (CONT'D)

Notes

Notes

11
ENDOCRINOLOGY

Section Editor: Dr. Laurie Mereu

Diabetes Mellitus — Canadian Diabetes Association Guidelines 2008

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**
- **GENETIC DEFECTS IN INSULIN ACTION**
- **OTHER GENETIC SYNDROMES ASSOCIATED WITH DIABETES**
- **DISEASES OF THE PANCREAS**—cystic fibrosis, hemochromatosis, neoplasia, pancreatitis, pancreatectomy
- **ENDOCRINOPATHIES**—acromegaly, Cushing's syndrome, glucagonoma, hyperthyroidism, pheochromocytoma
- **INFECTIONS**
- **UNCOMMON FORMS OF IMMUNE-MEDIATED DIABETES**
- **DRUG OR CHEMICAL INDUCED**—atypical antipsychotics, corticosteroids, nicotinic acid, pentamidine, phenytoin, protease inhibitors, thiazides

PATHOPHYSIOLOGY

CHRONIC COMPLICATIONS OF DIABETES

- **MACROVASCULAR DISEASE**—patients with diabetes have a 2–4× ↑ in cardiovascular complications (coronary artery disease, stroke/TIA, peripheral vascular disease)
- **RETINOPATHY**
  - **BACKGROUND**—microaneurysms, dot and blot hemorrhages, hard exudates
  - **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, ↑ glomerular pressure, microalbuminuria, overt proteinuria, nephrotic range proteinuria, end-stage renal disease

PATHOPHYSIOLOGY (CONT'D)

- **NEUROPATHY** (50% of all patients)
  - **MONONEUROPATHY**—cranial (III most 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's feet
  - **PROXIMAL SYMMETRIC POLYNEUROPATHY** (polyradiculopathy)—diabetic radiculoplexopathy or amyotrophy, usually involving L2–4 roots causing painful 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

REASONS WHY BLOOD SUGAR FLUCTUATES

- **LIFESTYLE**—diet (quantity/quality, timing), exercise
- **BLOOD SUGAR TESTING**—accuracy, timing
- **NEUROPATHY**—hypoglycemic awareness, gastroparesis
- **ILLNESS**—infections, stress
- **INSULIN**—injection site, technique, dose
- **DECREASED INSULIN REQUIREMENT**—renal failure, Addison's
- **MEDICATIONS**—interactions
- **OTHER ENDOCRINE CAUSES OF HYPERGLYCEMIA**—Cushing's, pheochromocytoma, hyperthyroidism

PRECIPITATING FACTORS FOR DKA—sepsis, acute abdomen, myocardial infarction, insulin omission, new-onset diabetes

CLINICAL FEATURES

HISTORY—**duration** and **type** of diabetes, **diabetic control** (frequency of monitoring, hypoglycemia,

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_11,

CLINICAL FEATURES (CONT'D)

hyperglycemia, previous HbA1C, previous DKA, 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—height, weight, BMI, vitals, fundi (diabetic or hypertensive retinopathy, cataracts), thyroid, chest, cardiac, abdominal examination, insulin injection sites, peripheral pulses, check for carotid and femoral bruits, diabetic foot examination including neurological examination

DIABETIC FOOT EXAMINATION

- **INSPECTION**—shoes, diabetic dermopathy, dry atrophic skin, fissures, callus, necrobiosis lipoidica diabeticorum, muscle atrophy, hair loss, pallor, ulcers (arterial, neuropathic, venous stasis), gangrene (look between toes), dystrophic nails, ingrown nails, fungal nail infections, Charcot's feet (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's test, ankle/brachial index
- **NEUROLOGICAL**—10 g sensory filament, vibration, glove and stalking sensory loss (light touch, pain, temperature), power (dorsiflexion, plantar flexion), ankle reflex

INVESTIGATIONS

BASIC

- **LABS**—glucose, lytes, anion gap, osmolality, ketones, creatinine, urea, HbA1C, fasting lipids, ALT, ALP, CK, TSH, C-peptide, urine albumin to creatinine ratio

SPECIAL

- **ANTIBODIES**—insulin antibody, GAD65 antibody, islet cell antibody

Related Topics
Autonomic Neuropathy (p. 328)
Coronary Artery Disease (p. 26)
Gastroparesis (p. 113)
Gestational Diabetes (p. 413)
Osteomyelitis (p. 248)
Peripheral Neuropathy (p. 327)
Peripheral Vascular Disease (p. 54)

DIAGNOSTIC ISSUES

DIAGNOSTIC CRITERIA FOR DIABETES

	Fasting BS	GTT (75 g, 2hr)
Normal	<5.6 mmol/L [<100 mg/dL]	<7.8 mmol/L [<140 mg/dL]
Impaired Fasting Glucose	5.6–6.9 mmol/L [100–125 mg/dL]	
Impaired Glucose Tolerance		7.8–11.0 mmol/L [140–199 mg/dL]
Diabetes*	≥7.0 mmol/L [≥126 mg/dL]	≥11.1 mmol/L [≥200 mg/dL]

GTT=glucose tolerance test
*random glucose ≥11.1 mmol/L [≥200 mg/dL] accompanied by classical symptoms (polyuria, polydipsia, unexplained weight loss) also sufficient for diagnosis

FACTITIOUS LABORATORY ABNORMALITIES—DKA itself may cause ↑ WBC, ↓ Na, and ↑ amylase, which should correct with resolution of DKA

ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS

ACUTE—**ABC**, O_2, IV, may need intubation

CORRECT ACID/BASE ELECTROLYTES ABNORMALITIES

- **MONITOR**—continuous cardiac monitor until patient is stable. Create flow sheet with time vs. pH, lytes, anion gap, ketones, glucose, insulin, IV fluids. Careful monitoring and frequent reassessment is required
- **HYDRATION**—NS 15–20 mL/kg/h IV bolus to fluid resuscitate then decrease IV accordingly
- **POTASSIUM**—once serum K is <5.0 mEq/L and patient is voiding, add supplemental KCL (see table on next page)
- **INSULIN**—give 0.1 units/kg of regular insulin IV push, then 0.1 units/kg/h (mix 25 units of regular insulin in 250 mL D5W. One unit of insulin is equal to 10 mL of drip). 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 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 hungry, 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 h
- **GLUCOSE**—once serum glucose is less than 15 mM, add glucose to IV fluids (e.g. D5NS, D5½NS). If patient is euvolemic and serum sodium is normal or high, D5½NS should be used
- **BICARB**—if pH <6.9, may be beneficial to give 1–2 amps of HCO_3 over 1–2 h. If pH 6.9–7.0, giving HCO_3 is optional. If pH >7.0, giving HCO_3 is not necessary

ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS (CONT'D)

- **PHOSPHATE**—no indication for replacement in the acute setting unless there is severe cardiac or respiratory depression
- **LABS**—obtain hourly ABGs, lytes, bicarb, anion gap, glucose, serum osmolality, ketones. Cerebral edema is a concern (particularly in children) if osmolality/sodium parameters are corrected too quickly

TREAT PRECIPITATING FACTOR(S)

AN EXAMPLE OF AN APPROACH TO THE MANAGEMENT OF DKA

	Hour 1	Hour 2	Hours 3–4	Hours 5–8	Hours 8–24
Hydration IV #1 NS or ½ NS ± potassium replacement	1 l NS (i.e. 15–20 mL/kg/h) Use ½NS if corrected Na >145 mmol/L (for every 10 mmol/L[182 mg/dL] ↑ in blood glucose, correct Na by ↑ 3 mmol/L)	500 mL/h NS	500 mL/h NS	250 mL/h NS When glucose <15 mmol/L [<270 mg/dL], change IV to D5½ NS @ 250 mL/h (if corrected sodium is low, use D5NS). If glucose <15 mM [<270 mg/dL], but AG still ↑, run D10W at 80 mL/h so that IV insulin can be ↑	125–250 mL/h D5½ NS
Insulin IV #2 Mix 25 units reg insulin in 250 ml D5W (1 unit =10 mL)	Bolus 0.1 units/kg regular IV insulin (e.g. 7 units for 70 kg) Then 0.1 units/kg/h initially following bolus (e.g. 5–10 units/h) Hold for 2 h if hypotensive or K <3.5 mEq/L Target glucose 10–15 mmol/L	Continue IV insulin Expect a glucose fall of 5 mmol/h [90 mg/dL/h] Titrate insulin against AG. Double dose if poor response A drop in glucose >3–5 mmol/h [>54–90 mg/dL/h] increases risk of cerebral edema (mostly in children	When glucose <15 mM [<270mg/d], decrease IV to 2–4 units/h, but continue IV until ketosis cleared; use following scale: **Glucose** / **mM** / **mg/dL** / **Insulin drip** <5 / <90 / Stop and recheck in 1 h 5.1–10 / 91–180 / Decrease by 1 units/h 10.1–15 / 181–270 / No change 15.1–20 / 271–360 / Increase by 1 units/h 20.1–24 / 361–437 / Increase by 2 units/h >24 / >438 / Increase by 3 units/h and call MD If glucose drops by more than 5 mM [90 mg/dL] in 2 h, decrease insulin to 0.5 units/h and call MD		After ketoacidosis has cleared, switch to SC insulin and thenstop IV insulin Usually keep IV insulin for first day; do not stop overnight
Potassium replacement (when voiding)	Serum potassium Potassium replacement	<3 mEq/L, give 40 mEq/h	3–4 mEq/L, give 30 mEq/h	4–5 mEq/L, give 20 mEq/h	5–6 mEq/L, give 10 mEq/h
Laboratory	Baseline: glucose, β-OH-butyrate, ABG, urinalysis, CBCD, electrolytes, Cr, PO_4, Mg, ± lipase, CXR, cultures, troponin, ECG	Glucose (C/S), lytes (VBG) ABGs if pH <7.0	Glucose (C/S), lytes (VBG) ABGs if pH <7.0	Glucose (C/S) hourly, lytes (VBG), PO_4	Glucose (C/S) q1–2h lytes q4–8h
Alkaline replacement	Rarely indicated unless severe acidosis (pH <6.9) with incipient circulatory collapse Dose 50–100 mEq, $NaHCO_3$ in ½NS over 30–60 mins 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/l/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 (ABG's, 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	

Abbreviations: ABG=arterial blood gas, AG=anion gap, CBCD=CBC and differential, C/S=chemstrips, NS=normal saline, VBG=venous blood gas

NOTE: this table should not replace individualized care and sound clinical judgment

SPECIFIC ENTITIES

NON-KETOTIC HYPEROSMOLAR HYPERGLYCEMIA

- **PATHOPHYSIOLOGY**—occurs in patients with type 2 diabetes
- **CLINICAL FEATURES**—characterized by profound dehydration, increased osmolar state, severe elevation in blood glucose along with hypernatremia. Ketones may be mildly elevated or absent. Patients often present in a comatose state or have a decreased level of conscience
- **TREATMENTS**—fluid resuscitation along with an insulin drip. Need to correct Na for elevated glucose (add 3 mEq/L to the serum Na for every rise of 10 mmol/L [182 mg/dL] of glucose above 10 mmol/L [182 mg/dL]. To minimize risk of cerebral edema, serum Na should ideally drop by no more than 8 mEq/L/day, serum osmolality should drop by no more than 3 mEq/L/h, and glucose should drop by no more than 3 mEq/l/h. Lower insulin requirement compared to DKA. Mortality 10–20%

SPECIFIC ENTITIES (CONT'D)

LONG-TERM MANAGEMENT

RISK REDUCTION ★ABCDEFG★

- **ASA/ACE INHIBITOR**—*ASA* 81 mg PO daily for secondary prevention, controversial for primary prevention. ACE inhibitor or ARB should be started if microalbuminuria
- **BLOOD PRESSURE CONTROL**—first-line therapy: ACE inhibitor, ARB, dihydropyridine CCB, or thiazide-like diuretics. Aim for <130/80 mmHg
- **CHOLESTEROL CONTROL**—the targets are LDL <2.0 mmol/L [<77 mg/dL], TGL <1.5 mmol/L [<130 mg/dL] and total chol/HDL ratio <4. Consider fibrates (↓ triglycerides, ↑ HDL), HMG-CoA

LONG-TERM MANAGEMENT (CONT'D)

reductase inhibitor (↓ LDL), bile acid sequestrants (↓ LDL), nicotinic acid (↓ triglycerides, ↓ LDL, ↑ HDL but may ↑ glucose)

- **DIABETIC CONTROL**—aim for HbA1C of less than 7.0% in all patients. A target HbA1C of ≤6.5% may be considered in selected patients. Fasting and before meals glucose should be 4.0–7.0 mmol/L [73–126 mg/dL]. The 2 h postprandial glucose ideally should be 5.0–10.0 mg/dL [91–182 mg/dL] or 5.0–8.0 mg/dL [91–145 mg/dL] if A1C 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. A1C 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. A baseline ECG or exercise ECG is advisable prior to embarking on an exercise program
- **EYE/NEUROLOGIC**—all patients with type 2 diabetes should be referred to an ophthalmologist 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. Amitriptyline, gabapentin, or pregabalin may be used for painful neuropathy. Domperidone, metoclopramide, erythromycin, or cisapride (beware long QT) may be used for gastroparesis
- **FAT REDUCTION** (lose 5–10 kg)—all patients should follow healthy eating guidelines and try to attain an ideal body weight. See OBESITY ISSUES (p. 403)
- **GET GOING TO QUIT SMOKING!**—there are many different options for patients, including nicotine gum, nicotine inhaler, Nicoderm patch, Bupropion SR, and varenicline. Smoking cessation classes
- **SCREENING FOR CARDIOVASCULAR DISEASE**—patients should have the following tests done at baseline if they meet any of the following criteria:
  - **ECG**—if age >40, have had diabetes for >15 years, or if they have hypertension, proteinuria, reduced pulses or vascular bruits. ECG should be repeated every 2 years in patients of high cardiovascular risk

LONG-TERM MANAGEMENT (CONT'D)

- **EXERCISE ECG STRESS TEST**—angina, atypical chest pain, dyspnea, abnormal ECG, peripheral artery disease, carotid bruits, transient ischemic attack, and stroke
- **STRESS MIBI**—individuals with an abnormal ECG (LBBB or ST-T wave changes) or who cannot exercise
- **REVASCULARIZATION**—prompt revascularization vs medical therapy for stable ischemia seems to have similar outcomes (death and major cardiovascular events)

ORAL HYPOGLYCEMIC AGENTS

BIGUANIDES (↓ hepatic glucose production, ↑ tissue sensitivity)—*metformin* 500–850 mg PO TID; adverse effects include GI upset and lactoacidosis; contraindications include hypoxia, hepatic and renal failure, HF, poor LV function; hold before giving IV contrast and 48 h post-contrast

THIAZOLIDINEDIONES (sensitizes tissues to insulin, ↓ hepatic glucose production)—*pioglitazone* 15–45 mg PO daily; adverse effects include hepatotoxicity and fluid retention, contraindications include liver failure, fluid overload, HF, and CAD; avoid concurrent use of insulin and thiazolidinediones as increased fluid retention. Recent evidence linking rosiglitazone with increased risk of myocardial infarction and cardiovascular death; thus the decision to prescribe rosiglitazone should be done after carefully balancing the risks and benefits of treatment. Rosiglitazone has been withdrawn from the European market

MEGLITINIDE (↑ pancreatic insulin release)—*repaglinide* 0.5–4 mg PO TID ac meals; adverse effects include hypoglycemia

SULFONYLUREA (↑ pancreatic insulin release)— *gliclazide* 80 mg PO daily to 160 mg BID; *glimepiride* 1–8 mg PO daily, *glyburide* 2.5–10 mg PO BID; adverse effects include hypoglycemia

α-GLUCOSIDASE INHIBITOR (delays glucose absorption)—*acarbose* 25–100 mg TID ac meals; adverse effects include bloating and diarrhea

INCRETIN MIMETICS AND DIPEPTIDYL PEPTIDASE-4 (DPP-4) INHIBITORS—*sitagliptin* 25–100 mg PO daily. Increases incretin levels, increases insulin release in response to glucose, and decreases glucagon resulting in improved postprandial control; weight neutral; long-term adverse effects are not yet known

GLUCAGON-LIKE PEPTIDE-1 (GLP-1) ANALOGUES—*exenatide* 5–10 μg SC BID 30 min before meals. 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

Principles of Insulin Use

NEJM 2005 352:2

STARTING INSULIN FOR NEW PATIENTS

CALCULATE TOTAL DAILY DOSE

- **STABLE NEW PATIENTS**—the total daily requirement is 0.5 units/kg of insulin per day SC in divided dosages
- **MULTIPLE DAILY INJECTIONS**—all diabetic patients should be encouraged to be on this regimen to achieve good control; 20% of total insulin should be given before breakfast, lunch, and supper as rapid or regular, 40% of total insulin dose should be given as basal insulin at bedtime using NPH, Lantus, or Levemir. If using rapid ac meals, a small dose of basal insulin will be necessary in the morning as well
- **TWO-THIRDS, ONE-THIRD RULE**—if a patient is unable to do multiple daily injections, consider the two-thirds, one-third rule, which establishes a baseline for insulin administration using the two main types of insulin (intermediate acting and fast acting). AM dose (given before breakfast) = 2/3 of total daily insulin (2/3=N, 1/3=R), supper dose = 1/3 of total daily insulin (2/3=N, 1/3=R)
- **BEDTIME INSULIN**—patients with type 2 diabetes who are on maximum oral hypoglycemic agents may be started on bedtime insulin at 0.1 units/kg to improve control using either NPH, Lantus, or Levemir

SPECIAL CONSIDERATIONS

- **DELAY DOSE**—patients may need to delay their insulin intake at times (e.g. if they were NPO for procedures). For every hour delay in giving NPH, subtract 10% of dose
- **RENAL FAILURE**—insulin is renally excreted, thus its dose must be reduced in patients with 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
- **THIAZOLIDINEDIONES AND INSULIN**—avoid using thiazolidinediones (e.g. rosiglitazone) in combination with insulin as both medications promote fluid retention
- **β-BLOCKERS USE IN DIABETICS**—non-selective β-blockers may mask signs and symptoms of hypoglycemia. Consider use of cardioselective β-blocker agents in diabetics

REGULAR INSULIN DOSE ADJUSTMENT PRINCIPLES

INSULIN ADJUSTMENTS—understanding the pharmacokinetics of different insulin types is essential for fine adjustments of insulin regimen. Blood sugar is checked 4 times/day, before meals and at bedtime

- **HIGH AM BLOOD SUGAR**—check 3 AM glucose first to see if there is nocturnal hypoglycemia. The bedtime basal insulin would have to be decreased. If the 3 AM glucose is high, then increase the bedtime basal insulin
- **HIGH LUNCH TIME BLOOD SUGAR**—should increase breakfast insulin R dose
- **HIGH SUPPER TIME BLOOD SUGAR**—should increase noon insulin R dose or morning basal dose
- **HIGH BEDTIME BLOOD SUGAR**—should increase supper insulin R dose

TYPES OF INSULIN

Insulin type/action	Trade names
Rapid acting (clear)	Humalog (insulin lispro)
Onset: 10–15 min	NovoRapid (insulin aspart)
Peak: 1–1.5 h	
Duration: 3–5 h	
Short acting (clear)	Humulin-R
Onset: 30 min	Novolin ge Toronto
Peak: 2–3 h	
Duration: 6.5 h	
Intermediate acting (cloudy)	Humulin-N
Onset: 1–3 h	Novolin ge NPH
Peak: 5–8 h	
Duration: up to 18 h	
Long-acting basal insulin analogues (clear)	Insulin detemir (Levemir)
Onset: 90 min	Insulin glargine (Lantus)
Duration: up to 24 h	
Premixed	Humulin 30/70
Premixed regular insulin-NPH (cloudy)	Novolin ge 30/70
	Novolin ge 40/60
Premixed insulin analogues (cloudy)	Novolin ge 50/50
	Humalog Mix 25
	Humalog Mix 50
	Novo Mix 30

Canadian Diabetes Association Guidelines 2008

SAMPLE SLIDING SCALE TEMPLATE

INSULIN SLIDING SCALE

Glucometer QID with insulin SC QID

Blood sugar	Regular or rapid insulin SC TID ac meals	NPH or basal insulin SC qhs
0–4	give juice, call MD	give juice, call MD
4.1–6		
6.1–8		
8.1–10	Individualized	Individualized
10.1–12	dosing	dosing
12.1–16		
16.1–18		
18.1–20		
>20	Notify MD	Notify MD

NOTE: dose of insulin varies depending on individual patient. For insulin requiring patients, total daily dose is 0.5 units/kg/day; 20% of this dose to be given as regular or Rapid with meals and 40% to be given as bedtime NPH or basal insulin

TREATMENT ISSUES

LOCAL COMPLICATIONS OF INSULIN INJECTION—lipoatrophy (human insulin), lipohypertrophy (animal insulin), edema, itching, pain or warmth at injection site, scar tissue

TREATMENT ISSUES (CONT'D)

LONG-TERM COMPLICATIONS OF INSULIN USE—weight gain and risk of hypoglycemia. Possible association between long-acting insulin and malignancy has been raised; however, further studies are required

Hypoglycemia

DIFFERENTIAL DIAGNOSIS

↓ **GLUCOSE,** ↓ **INSULIN, AND** ↓ **C-PEPTIDE**—alcoholism, sepsis, adrenal insufficiency, panhypopituitarism, liver failure, HF, renal failure, anorexia, inborn errors of metabolism, drugs (β-blockers, salicylates, haloperidol)

↓ **GLUCOSE,** ↑ **INSULIN, AND** ↓ **C-PEPTIDE**—exogenous insulin, insulin autoantibodies

↓ **GLUCOSE,** ↑ **INSULIN, AND** ↑ **C-PEPTIDE**—drugs (sulfonylurea, meglitinide, pentamidine, quinine) β-cell tumor (insulinoma, islet cell hyperplasia-nesidioblastosis)

PATHOPHYSIOLOGY

DEFINITION OF HYPOGLYCEMIA—glucose <2.5 mM [<45 mg/dL]

REACTIVE HYPOGLYCEMIA—hypersecretion of insulin postprandially

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

CLINICAL FEATURES

SYMPTOMS—sweating, palpitations, tachycardia, dizziness, blurred vision, mental deficits, altered level of consciousness

CLINICAL FEATURES (CONT'D)

WHIPPLE'S TRIAD—hypoglycemia, symptoms of hypoglycemia, reversal of symptoms with glucose

INVESTIGATIONS

BASIC

- **LABS**—Whenever the glucose is found to be low, serum glucose, insulin, C-peptide, and proinsulin should be sent along with a spot urine for sulfonylurea screen. Also send for cortisol, ACTH, TSH, free T4, glucagon, and ketones along with liver function studies and renal function. If sepsis is suspected, order CBCD, blood and urine cultures, and CXR

SPECIAL

- **72-HOUR FASTING STUDY**—may help in the diagnosis of insulinoma if spontaneous hypoglycemic episodes are infrequent. Consult endocrinology
- **THIN CUT CT OF PANCREAS WITH PANCREATIC ANGIOGRAM**—if suspect pancreatic tumor
- **OTHER IMAGING MODALITIES**—endoscopic ultrasound, MRI pancreas, and octreotide scan

MANAGEMENT

ACUTE—*glucose tablets* 15 g PO, ensure snack or meal afterward. If hypoglycemia is severe and patient is unresponsive, give D50W IV push and *glucagon* 1 mg SC/IM ×1 dose. Monitor chemstrips q1h to ensure glucose is recovering

TREAT UNDERLYING CAUSE—**pancreatic adenoma** (resection. If unresectable cancer, consider diazoxide or octreotide)

Hypothyroidism

DIFFERENTIAL DIAGNOSIS

PRIMARY HYPOTHYROIDISM

- **THYROIDITIS**—Hashimoto's, subacute, postpartum, irradiation
- **IATROGENIC**—radioactive I^{131}, thyroidectomy
- **DRUGS**—methimazole, propylthiouracil, iodide (kelp, radiocontrast dyes), lithium, amiodarone
- **CONGENITAL**—thyroid agenesis, thyroid dysgenesis
- **OTHERS**—iodine deficiency, idiopathic

SECONDARY 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, carpel tunnel syndrome, menorrhagia, amenorrhea, weight gain, medications, family history of thyroid disease

PHYSICAL—bradycardia, bradypnea, diastolic hypertension, hypothermia, cool and dry skin, vitiligo, orange skin (from carotonemia), carpel tunnel syndrome, hair thinning, periorbital edema, anemia, goiter, pleural effusion, pericardial effusion, proximal myopathy, pseudo-myotonia, delayed relaxation phase of the reflexes, edema (non-pitting)

INVESTIGATIONS

BASIC

- **LABS**—TSH

SPECIAL

- **ANTI-TPO ANTIBODIES AND ANTITHYROGLOBULIN**
- **ANTIBODIES**—Hashimoto's

DIAGNOSTIC ISSUES

TSH—is all that is required to make a diagnosis. Free T4 and free T3 are not done in the setting of hypothyroidism. If you suspect secondary hypothyroidism from panhypopituitarism, then measuring TSH along with free T4 is warranted. In sick euthyroid, the thyroid is okay but abnormal lab parameters may occur because the patient is medically unwell. Free T3 will be low due to decreased conversion of free T4 to free T3

INTERPRETATION

	TSH	fT4	fT3
Subclinical hypothyroidism	↑	N	N
Primary hypothyroidism	↑	↓	↓
Secondary hypothyroidism	↓	↓	↓

DIAGNOSTIC ISSUES (CONT'D)

	TSH	fT4	fT3
Sick euthyroid syndrome	N/↑/↓	N/↓	↓
Secondary or tertiary hypothyroidism, nephrotic syndrome, anticonvulsants (phenytoin, carbamazepine), and some sick euthyroid syndrome	N	↓	↓

MANAGEMENT

MYXEDEMA COMA—ABC, O_2, IV. ***Levothyroxine*** 200–500 μg IV, then 100 μg IV daily. ***Hydrocortisone*** 100 mg IV q6h. **Warming blankets.** Important to rule out adrenal crisis as cause of symptoms as above treatment regimen can cause severe decompensation in patients with adrenal disorder

TREAT UNDERLYING CAUSE—***levothyroxine*** (T4) 75–100 μg PO daily (1.6 μg/kg/day). But in elderly or those with risk factors for heart disease, it is important to initiate treatment at a dose of 25–50 μg daily and titrate up by 25 μg/month

TREATMENT ISSUES

SUBCLINICAL HYPOTHYROIDISM—treatment should be considered if the patient is only mildly symptomatic, but has a TSH level greater than normal or has a positive antithyroid antibody status

ADJUSTMENTS—T4 half-life is 7 days. It takes 6–8 weeks for serum TSH to equilibrate after thyroid medication adjustments

FREE T4—should be used to follow treatment progress in patients with secondary hypothyroidism

SPECIFIC ENTITIES

AUTOIMMUNE DISEASES—Hashimoto's, Graves' disease, type 1 diabetes, myasthenia gravis, Addison's, Sjogren's, pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis

SICK EUTHYROID SYNDROME—in sick and euthyroid patients! Secondary to hypothalamic–pituitary axis disruption, with ↓ T4→T3 conversion. Mildly altered N/↑/↓ TSH, N/↓ total T4, ↓ fT3, ↑ rT3. Thyroid replacement is not needed. Repeat TSH when acute illness resolved

Related Topic
Hypothyroidism in Pregnancy (p. 414)

Hyperthyroidism

NEJM 2007 358:24

DIFFERENTIAL DIAGNOSIS

PRIMARY HYPERTHYROIDISM

- **GRAVES' DISEASE** (diffuse toxic goiter)—most common cause of hyperthyroidism
- **TOXIC NODULAR GOITER/TOXIC MULTINODULAR GOITER**—most common in elderly
- **THYROIDITIS**—subacute thyroiditis, silent thyroiditis, Hashimoto's thyroiditis ("Hashitoxicosis"), postpartum thyroiditis, radiation-induced thyroiditis, drug-induced thyroiditis (lithium, amiodarone, interferon)
- **IODINE EXPOSURE**—kelp, seaweed, radiocontrast dye
- **EXOGENOUS**—L-thyroxine ingestion, hamburger thyrotoxicosis
- **ECTOPIC**—Struma ovarii (thyroid tissue present in an ovarian tumor), hydatiform mole (β-hCG similar to TSH)

SECONDARY HYPERTHYROIDISM—pituitary adenoma

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. As with many other autoimmune disorders, 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

PHYSICAL—vitals (tachycardia, atrial fibrillation, tachypnea, systolic hypertension, fever), systolic flow murmur, systolic pleuro-pericardial scratch (Means–Lerman scratch), thyroid acropachy (clubbing, Graves' only), onycholysis (Plummer's nails), palmar erythema, tremor, warm and moist skin ("velvet skin"), stare, exophthalmos (Graves' only), 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 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

CLINICAL FEATURES (CONT'D)

CLASSIFICATION OF GRAVES' OPHTHALMOPATHY
★NO SPECS★

Class	Findings
0	**N**o symptoms or signs
I	**O**nly symptoms of ocular irritation (dryness, grittiness)
II	**S**oft tissue involved (periorbital edema)
III	**P**roptosis
IV	**E**xtraoccular muscle involved (ophthalmoplegia)
V	**C**orneal involvement
VI	**S**ight loss

THYROID STORM—may be precipitated by anesthetics, surgery, systemic illness (especially sepsis). 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 qualifies as thyroid storm

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A GOITER?

NORMAL—15–20 g

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)"

JAMA 1995 273:10

INVESTIGATIONS

BASIC

- **LABS**—TSH, fT4, fT3, TSH receptor antibody (Graves'), anti-TPO antibody (Hashimoto's, Graves'), thyroglobulin (↓ if factitious), ESR (↑ in thyroiditis), CBCD, ALT, AST, ALP, bili

INVESTIGATIONS (CONT'D)

SPECIAL

- **THYROID SCAN**—diffuse homogeneous increased iodine uptake suggests Graves' disease, multifocal uptake suggests toxic multinodular goiter, increased single focus suggests toxic adenoma, while decreased global uptake suggests thyroiditis or factitious hyperthyroidism
- **RADIOACTIVE IODINE UPTAKE**—normal 2 h uptake = 6–10%; <1% suggests thyroiditis, 1–6% suggests iodine exposure, >10% suggests Graves', toxic nodule, or toxic multinodular goiter

DIAGNOSTIC ISSUES

THYROID HORMONE LEVELS AND INTERPRETATION

	TSH	fT4	fT3
Subclinical hyperthyroidism	↓	N	N
Primary hyperthyroidism	↓	↑	↑
T3 thyrotoxicosis	↓	N	↑
Secondary hyperthyroidism	↑/N	↑	↑

MANAGEMENT

THYROID STORM—ABC, O_2, IV. ***Propylthiouracil*** 1000 mg PO/NG stat, then 300 mg PO q6h. ***Iodide drops*** 2–3 PO q6h to be given 1 h after each dose of PTU. ***Dexamethasone*** 2 mg IV q6h, ***propranolol*** 20 mg PO q6h. **Cooling blankets**

TREAT UNDERLYING CAUSE

- **ANTITHYROID DRUGS**—inhibit thyroid hormone synthesis; for Graves', multinodular goiter and toxic adenoma only. *Methimazole* 20–40 mg PO div BID, *propylthiouracil* 300–600 mg PO div BID-TID (PTU is no longer first line agent for hyperthyroidism due to potentially fatal hepatotoxicity)
- **SODIUM IODATE**—potent inhibitor of peripheral T4 conversion and decreases thyroid hormone release

MANAGEMENT (CONT'D)

- **β-BLOCKERS**—↓ tissue response to catecholamines and ↓ peripheral conversion of T4 to T3; use as adjunct
- **STEROIDS**—↓ immune response and ↓ peripheral conversion of T4 to T3; for severe hyperthyroidism
- **RADIOIODINE I^{131} ABLATION**—for Graves', multinodular goiter and toxic adenoma. Only give once the thyroid levels have been stabilized. Must discontinue antithyroid drugs 3–7 days in advance. Withhold if severe ophthalmopathy, smoking, or severe thyrotoxicosis as may make eye disease worse or lead to thyroid storm. Hypothyroidism within 2 months is to be expected. Patients will require thyroid hormone replacement at 1.6 μg/kg/day. Hypothyroidism is permanent
- **THYROIDECTOMY**—for patients who do not wish to do the radioactive drink, compressive goiter, and for those with severe Graves' eye disease

TREATMENT ISSUES

PROPHYLTHIOURACIL (PTU) MECHANISM—inhibits thyroid hormone synthesis *and* peripheral conversion of T4 to T3 (T3 is more active form). Hold PTU for 4 days prior to radioiodine ablation

SPECIFIC ENTITIES

APATHETIC HYPERTHYROIDISM—in the elderly, lack of signs and symptoms of thyrotoxicosis despite biochemical evidence

THYROIDITIS—subacute thyroiditis is painful whereas silent thyroiditis is painless. Thyroiditis typically leads to hyperthyroidism initially as the thyroid cells lyse, then a period of hypothyroidism before recovering to euthyroid state

Related Topic
Hyperthyroidism in Pregnancy (p. 414)

Solitary Thyroid Nodule

NEJM 2004 351:17

DIFFERENTIAL DIAGNOSIS

BENIGN (95%)—colloid nodule, cyst, thyroiditis, benign follicular neoplasm

MALIGNANT (5%)—thyroid carcinoma (papillary, follicular, medullary, anaplastic)

CLINICAL FEATURES

RISK FACTORS FOR THYROID CANCER

- **HIGH RISK**—family history of medullar thyroid carcinoma or MEN, rapid tumor growth, firm or hard nodule, fixation of nodule, paralysis of vocal cords, regional lymphadenopathy, distant metastases

CLINICAL FEATURES (CONT'D)

- **MODERATE RISK**—age <20 or >70, male, previous head and neck radiation, nodule >4 cm [>1.6 in.] in diameter or partially cystic, symptoms of compression (dysphagia, dysphonia, hoarseness, dyspnea, cough)

INVESTIGATIONS

BASIC

- **LAB TESTS**—TSH
- **IMAGING**—U/S-guided FNA

INVESTIGATIONS (CONT'D)

SPECIAL

- **CALCITONIN LEVEL**—if family history of medullary thyroid cancer (MTC) or MEN2
- **THYROID SCAN**—if hyperthyroidism

DIAGNOSTIC ISSUES

SIZE CUTOFF FOR EVALUATION—low-risk patients with lesions <1 cm [<0.4 in.] on U/S do not require FNA, but need to be followed over time with a repeat U/S in 6–12 months. Nodules of 1.5 cm [0.6 in.] or more should be biopsied

THYROID FUNCTION AND CANCER RISK—thyroid nodules have a 5% risk of being malignant; 1/3 of all nodules are cold and less than 1/3 of cold nodules are malignant. Functioning nodules are usually benign. Follicular lesions have an increased risk of malignancy of 20% and should be removed by thyroidectomy. Cold nodules in the setting of Graves' disease also have a higher risk of malignancy

MANAGEMENT

NON-MALIGNANT THYROID NODULE—observe with serial U/S, thyroidectomy if there is a pattern of growth, **radioiodine** (if functional nodule)

MALIGNANT THYROID NODULE—**total thyroidectomy** followed by **radioactive iodine ablation**

TREATMENT ISSUES

OVERALL APPROACH TO DIAGNOSIS AND TREATMENT

- **LOW TSH**—obtain thyroid scan → functioning nodule → radioiodine; alternatives include no treatment or surgery. If patient has Graves' disease with cold nodules, then total thyroidectomy is recommended
- **NORMAL OR HIGH TSH**—if strong suspicion of cancer, proceed to surgery. Otherwise, U/S-guided FNA → if malignant or suspicious, proceed to surgery. If benign, no treatment necessary with clinical follow-up only → repeat thyroid U/S in 6–12 months; alternatives include surgery. If non-diagnostic FNA, repeat FNA

Pituitary Tumors NEJM 2003 349:21

DIFFERENTIAL DIAGNOSIS OF PITUITARY TUMORS

FUNCTIONAL—prolactinoma is the most common, Cushing's disease and acromegaly are rare, functional LH, FSH, TSH tumors are very rare

NON-FUNCTIONAL—gonadotroph tumors are the most common non-functional pituitary tumors

OTHER NON-PITUITARY TUMORS—meningioma, craniopharyngioma, dysgerminoma, optic glioma, brain metastases

DIFFERENTIAL DIAGNOSIS OF HYPERPROLACTINEMIA

PHYSIOLOGIC—pregnancy, exercise, stress

TUMORS—pituitary (prolactinoma, other functional tumors (acromegaly), non-functional tumor with stalk compression), non-pituitary

DRUGS—metoclopramide, domperidone, phenothiazines, butyrophenones, risperidone, MAOI, TCA, SSRI, verapamil, estrogen, narcotics

OTHERS—hypothyroidism (↑ TRH), chronic kidney disease

Important: prolactin secretion is normally inhibited by dopamine. Therefore, anything that interferes with dopamine secretion/delivery can lead to ↑ prolactin secretion

CLINICAL FEATURES

SYMPTOMS—bitemporal hemianopsia (loss of peripheral vision), hormone deficiencies or excess and mass effect (**★GO LOOK FOR THE ADENOMA PLEASE★** A compressive pituitary adenoma will

CLINICAL FEATURES (CONT'D)

affect hormone production in this order: ↓ **G**H, ↓ **L**H and **F**SH, ↓ **T**SH, ↓ **A**CTH, and ↑ **P**rolactin)

PROLACTINOMA IN ♀—infertility, oligomenorrhea, galactorrhea

PROLACTINOMA IN ♂—erectile dysfunction, infertility

FSH/LH ADENOMA—asymptomatic/mass effect

INVESTIGATIONS

BASIC

- **LABS**—prolactin, IGF-1 (simpler than GH to interpret), LH, FSH, TSH, ACTH, AM cortisol, free T4, estrogen, progesterone, AM testosterone
- **IMAGING**—MRI pituitary

SPECIAL

- **ORAL GLUCOSE TOLERANCE TEST**—if GH tumor, hyperglycemia cannot suppress serum GH levels), dexamethasone suppression test (Cushing's syndrome

DIAGNOSTIC ISSUES

MRI PITUITARY—should be done for all patients with elevated prolactin to check for any hypothalamic-pituitary tumors, unless they are on a medication classically known to cause hyperprolactinemia

MACROADENOMA (>1 cm [0.4in])—should investigate anterior pituitary function (IGF-1, LH, FSH, TSH, ACTH, prolactin, AM cortisol, freeT4, estrogen, progesterone, AM testosterone), and formal visual field testing

MANAGEMENT

PROLACTINOMA—**dopamine agonists** (*bromocriptine* 2.5–10 mg PO daily, *cabergoline* 0.25–1 mg PO 2/week). **Transsphenoidal resection** (only if visual field compromise). Indications for treatment of prolactinoma include infertility, galactorrhea, hypogonadism and macroadenoma

ACROMEGALY—**transsphenoidal resection** (preferred). See SPECIFIC ENTITIES below for details

CUSHING'S DISEASE—**transsphenoidal resection**. See p. 350 for details

TSH SECRETING—**transsphenoidal resection** (first line but rarely cures). **Octreotide**

LH/FSH SECRETING—**transsphenoidal resection** (if tumor growth causes symptoms). **Bromocriptine** (10% response rate)

NON-FUNCTIONAL—**transsphenoidal resection** (if tumor growth causes symptoms)

SPECIFIC ENTITIES

ANTERIOR PITUITARY DEFICIENCY

- **CAUSES**—infiltration (tumor, sarcoidosis), infection (TB, actinomycosis), infarction (Sheehan's), autoimmune hypophysitis, inherited, irradiation
- **CLINICAL FEATURES**—growth failure, deficient or absent lactation, hypogonadism, hypothyroidism, and adrenal insufficiency. In pituitary apoplexy may have severe headache and visual disturbance
- **TREATMENTS**—dexamethasone, surgery

POSTERIOR PITUITARY DEFICIENCY

- **CAUSES**—infiltration (tumor, sarcoidosis), infection (TB), infarction (Sheehan's), irradiation, iatrogenic (neurosurgery)

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—diabetes insipidus
- **TREATMENTS**—*desmopressin/DDAVP*—see diabetes insipidus (p. 347) for more details

ACROMEGALY

- **PATHOPHYSIOLOGY**—usually due to excessive growth hormone secretion by pituitary adenoma
- **CLINICAL FEATURES**—vitals (hypertension), large, doughy, spade-like hands, increased ring, glove, shoe, and hat size, increased sweating, osteoarthritis (DIP, PIP, CMC, wrists), carpal tunnel syndrome, proximal muscle weakness, course facial features, frontal bossing, bitemporal hemianopsia, sleep apnea, wide-spaced teeth, enlarged tongue, hoarse voice, prognathism (prominent mandible), acrochordons (skin tags), acanthosis nigricans (insulin resistance), cardiomegaly with or without HF, enlarged liver/spleen/kidneys, testicular atrophy, foot drop (common peroneal nerve)
- **DIAGNOSIS**—serum IGF-1. Also check prolactin, TSH, LH/FSH, and ACTH. MRI pituitary. Oral glucose tolerance test (failure to suppress GH is gold standard)
- **TREATMENTS**—**transsphenoidal resection** (preferred, 5–20% recurrence). **Irradiation of pituitary**. **Octreotide** (long-acting analogue of somatostatin). **Bromocriptine**

NEJM 2006 355:24

Polyuria

DIFFERENTIAL DIAGNOSIS

OSMOTIC DIURESIS (~3 L/day, urine osmo ~500 mOsm/kg)—glucose, urea, mannitol

WATER DIURESIS (~20 L/day, urine osmo <100 mOsm/kg)

- **NEPHROGENIC DIABETES INSIPIDUS**—chronic kidney disease, hypercalcemia, hypokalemia, lithium, demeclocycline
- **CENTRAL DIABETES INSIPIDUS**—**granulomatous infiltration** (sarcoidosis, TB, histiocytosis X), **trauma** (closed head injury, neurosurgery), **tumor** (craniopharyngioma, metastatic breast cancer, metastatic lung cancer)
- **PSYCHOGENIC POLYDIPSIA**

SALINE DIURESIS (~3 L/day, urine osmo ~300 mOsm/kg)—post-ATN, post-obstructive

PATHOPHYSIOLOGY

DEFINITION OF POLYURIA—urine >3 L/day

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, Cr, glucose, osmolality (if diabetes insipidus, >290 mOsm/kg), urine lytes, urine osmolality (if diabetes insipidus, <275 mOsm/kg)

SPECIAL

- **WATER DEPRIVATION TEST**—consult endocrinology. In the dehydrated state, the body normally starts to concentrate the urine. In diabetes insipidus, the urine remains dilute. Administration of 1 μg desmopressin/DDAVP SC causes concentration of the urine in central DI but not nephrogenic. Measure urine osmolality 30 min, 60 min, and 120 min after. ↑ in urine osmolality by 50% suggests central DI

MANAGEMENT OF DIABETES INSIPIDUS

TREAT UNDERLYING CAUSE—**central diabetes insipidus** (*desmopressin* DDAVP 5–40 μg/day nasal or 0.05–1.2 mg/day PO or 1–2 μg SC/IV/day. Note the risk of hyponatremia)

MANAGEMENT OF DIABETES INSIPIDUS (CONT'D)

Adrenal Incidentaloma NEJM 2007 356:6

DIFFERENTIAL DIAGNOSIS

BENIGN

- **FUNCTIONAL TUMOR**—Cushing's, Conn's (primary hyperaldosteronism), pheochromocytoma
- **NON-FUNCTIONAL TUMOR**

MALIGNANT

- **FUNCTIONAL TUMOR**—Cushing's, aldosterone secreting, pheochromocytoma, adrenocortical carcinoma
- **NON-FUNCTIONAL TUMOR, METASTASES**—lung, breast, GI, renal, melanoma

PATHOPHYSIOLOGY

SYMPATHETIC RESPONSE—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 low blood pressure, low [Na], and the sympathetic nervous system. It causes the activation of angiotensin I, II, and III. Aldosterone release is then stimulated by RAS (AII, AIII), hyperkalemia, and ACTH. Aldosterone's effects include increased Na reabsorption and K secretion at the distal tubule

BILATERAL ADRENAL MASSES—occur in 15% of patients with adrenal incidentaloma. Causes include metastatic disease, congenital adrenal hyperplasia, bilateral adrenal adenomas, and infiltrative disease of the adrenals

CLINICAL FEATURES

HISTORY

- **SYMPTOMS OF CUSHING'S**—weight gain, truncal obesity, thin extremities, acne, emotional and cognitive changes, opportunistic infections, altered reproductive function, hirsutism. Typical symptoms and signs of Cushing's may be minimal or absent with ectopic ACTH production. Hypokalemic alkalosis may be the only obvious initial finding
- **SYMPTOMS OF PHEOCHROMOCYTOMA**—episodic spells of palpitations, pallor, tremor, headache, diaphoresis

CLINICAL FEATURES (CONT'D)

- **SYMPTOMS OF CONN'S**—hypokalemia, hypertension
- **SYMPTOMS OF ADRENOCORTICAL CARCINOMA**—androgen secretion leading to virilization, severe hirsutism, acne, amenorrhea
- **PAST MEDICAL HISTORY**—particularly lung, breast, gastrointestinal, and renal cell cancer or melanoma, smoking history

PHYSICAL—vitals (tachycardia, paroxysmal or sustained hypertension, orthostatic hypotension), pallor, tremor, thin skin, proximal muscle weakness, hypertensive retinopathy, moon face, plethora, acne, hirsutism, supraclavicular and dorsocervical fat pad, supraclavicular lymphadenopathy, left ventricular hypertrophy, central obesity, abdominal masses

INVESTIGATIONS

BASIC

- **LABS**—cortisol and ACTH, 24 h urine cortisol and creatinine, DHEAS androstenedione, testosterone, plasma renin and aldosterone, lytes urea, creatinine, 24 h urine for metanephrines and creatinine
- **IMAGING**—CT or MRI abdomen

SPECIAL

- **CT-GUIDED BIOPSY**—adrenal tumor
- **SELECTIVE ADRENAL VEIN SAMPLING**—for primary hyperaldosteronism
- **PHEOCHROMOCYTOMA WORKUP**—metaiodobenzylguanidine scintigraphy MIBG scan

DIAGNOSTIC ISSUES

APPROACH TO DIAGNOSIS OF ADRENAL INCIDENTALOMA—always start with history and physical, and baseline labs to determine if tumor is functioning

SIZE MATTERS—adrenal adenoma usually <3 cm and secretes only cortisol or aldosterone, lesions >6 cm or secreting more than one hormone (glucocorticoid, mineralocorticoid, androgen) are usually malignant

DISTINGUISHING FEATURES OF ADRENAL TUMORS ON CT SCAN

- **ADENOMA**—smooth border, homogeneous density, <4 cm, unilateral, low enhanced attenuation (≤ 10 Hounsfield Units (HU)), CT contrast-medium washout $\geq 50\%$ at 10 min
- **PHEOCHROMOCYTOMA**—cystic, hemorrhagic, variable size, may be bilateral, high enhanced attenuation

DIAGNOSTIC ISSUES (CONT'D)

- **ADRENOCORTICAL CARCINOMA**—irregular, heterogeneous density, >4 cm [>1.6 in.], unilateral, high unenhanced attenuation(>10 HU, CT contrast washout <50% at 10 min)—perform CT-guided biopsy or proceed to surgery directly, or close follow-up imaging every 3 months
- **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 and tumors >6 cm [>2.4 in.] should be resected

SPECIFIC ENTITIES

MULTIPLE ENDOCRINE NEOPLASIA (MEN) SYNDROMES

- **MEN I**—pituitary tumor, pancreatic tumor, parathyroid tumor
- **MEN II**—pheochromocytoma, medullary thyroid cancer (MTC), parathyroid tumor
- **MEN III**—pheochromocytoma, medullary thyroid cancer (MTC), mucosal neuroma

PHEOCHROMOCYTOMA

- **PATHOPHYSIOLOGY**—tumor produces mainly NE
- **CLINICAL FEATURES**—triad of headaches, palpitations, cold sweats. **★10% tumor★** 10% incidental, 10% bilateral, 10% extra-adrenal, 10% malignant, 10% recurrence, 10% in children, 10% familial (MEN, VHL)
- **DIAGNOSIS**—24-h urinary metanephrine and creatinine
- **TREATMENTS**—volume repletion (reduce postural hypotension from adrenergic blockage). α-Blockade (*phenoxybenzamine* 10 mg PO BID and ↑ dose overtime or *prazosin* 4–20 mg PO daily in divided doses 2–4 times daily). β-blockade only after well α-Blocked (to control tachycardia and other arrhythmias). Note that medical therapy should precede surgery by at least 2 weeks)

SPECIFIC ENTITIES (CONT'D)

HYPERALDOSTERONISM

- **PATHOPHYSIOLOGY**—Conn's (primary hyperaldosteronism) can be due to adrenal adenoma or hyperplasia. Secondary hyperaldosteronism can be due to ↑ renin from edematous states, dehydration, diuretics, and renal artery stenosis
- **CLINICAL FEATURES**—hypertension, ↓ K
- **DIAGNOSIS**—↓ renin and ↑ aldosterone for Conn's, ↑ renin and ↑ aldosterone for secondary hyperaldosteronism
- **TREATMENTS**—for unilateral Conn's amenable to surgery, consider adrenalectomy. Otherwise, consider medical therapy (*spironolactone* 12.5–100 mg PO BID or *amiloride* 5–10 mg PO daily)

Adrenal Insufficiency

DIFFERENTIAL DIAGNOSIS

PRIMARY (Addison's disease)

- **AUTOIMMUNE**
- **INFECTIONS**—TB, histoplasmosis, coccidioidomycosis, AIDS
- **HEMORRHAGE**—anticoagulants, sepsis (Waterhouse–Friderichsen syndrome, associated with meningococcemia), trauma, anticardiolipin antibodies
- **INFILTRATION**—cancer, sarcoidosis, amyloidosis

SECONDARY (↓ ACTH secretion)—exogenous glucocorticoid therapy, pituitary or hypothalamus tumor, infarction, infection, infiltration, irradiation

CLINICAL FEATURES

HISTORY—fatigue, weight loss, nausea and vomiting, syncope, severe abdominal pains, muscle weakness, dehydration, salt cravings, hyperpigmentation (Addison's only), visual field changes (pituitary tumor), evidence of steroid use, past medical history (TB, cancer, sarcoidosis), medications (anticoagulation)

PHYSICAL—orthostatic hypotension, hyperpigmentation (Addison's only)

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY ADRENAL INSUFFICIENCY

	Addison's disease	**Secondary adrenal insufficiency**
Adrenal hormones affected	Cortisol DHEAS Aldosterone	Cortisol DHEAS
ACTH	↑	↓
Electrolytes	↓ Na, ↑ K	↓ Na only
Symptoms	Hyper-pigmentation	No skin changes. GI symptoms and hypotension less prominent

INVESTIGATIONS

BASIC

- **ACTH STIMULATION TEST**—obtain cortisol and ACTH at baseline, give 250 μg of ACTH IV push, measure cortisol at 30 and 60 min
- **LABS**—CBCD, lytes, urea, creatinine, DHEAS, TSH, free T4
- **MICROBIOLOGY**—blood and urine cultures if suspect sepsis

DIAGNOSTIC ISSUES

ACTH STIMULATION TEST

- **STANDARD HIGH DOSE**—baseline cortisol and ACTH, give cosyntropin 250 μg IV, measure cortisol 30 and 60 min after; cortisol level should double from its baseline and be >550 nmol/L to exclude adrenal insufficiency
- **LONG VERSION**—same as above except give cosyntropin 250 μg IV over 8 h daily ×3 days. The response will be abnormal by the third day if primary adrenal insufficiency, but normal if secondary

MANAGEMENT

ACUTE ADRENAL CRISIS—ABC, O_2, IV. Fluids (D5NS 2–3L IV bolus). **Corticosteroid** (*hydrocortisone* 100 mg IV q6h or *dexamethasone* 4 mg IV q6h (dexamethasone does not interfere with ACTH stimulation test). **Treat precipitant** (sepsis, viral gastroenteritis)

LONG-TERM TREATMENT—**physiologic replacement** (*prednisone* 5 mg PO qAM and 2.5 mg PO qPM, plus *fludrocortisone* 0.1 mg PO daily). Advise regarding **medical alert bracelet** and **emergency prefilled hydrocortisone syringe**

STRESS DOSE REPLACEMENT (prevention)—if patients have been taking suppressive dose of glucocorticoids for >3 weeks during the preceding year, they should be on stress dose during illnesses or surgical procedures

- **MINOR STRESS** (e.g. flu, procedure under local anaesthetic)—double the regular dose of glucocorticoids (e.g. *prednisone* 15 mg/day)
- **MODERATE STRESS** (e.g. orthopedic surgery, perivascular surgery)—*hydrocortisone* 100 mg IV on call to OR, followed by 100 mg IV q8h ×24 h postop, then regular daily dose
- **HIGH STRESS** (e.g. intraabdominal operations, cardiac surgery)—*hydrocortisone* 100 mg IV, followed by 50 mg IV q8h ×24 h, and taper by 50% per day until regular daily dose

Cushing's Syndrome

DIFFERENTIAL DIAGNOSIS

IATROGENIC (↓ ACTH)
PITUITARY (↑ ACTH)—Cushing's disease
ECTOPIC (↑ ACTH)—small cell lung cancer
ADRENAL (↓ ACTH)—adenoma, carcinoma

CLINICAL FEATURES

SIGNS AND SYMPTOMS OF CUSHING'S SYNDROME

- **NEUROLOGICAL**—euphoria, depression, psychosis, restlessness, irritability, insomnia
- **OPHTHALMIC**—glaucoma, cataract
- **CARDIOVASCULAR**—hypertension, fluid retention
- **GASTROINTESTINAL**—gastritis, ulcers, GI bleed
- **HEMATOLOGICAL**—leukocytosis, immunosuppression
- **ENDOCRINE**—hyperglycemia, insulin resistance, hypogonadism, central obesity, hirsutism, weight gain
- **MUSCULOSKELETAL**—osteoporosis, avascular necrosis, proximal myopathy
- **DERMATOLOGICAL**—striae, moon face, buffalo hump, supraclavicular fat pad, skin thinning, easy bruising, acne, poor wound healing

CLINICAL FEATURES (CONT'D)

Note that typical symptoms and signs of Cushing's may be absent or minimal with ectopic ACTH production. Hypokalemic alkalosis may be the only obvious initial finding

INVESTIGATIONS

BASIC

- **LABS**—8 AM and 5 PM cortisol and ACTH, 24 h urine for cortisol and creatinine, CBCD (leukocytosis with relative lymphopenia), lytes, urea, Cr, glucose, HbA1C, fasting lipid profile
- **DEXAMETHASONE SUPPRESSION TEST**—a functional test to determine the cause of Cushing's syndrome. See diagnostic issues for details

SPECIAL

- **CT ADRENAL**—unilateral mass suggests adrenal lesion. Bilateral adrenal hyperplasia suggests ACTH oversecretion (central or ectopic lesion)
- **MRI PITUITARY**—if suspect Cushing's disease
- **INFERIOR PETROSAL SINUS SAMPLING AFTER CRH STIMULATION**—for further testing of pituitary source

INVESTIGATIONS (CONT'D)

- **SERUM ACTH AFTER CRH STIMULATION**—ACTH would increase as pituitary tumors respond to CRH, but not in ectopic sources
- **MIDNIGHT SALIVARY CORTISOL**—serum free cortisol diffuses into saliva. Thus, salivary cortisol is a marker of free cortisol concentration

DIAGNOSTIC ISSUES

1 MG OVERNIGHT DEXAMETHASONE SUPPRESSION TEST

- **PROCEDURE**
  - **DAY 1**—baseline 8AM serum cortisol and ACTH. Give 1 mg dexamethasone at 10PM
  - **DAY 2**—measure 8AM serum cortisol
- **INTERPRETATION**—serum cortisol should be less than 50 nmol/L following 1 mg of dexamethasone at night. A normal dexamethasone suppression test rules out Cushing's syndrome. Failure to suppress cortisol to $<$50 nmol/L is a positive test which may be a false positive or true Cushing's syndrome. Confirmatory testing is now required. Consult Endocrinology

LOW-DOSE DEXAMETHASONE SUPPRESSION TEST—give dexamethasone 0.5 mg PO q6h for 2 days and measure AM cortisol, ACTH, afternoon cortisol, and 24 h urine cortisol and creatinine for 2 days. Suppression of cortisol rules out Cushing's syndrome. Failure to suppress cortisol confirms Cushing's syndrome

HIGH-DOSE DEXAMETHASONE SUPPRESSION TEST—give dexamethasone 2 mg PO q6h for 2 days and measure AM cortisol, ACTH, afternoon cortisol, and 24 h urine cortisol and creatinine for 2 days. Partial suppression of cortisol confirms pituitary Cushing's. Failure to suppress cortisol confirms ectopic or adrenal Cushing's

DIAGNOSTIC ISSUES (CONT'D)

CORTISOL-BINDING GLOBULIN—plasma cortisol is bound to cortisol-binding globulin. Oral contraceptive pills increase cortisol-binding globulin and thus the measured plasma cortisol. However, 24 h urinary cortisol will be normal as it measures unbound cortisol

MANAGEMENT

TREAT UNDERLYING CAUSE

- **IATROGENIC**—avoid or reduce the dose of steroids if possible
- **PITUITARY**—first-line transsphenoidal surgery (90% cure rate) or pituitary irradiation. Second-line bilateral adrenalectomy. Third-line ketoconazole or metyrapone.
- **ADRENAL**—unilateral adrenalectomy
- **ECTOPIC**—resection of ectopic source if appropriate; otherwise, bilateral adrenalectomy and ketoconazole may be considered

Related Topic
Lung Cancer (p. 185)

TREATMENT ISSUES

GLUCOCORTICOID REPLACEMENT—required in the post operative period. If pituitary or unilateral adrenal surgery done, recovery from the resultant HPA axis suppression can be expected in 3–12 months. If bilateral adrenal surgery or adrenocorticolytic medical therapy, lifelong replacement is needed. Do not forget stress dose!

EQUIVALENT DOSING TABLE

	Half-life (h)	Equivalent anti-inflammatory potency[a]	Equivalent mineralocorticoid potency[a]
Glucocorticoids			
Short acting			
Cortisone	8–12	0.2	2
Hydrocortisone	8–12	0.25	2
Intermediate acting			
Methylprednisolone	18–36	1.25	0
Prednisolone	18–36	1	1
Prednisone	18–36	1	1
Triamcinolone	18–36	1.25	0
Long acting			
Betamethasone	36–54	8.33	0
Dexamethasone	36–54	6.66	0
Mineralocorticoid			
Fludrocortisone	12–24	0.5	125

[a]Higher number indicates greater potency as compared to predisone

SPECIFIC ENTITIES

PSEUDO-CUSHING'S SYNDROME

- **CAUSES**—hypercortisolism associated with severe stress, depression, obesity, and chronic alcoholism
- **CLINICAL FEATURES**—may mimic Cushing's syndrome clinically, but rarely associated with dermatologic and muscular complications (e.g. bruising, thinning of skin, proximal muscle weakness)

NELSON'S SYNDROME

- **PATHOPHYSIOLOGY**—following bilateral adrenalectomy for Cushing's disease, residual pituitary tumor enlarges and marked skin pigmentation results

SPECIFIC ENTITIES (CONT'D)

- **DIAGNOSIS**—clinical history and ↑ ACTH (>44 pmol/L [>200 pg/mL]) associated with hyperpigmentation
- **TREATMENTS**—most cases preventable with pituitary irradiation with bilateral adrenalectomy. Medical therapy relatively ineffective. Refer for transsphenoidal surgery or irradiation before development of macroadenoma. Consult endocrinology

Hypocalcemia

DIFFERENTIAL DIAGNOSIS

PTH ABNORMALITIES (PO_4 ↑)

- **HYPOPARATHYROIDISM**—surgery, irradiation, autoimmune, congenital, infiltrative, DiGeorge's syndrome
- **FUNCTIONAL HYPOPARATHYROIDISM**—Mg deficiency
- **PTH RESISTANCE**—pseudohypoparathyroidism

VITAMIN D ABNORMALITIES (PO_4 ↓)

- **VITAMIN D DEFICIENCY**—nutritional, malabsorption
- **ALTERED VITAMIN D METABOLISM**—cirrhosis, chronic renal failure, anticonvulsant
- **VITAMIN D RESISTANCE**

DRUGS—phosphates (hyperphosphatemia), calcitonin, bisphosphonates, plicamycin, loop diuretics
ACUTE CAUSES—acute pancreatitis, rhabdomyolysis, tumor lysis, large transfusions of citrate-containing blood products, toxic shock syndrome
OTHERS—calcium malabsorption, hypoalbuminemia

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]
PTH AND VITAMIN D

- **VITAMIN D FORMATION**—7-dihydrocholesterol → skin with UV → cholecalciferol (vitamin D_3 may be obtained via diet as well) → liver → 25OH D_3 (used to determine vitamin D status) → kidney (stimulated by PTH or hypo-PO_4) → $1,25(OH)_2D_3$ (also known as calcitriol, the active form of vitamin D)
- **$1,25(OH)_2D_3$**—↑ Ca reabsorption at gut, kidney, and bone, ↑ PO_4 reabsorption at gut and kidney
- **PTH ACTION**—↑ Ca reabsorption at distal tubule and bone, ↓ PO_4 reabsorption at proximal tubule, ↑ $1,25(OH)_2D_3$

CLINICAL FEATURES

HISTORY—tetany, stridor (laryngospasm), seizures, confusion, weakness, past medical history (thyroid surgery), medications (loop diuretics, bisphosphonates, calcitonin, anticonvulsants)
PHYSICAL—hypotension, Trousseau's sign, Chvostek's sign, carpal/pedal spasm, weakness

CLINICAL FEATURES (CONT'D)

INVESTIGATIONS

BASIC

- **LABS**—Ca, albumin, Mg, PO_4, PTH, ALP, 25OH D_3, $1,25(OH)_2D_3$, lytes, urea, creatinine

SPECIAL

- **ECG**—may show prolonged QT interval

MANAGEMENT

SYMPTOM CONTROL—if severe symptoms, *Ca gluconate* 1–2 amps IV push then run a calcium drip 0.5–1.5 mg/kg/h, and *$MgSO_4$* 2 g IV over 2 h. If mild symptoms, *$CaCO_3$* 1–2 g PO TID, *calcitriol* ($1,25(OH)_2D_3$) 0.25–1 μg daily
TREAT UNDERLYING CAUSE

Related Topic
Hypophosphatemia (p. 83)

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 (renal loss), medications (anticonvulsants, glucocorticoids, immunosuppressants and HAART may lead to increased inactivation of $1,25(OH)_2D_3$), chronic kidney disease (decreased activation), liver failure (decreased activation)

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—hypocalcemia, hypophosphatemia, osteomalacia with associated bone pain, osteoporosis with fractures and hyperparathyroidism. Vitamin D deficiency has also been postulated to be associated with chronic diseases such as cancer, cardiovascular diseases, diabetes, autoimmune disorders, and osteoarthritis
- **DIAGNOSIS**—25-hydroxyvitamin D is used to determine the level of vitamin D as it represents the combined level from both dietary and skin sources. A level <80 nmol/L is considered to be abnormal
- **TREATMENTS**—*vitamin D2* 50,000 IU per week ×8 weeks for most causes; repeat for another 8 weeks if 25-hydroxyvitamin D still low. Long- term use of *vitamin D3* 800–1000 IU PO daily. For renal failure, *calcitriol* 0.25–1 μg PO BID should be given

NEJM 2007 357:3

Hypercalcemia

DIFFERENTIAL DIAGNOSIS

HYPERPARATHYROIDISM (most common cause among outpatients)—parathyroid adenoma, parathyroid hyperplasia, parathyroid carcinoma (rare)
MALIGNANCY (most common cause among inpatients)—lung, breast, prostate, renal, thyroid, GI, melanoma, sarcoma, multiple myeloma, lymphoma, leukemia
GRANULOMATOUS DISEASE—TB, sarcoidosis, lymphoma
ENDOCRINE—Addison's, hyperthyroidism, acromegaly
DRUGS—vitamin D toxicity, thiazide, lithium, tamoxifen
NUTRITIONAL—calcium supplement, vitamin D, vitamin A, milk alkali syndrome
OTHERS—immobility, Zollinger–Ellison syndrome, familial hypocalciuric hypercalcemia, acute renal failure

PATHOPHYSIOLOGY

DEFINITION OF HYPERCALCEMIA—corrected serum Ca >2.6 mmol/L [10.4 mg/dL]. For every 10 g/L (1 g/dL) ↓ in albumin, correct serum Ca by adding 0.2 mmol/L [0.8 mg/dL]
PTH ACTION—↑ Ca reabsorption at distal tubule and bone, ↓ PO_4 reabsorption at proximal tubule, ↑ $1,25(OH)_2D_3$
MALIGNANCY-RELATED MECHANISMS—local osteolytic bone lesions, humoral hypercalcemia of malignancy (PTH-related peptide), $1,25(OH)_2D_3$-secretion (lymphomas), ectopic hyperparathyroidism (very rare)
SARCOIDOSIS MECHANISM—unregulated synthesis of $1,25(OH)_2D_3$, the active metabolite of vitamin D, in macrophages of granulomas

CLINICAL FEATURES

SYMPTOMS

- **GI**—abdominal pain from constipation, pancreatitis, or peptic ulcer disease (moans), N&V
- **MSK**—bony pain (groans)
- **RENAL**—calculi (stones), polyuria
- **CNS**—delirium (psychiatric overtone)

INVESTIGATIONS

BASIC

- **LABS**—Ca, albumin, Mg, PO_4, PTH, ALP, $1,25(OH)_2D_3$, lytes, urea, creatinine

SPECIAL

- **MALIGNANCY WORKUP**—consider PTHrP, serum protein electrophoresis, urine protein electrophoresis, PSA, CEA, CA19–9, CA125, CA15–3, CXR
- **HYPERPARATHYROIDISM WORKUP**—consider U/S neck/thyroid and Tc-sestamibi parathyroid scan
- **FAMILIAL HYPOCALCIURIC HYPERCALCEMIA WORKUP**—consider 24 h urine Ca and creatinine
- **MEN2A WORKUP**—24 h urinary metanephrine
- **ECG**—may show shortened QT interval

DIAGNOSTIC ISSUES

PTH LEVEL—↑ in hyperparathyroidism, ↑/N in familial hypocalciuric hypercalcemia, ↓ in vitamin D excess or PTHrP

DISTINGUISHING FEATURES BETWEEN IMPORTANT CAUSES OF HYPERCALCEMIA

	Primary PTH	Sarcoidosis	PTHrP	FHH
Ca	↑↑	↑	↑↑	↑
PO_4	↓	↑	↓	↓
PTH	↑↑/N	↓	↓	↑/N
PTHrP	–	–	↑	–
Calcitriol	↑	↑	↑	↓/N
Urine Ca	↑	↑/N	↑	↓

MANAGEMENT

SYMPTOM CONTROL—**NS** 200–500 mL/h IV ± ***furosemide*** 20–40 mg IV TID PRN. If Ca is 3.0 mmol/L [12 mg/dL] or more give **bisphosphonates** (*pamidronate* 60–90 mg in 500 mL NS IV over 4 h or *zoledronate* 4 mg in 50 mL NS IV over 15 min). Malignancies may also respond to giving **steroids** (*prednisone* 60 mg PO daily ×10 days, *hydrocortisone* 200–500 mg IV daily), along with ***calcitonin*** 4–8 IU/kg IM/SC BID. Note that intranasal calcitonin has not been shown to be efficacious
TREAT UNDERLYING CAUSE

TREATMENT ISSUES

INDICATIONS FOR PARATHYROIDECTOMY IN PATIENTS WITH ASYMPTOMATIC HYPERPARATHYROIDISM—age <50, Ca >2.85 mmol/L [>11.4 mg/dL], GFR <60 mL/min, osteoporosis with a *T* score of −2.5 at any site and/or previous fragility fracture or difficult to provide follow-up

SPECIFIC ENTITIES

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FHH)

- **PATHOPHYSIOLOGY**—autosomal dominant inactivating mutations in the calcium sensor receptor in parathyroid gland and kidneys, leading to a change in set point and increased serum calcium level to suppress PTH release and reabsorption of calcium in the kidneys
- **CLINICAL FEATURES**—usually asymptomatic. Renal stones uncommon
- **DIAGNOSIS**—↑ serum calcium, ↓ urinary calcium, ↑/N PTH. Family history can be helpful. Important to differentiate from primary hyperparathyroidism as

SPECIFIC ENTITIES (CONT'D)

15–20% of FHH will have elevated PTH, and FHH does not require treatment

- **TREATMENTS**—not required

MILK ALKALI SYNDROME

- **PATHOPHYSIOLOGY**—ingestion of significant amounts of calcium and absorbable alkali (e.g. $CaCO_3$) used as antacids and treatment of osteoporosis. The combination of increased alkali intake, decreased renal function, and hypercalcemia contributes to metabolic alkalosis, which decreases calcium excretion and in turn contributes to hypercalcemia
- **CLINICAL FEATURES**—triad of hypercalcemia, metabolic alkalosis, and renal insufficiency. May be acute or chronic (Burnett's syndrome) in presentation
- **DIAGNOSIS**—history of significant intake of calcium and absorbable alkali. ↑ serum calcium, N urinary calcium, ↓ PTH, and ↑/N PO_4
- **TREATMENTS**—low calcium diet. Hydration. Supportive measures

Osteoporosis

Canadian Osteoporosis Guidelines 2002
NEJM 1998 338:11
NEJM 2005 353:2

CAUSES

ENDOCRINE—estrogen deficiency (post-menopausal), hypogonadism (both female and male), hyperthyroidism, hyperparathyroidism

NUTRITION—decreased calcium/vitamin D intake, malabsorption syndromes (celiac disease), smoker, alcohol, caffeine intake

MEDICATIONS—steroids, heparin, cyclosporine

OTHERS—age >50, liver disease (primary biliary cirrhosis), immobilization, small frame, decreased BMI <21 kg/m^2, Caucasian, Asian, Indo-Asian, family history

PATHOPHYSIOLOGY

DEFINITION—a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. WHO defines osteoporosis based on bone mineral density (BMD) measurements, relative to a normal young adult population of the same sex and ethnicity. *T*-score is the number of standard deviations above/below the mean BMD for normal young adults, while *Z*-score compares with peers (of the same age, sex, and ethnicity)

Status	T-score
Normal	+ 2.5 to −1.0 (inclusive)
Osteopenia	Between −1.0 and −2.5

PATHOPHYSIOLOGY (CONT'D)

Status	T-score
Osteoporosis	≤−2.5
Severe osteoporosis	≤−2.5 and fragility fracture

CLINICAL FEATURES

HISTORY—history of fragility fractures, height loss, Dowager's hump (thoracic kyphosis), milk/calcium consumption, sedentary lifestyle, other risk factors, past medical history, medications (steroids, heparin), family history, 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
Kyphosis	3.1	0.8
Tooth count <20	3.4	0.8
Rib–pelvis distance ≤2 finger breadths (indicative of spinal fracture)	3.8	0.6
Wall–occiput distance >0 cm (indicative of spinal fracture)	4.6	0.5

CLINICAL FEATURES (CONT'D)

	LR+	LR−
Decision Rules		
Simple calculated osteoporosis risk estimation (score ≥6)	1.2	0.02
Osteoporosis risk assessment instrument (score ≥9)	1.4	0.1
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"

JAMA 2004 292:23

INVESTIGATIONS

BASIC

- **LABS**—Ca, PO_4, albumin, 25-OH vitamin D, PTH, ALP, CBC, serum protein electrophoresis, TSH
- **IMAGING**—bone density scan (dual-energy X-ray absorptiometry, DEXA), spine XR

DIAGNOSTIC AND PROGNOSTIC ISSUES

OSTEOPOROSIS RISK ASSESSMENT INSTRUMENT

- **SCORING**—age 55–64 (+5), age 65–74 (+10), >75 (+10), weight 60–70 kg (+3), <60 kg (+9), not currently on estrogen (+2)
- **UTILITY**—consider bone density if score ≥9 points in postmenopausal women (sens=94.2% for *T*-score <−2.0, spc=43.7% for *T*-score >−1)>

WHO SHOULD BE SCREENED WITH DEXA?

Canadian guidelines suggest testing if personal history of fragility fracture after age 40 or any clinical risk factors (1 major or 2 minor)

- **MAJOR**—age >65, vertebral fracture, family history, systemic glucocorticoid treatment >3 months, malabsorption syndrome, primary hyperparathyroidism, propensity to fall, osteopenia apparent on X-ray, hypogonadism, early menopause age <45
- **MINOR**—rheumatoid arthritis, hyperthyroidism, chronic anticonvulsant treatment, low dietary calcium, smoker, excessive alcohol, excessive caffeine, weight <57 kg [<126 lb], weight loss >10% of weight at 25 years, chronic heparin treatment

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

PROGNOSIS—an average 50-year-old Caucasian woman has a remaining lifetime risk of 40% of developing hip, vertebra, or wrist fractures

MANAGEMENT

LIFESTYLE CHANGES—***$CaCO_3$*** 500 mg PO TID. ***Vitamin D*** 800 IU PO daily. **Physical activity** >30 min 3×/week. **Avoid excess caffeine** (>4 cups/day) and **avoid dietary Na** (>2100 mg/day)

MEDICATIONS—**bisphosphonates** (patients over the age of 50 should be stratified as to their 10-year fracture risk. Patients who are at high risk of having a fracture in the next 10 years should be started on bisphosphonates. 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, *etidronate/Didrocal kit* 1 tablet/day). Duration of therapy is controversial (e.g. 5–10 years, with possibly "drug holiday" for 1–5 years between treatment courses). **SERM** (*raloxifene* 60 mg PO daily). **hPTH(1–34)** (first line for treatment if severe osteoporosis). **Calcitonin** (second line for prevention, first line for pain. *Calcitonin nasal spray* 200 IU NAS daily alternate nostrils). **Hormone replacement** (no longer used in osteoporosis, used only for control of hot flashes)

TREATMENT ISSUES

WHO SHOULD BE TREATED?

- **IF −2.5 <BMD< −1.5** plus any one of following: personal history of fragility fracture after age 40, non-traumatic vertebral deformities, or clinical risk factors (1 major or 2 minor)—lifestyle Δ + medications
- **IF BMD <−2.5**—lifestyle Δ + medications

FRACTURE INDEX FOR POSTMENOPAUSAL WOMEN

- **SCORING**—age 65–69 (+1), age 70–74 (+2), age 75–79 (+3), age 80–84 (+4), age >85 (+5), history of any fracture after 50 years of age (+1), mother had hip fracture after 50 years of age (+1), weight <57 kg [<126 lb] (+1), current smoker (+1), uses arms to assist in standing from a chair (+2), total hip *T*-score −1 to −2 SD (+2), −2 to −2.5 SD (+3), <−2.5 SD (+4)
- **5-YEAR FRACTURE RISK**—for vertebral, non-vertebral and hip fractures, score 1–2=1.2, 9.6, 0.4%, respectively. Score 3–4=2.5, 13.1, 0.9%. Score 5=5.3, 16.5, 1.9%. Score 6–7=7.1, 19.8, 3.9%. Score 8–13=11.2, 27.5, 8.7%. A score of 4 or greater warrants treatment

SPECIFIC ENTITIES

PAGET'S DISEASE OF BONE

- **PATHOPHYSIOLOGY**—aggressive bone resorption by osteoclasts (skull, pelvis, vertebra, femur, tibia) that

SPECIFIC ENTITIES (CONT'D)

extends by 1 cm/year. This is followed by imperfect bone repair, leading to bone expansion and softening → pain, fracture, deformity, and rarely neoplastic transformation

- **CLINICAL FEATURES**—usually asymptomatic in early disease. Bone pain (achy, deep) and weakness develops later in the course, persists throughout the day and at rest, and may be worse at night. Bony deformity may lead to difficulties with weight bearing (femur, tibia), headaches and hearing loss (skull), and even neurological symptoms and paralysis (spine)
- **DIAGNOSIS**—↑ ALP is an excellent marker of disease extent and activity and can be used to follow treatment. Bone scan and plain X-rays can be diagnostic. In "mixed-stage" disease, cortical thickening (hyperostosis) disorganized coarse trabeculae (osteosclerosis), and bone expansion may be seen. In advanced ("burnt out") disease, bones are widened and heterogeneously ossified
- **TREATMENTS**—supportive care. Treatments include **bisphosphonates** (*alendronate* 40 mg PO daily ×6 months, *risedronate* 30 mg PO daily ×2 months, or zoledronate 5 mg IV), ***calcitonin*** 50–100 U SC/IM daily ×6–18 months (not as effective). Bisphosphonates can provide pain control, improve skeletal scintigraphy, and sometimes heal osteolytic lesions. Indications for therapy include symptoms related to active bone lesions (bone pain, headache, back pain, any other neurological syndromes, fissure fractures), prophylaxis in asymptomatic patients (weight-bearing bones involved and likely to progress), and elective surgery planned for pagetic site (e.g. hip replacement) and hypercalcemia

NEJM 2006 355:6

Hypertension

See HYPERTENSION (p. 57)

Hyperlipidemia

See HYPERLIPIDEMIA (p. 61)

Amenorrhea

DIFFERENTIAL DIAGNOSIS

PRIMARY AMENORRHEA

- **HYPOTHALAMIC DYSFUNCTION**—functional
- **PITUITARY DYSFUNCTION**—prolactinoma, adenomas, craniopharyngioma
- **OVARIAN FAILURE**—Turner's syndrome (XO)
- **UTERUS/VAGINA MALFORMATION**—androgen insensitivity syndrome (XY), agenesis of uterus/vagina (Mullerian agenesis), imperforated hymen
- **OTHERS**—constitutional delay, causes of secondary amenorrhea

SECONDARY AMENORRHEA

- **PREGNANCY**
- **HYPOTHALAMIC SUPPRESSION**—physiologic or emotional stress, strenuous exercise, weight loss, anorexia nervosa, infiltrative disease (lymphoma, sarcoidosis)
- **PITUITARY DISEASE**—prolactinoma, Sheehan's syndrome, hypothyroidism

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **OVARIAN**—PCOS, menopause (chemotherapy, radiation, birth control pills), premature ovarian failure
- **UTERUS**—Asherman syndrome

PATHOPHYSIOLOGY

DEFINITION OF AMENORRHEA

- **PRIMARY AMENORRHEA**—absence of menstruation by age 14 with the absence of secondary sexual characteristics or absence of menstruation by age 16 with the presence of secondary sexual characteristics
- **SECONDARY AMENORRHEA**—cessation of menses for at least 3 consecutive cycles or 6 months

CLINICAL FEATURES

HISTORY—characterize amenorrhea (onset, duration, previous menstruation), pregnancy and related symptoms, puberty milestones, headaches, visual

CLINICAL FEATURES (CONT'D)

field defects, fatigue, polyuria, polydipsia, weight change, physiologic or emotional stressors, galactorrhea, hot flashes, vaginal dryness, poor sleep, or decreased libido, hirsutism, acne, past medical history (PCOS, obesity, hypothyroidism, D&C), medications (birth control pills)

PHYSICAL—height and weight, vitals, visual fields, galactorrhea, tanner staging (breasts, genitalia, pubic hair), pelvic examination. Also assess for hirsutism, acne, striae, acanthosis nigricans, vitiligo, and signs of hypothyroidism. Perform pelvic examination

INVESTIGATIONS

BASIC

- **LABS**—glucose, TSH, prolactin, βhCG, LH, FSH, estradiol, testosterone, DHEA-S
- **IMAGING**—U/S pelvis (if suspect PCOS), CT abd/pelvis (if suspect adrenal tumor)

INVESTIGATIONS (CONT'D)

SPECIAL

- **LAPAROSCOPY**
- **HYSTEROSALPINGOGRAM**—Asherman syndrome
- **PROGESTERONE CHALLENGE TEST**—administer progesterone for 7 days. Presence of withdrawal bleed within 7 days of completion of progesterone suggests anovulation with progesterone deficiency (e.g. PCOS). Absence of withdrawal bleed suggests ovarian failure or outflow tract obstruction

MANAGEMENT

TREAT UNDERLYING CAUSE—**hypothalamic suppression** (weight gain, treat illness). **Prolactinoma** (*bromocriptine* 5–10 mg PO daily, preferred especially if pregnancy wanted; *cabergoline* 0.25–1 mg PO 2/week). **PCOS** (weight loss, birth control pill, spironolactone, metformin)

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, hilus-cell tumor
- **ADRENAL TUMORS**—carcinoma, adenoma
- **ANDROGEN THERAPY**—testosterone

DHEAS EXCESS

- **CONGENITAL ADRENAL HYPERPLASIA**
- **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 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 or caused by systemic disorders (hypothyroidism, anorexia nervosa, malnutrition, porphyria, and dermatomyositis) or medications (phenytoin, penicillamine, diazoxide, minoxidil, or cyclosporine)

PATHOPHYSIOLOGY (CONT'D)

CLINICAL FEATURES

HISTORY—time course of symptoms, hirsutism and virilization symptoms, menstrual history, weight history, medications, family history

PHYSICAL—BMI, skin and hair growth pattern, signs of virilization, abdominal and pelvic examination

INVESTIGATIONS

BASIC

- **LABS**—testosterone, DHEA-S, prolactin, LH and FSH (may be elevated in PCOS), 17-OH progesterone
- **IMAGING**—U/S pelvis (if suspect PCOS), CT abd/pelvis (if suspect adrenal tumor)

SPECIAL

- **LAPAROSCOPY/LAPAROTOMY**—if suspect ovarian tumor

DIAGNOSTIC ISSUES

DISTINGUISHING FEATURES

	PCOS	CAH	Idio-pathic	Ovary tumor
Age	Puberty	Puberty	Puberty	30 s
Menstruation	Altered	May be altered	Normal	Normal
Hirsutism	+	+	+	+++ virilization
Course	Slow	Slow	Slow	Acute
Testosterone/DHEAS	+	+	Normal	++
17-OH prog.	−	+	−	−

MANAGEMENT

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

POLYCYSTIC OVARIAN SYNDROME (PCOS)

- **PATHOPHYSIOLOGY**—increased androgen production in both puberty (increased ovarian steroid production) and adrenarche (increased adrenal androgen production). Increased insulin resistance leads to maturation arrest of the developing follicle. Increased testosterone is released from the ovaries instead. Cycles are anovulatory
- **CLINICAL FEATURES**—menstrual irregularity, hyperandrogenism (hirsutism, acne, male pattern balding)
- **DIAGNOSIS**—**clinical** (oligomenorrhea, evidence of hyperandrogenism, and exclusion of other causes of hyperandrogenism/menstrual irregularity), **laboratory** (elevated testosterone levels, LH/FSH >2)
- **TREATMENTS**—weight loss, birth control pills (hirsutism, and endometrium protection), spironolactone (hirsutism), metformin (ovulatory induction), electrolysis, and laser therapy

SPECIFIC ENTITIES (CONT'D)

IDIOPATHIC HIRSUTISM

- **CLINICAL FEATURES**—no menstrual irregularity, hirsutism
- **DIAGNOSIS**—normal androgen levels, diagnosis of exclusion
- **TREATMENTS**—hair removal (electrolysis, laser therapy), birth control pills, spironolactone

CONGENITAL ADRENAL HYPERPLASIA (LATE-ONSET)

- **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, elevated DHEAS
- **TREATMENTS**—birth control pills, spironolactone, glucocorticoid at hs to turn off ACTH stimulation, hair removal (electrolysis, laser therapy)

Notes

Notes

12
DERMATOLOGY

Section Editor: Dr. Susan Chon

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
- **PSORIASIS**
- **URTICARIA**
- **DERMATITIS HERPETIFORMIS**

INFECTIONS—tinea, scabies

NEOPLASTIC—lymphoma (mycosis fungoides), myeloma, solid tumors

IATROGENIC

- **DRUG ERUPTION**—antibiotics, anti-seizure
- **DRUG-INDUCED PRURITUS**—opiates, steroids, aspirin, antimalarials

SYSTEMIC

- **ENDOCRINE**—diabetes, hypothyroidism, hyperthyroidism
- **HEPATOBILIARY**—PBC, cholestasis
- **RENAL**—uremia, hemodialysis
- **INFECTIONS**—HCV, HIV
- **OTHERS**—sarcoidosis, iron deficiency

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. 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. Pustules, honey-colored crusts, and weeping may be a sign of secondary infection

TYPES OF ECZEMA

- **ASTEATOTIC ECZEMA**—dry irritable skin in the elderly

CLINICAL FEATURES (CONT'D)

- **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**—CBCD (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% for the face, 0.1% triamcinolone for the body), and topical calcineurin inhibitors (tacrolimus, pimecrolimus). **Antihistamines** (diphenhydramine, loratadine, fexofenadine, hydroxyzine, and doxepin. Side effects depend on the individual patient)

SPECIFIC ENTITIES

DERMATITIS HERPETIFORMIS

- **ASSOCIATIONS**—celiac disease, IgA nephropathy, autoimmune thyroid disease, type 1 diabetes, SLE, Sjogren's syndrome, sarcoidosis, vitiligo, and alopecia areata. Strong linkage to HLA-B8, DR3, and DQw2. Increased risk of non-Hodgkin's lymphoma
- **CLINICAL FEATURES**—pruritic papulovesicles on extensor surfaces and buttocks, rarely mucous membranes
- **TREATMENTS**—dapsone and gluten-free diet. See Celiac disease (p. 124)

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 blood into the surrounding tissues, the lesions become darker, scalier, and may even form stasis ulcers

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_12,

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—treat underlying cause. Leg elevation. Supportive stockings (after ankle–brachial index checked). Topical steroids for acute exacerbations

SCABIES

- **CLINICAL FEATURES**—excoriations, eczematized and urticarial papules over trunk. Linear white burrows over finger webs, sides of hand, and flexural aspects of wrists

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—first-line therapy with *permethrin* 5% cream ×1 dose, rinse off after 8–14 h. Second-line treatments include *ivermectin* 200 mcg/kg PO ×1 dose and repeat PO ×1 dose 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

NEJM 2006 354:16

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, squamous cell carcinoma
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, 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 which may be helpful in making the diagnosis. All patients regardless of skin severity should be screened for arthritis that is often worse in the mornings and shows asymmetric swelling of joints. 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 reveals punctate blood droplets (Auspitz sign)
- **GUTTATE PSORIASIS**—predilection for trunk. May follow a streptococcal infection. Multiple discrete erythematous papules with silvery scales
- **PALMOPLANTAR 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 ± 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

CLINICAL FEATURES (CONT'D)

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, and clobetasol) and vitamin D analogs. 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, 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 TNFα inhibitors should be considered. Avoid systemic steroids as discontinuation may cause generalized pustular psoriasis

SPECIFIC ENTITIES

PITYRIASIS ROSEA

- **PATHOPHYSIOLOGY**—human herpesvirus-7 may be the etiologic agent, although this disorder does not seem to be contagious

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—herald plaque (2–5 cm, round, redder, scaly) followed by many smaller plaques. 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, methyldopa, penicillamine, NSAIDs, ACE inhibitors, carbamazepine, gold, lithium), HCV infection
- **CLINICAL FEATURES ★5 P's★**—**P**urple, **P**ruritic, **P**olygonal, **P**lanar (flat-topped) **P**apules. May also see fine white lines on the surface (Wickham's striae). Commonly seen in flexor wrists, forearms, and buccal mucosal (lacy white reticular lesions). Lesions may last for a year
- **TREATMENTS**—no treatment needed usually. Topical steroids, antihistamines, and antiinflammatories to relieve pruritus

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 *Pityrosporum ovale*, with increased host response leading to dermatitis. It is also known as "dandruff" in adults
- **CLINICAL FEATURES**—pink to erythematous plaques with yellow scales or greasy crusts, which may occasionally be pruritic
- **TREATMENTS**—gentle emollients, ketoconazole shampoo or cream, and 1–2.5% hydrocortisone cream. 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. 282)

URTICARIA (HIVES)

- **PATHOPHYSIOLOGY**—an acute (<6 weeks) or chronic (>6 weeks) type I hypersensitivity reaction. Most cases are idiopathic but triggers may include infections and medications

SPECIFIC ENTITIES (CONT'D)

- **CLINICAL FEATURES**—characterized by superficial transient edema with pink highly pruritic papules or plaques with individual lesions having rapid onset and resolution within 24 h. Dermatographism is common where wheals may be induced after stroking the skin
- **TREATMENTS**—non-sedating antihistamines during the day and scheduled sedating antihistamines at night. Systemic glucocorticoids may be used when severe, but courses should last for at least 2 weeks

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 LFTs)

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), **systemic** (ketoconazole, terbinafine, itraconazole)

GROIN SKIN LESIONS—common causes include tinea cruris, candidiasis, erythrasma (*Corynebacterium minutissimum*), and inverse psoriasis

Acne Vulgaris NEJM 2005 352:14

DIFFERENTIAL DIAGNOSIS OF ACNEIFORM LESIONS

ACNE VULGARIS
ROSACEA
PERIORAL DERMATITIS
DRUGS—**EGFR inhibitors** (erlotinib, gefitinib, cetuximab, panitumumab) can cause pustular folliculitis

PATHOPHYSIOLOGY

PATHOGENESIS—condition affecting pilosebaceous units, commonly seen during puberty. Pathogenesis involves androgens, follicular kertinization, and the Gram-positive bacteria *Proprionibacterium acnes*. Lesions may present as non-inflammatory comedones or inflammatory papules. Inflammatory cysts

PATHOPHYSIOLOGY (CONT'D)

may leave behind hyperpigmentation and sometimes scaring

RISK FACTORS—**drugs** (steroids, phenytoin, lithium), **androgen excess** (PCOS, Cushing's, congenital adrenal hyperplasia)

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 (white heads), erythematous papules, pustules, cysts and scarring over face, shoulders, upper chest, and back

INVESTIGATIONS

SPECIAL (not typically performed)

- **ENDOCRINE WORKUP**—testosterone, sex hormone-binding globulin, LH, FSH, 24-h urinary cortisol

MANAGEMENT

TREAT UNDERLYING CAUSE

- **FIRST-LINE AGENTS**—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**—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 photosensitivity. Retinoids should never be used in pregnant women as highly teratogenic. Fertile women should take oral contraceptive pills 2 months before and 1 month after oral retinoids

SPECIFIC ENTITIES

ROSACEA

- **CLINICAL FEATURES**—middle age adults with central facial telangiectasias, flushing (especially after ingestion of hot liquids, spicy foods, and other triggers), and acneiform papulopustules in cheeks, nose, forehead, and chin. No comedones. Maybe also associated with rhinophyma (more in men), conjunctivitis, iritis, and keratitis
- **TREATMENTS**—oral antibiotics (tetracycline, erythromycin), topical antibiotics (metronidazole 0.75%), sulfur-based products (sodium sulfacetamid lotion 10%), pulsed dye laser

PERIORAL DERMATITIS

- **CLINICAL FEATURES**—young woman with papules and pustules over chin, upper lip, and nasal labial folds
- **TREATMENTS**—oral antibiotics (tetracycline, erythromycin)

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. 372)

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. 234)

SPECIFIC ENTITIES

PARVOVIRUS B19—slapped cheek rash on face and erythematous eruption on trunk, neck, and extremities. Also called fifth disease or erythema infectiosum. Fever may be present. Parvovirus B19 is also associated with aplastic anemia, polyarthritis, and fetal hydrops

STAPHYLOCOCCAL SCALDED SKIN SYNDROME (SSSS)

- **PATHOPHYSIOLOGY**—exfoliatins by specific strains of staphylococci leading to desquamative disorder with cleavage at the granular layer of the dermis
- **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
- **DIAGNOSIS**—culture from a site other than the blisters (blood, conjunctivae, nasopharynx) demonstrating staphylococci
- **TREATMENTS**—antibiotics for treatment of staphylococci

TOXIC SHOCK SYNDROME

- **PATHOPHYSIOLOGY**—exotoxin by specific strains of *S. aureus* or group A *Streptococcus* leading to cleavage at the granular layer of the dermis

SPECIFIC ENTITIES (CONT'D)

- **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. Hypotension and organ failure may occur
- **TREATMENTS**—fluid resuscitation as needed, *vancomycin* (30 mg/kg/day IV divided BID) or β-lactam plus *clindamycin* (600 mg IV q8h). If unresponsive to fluids or vasopressors, consider *IVIG* (400 mg/kg ×1 dose, limited evidence)

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 to sandpaper-like appearance. Desquamation happens 7–10 days after resolution of rash
- **TREATMENTS**—antibiotics and 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

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

PATHOPHYSIOLOGY (CONT'D)

COMMONLY ASSOCIATED DRUGS ★4A'S★

- **A**llopurinol
- **A**ntibiotics—sulfamethoxazole, cephalosporins, penicillins, quinolones, macrolides
- **A**ntiinflammatory drugs—NSAIDs, salicylates
- **A**nticonvulsants—carbamazepine, phenytoin, lamotrigine, phenobarbital

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. 90% of patients have mucous membrane involvement and 60% have ocular involvement

CLINICAL FEATURES (CONT'D)

NIKOLSKY'S 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**—CBCD, lytes, Cr, urea
- **MICROBIOLOGY**—fluid C&S, HSV serology, VZV serology
- **SKIN BIOPSY**

PROGNOSTIC ISSUES

PROGNOSIS—mortality rate for SJS and TEN is about 5 and 30–50%, respectively, typically from sepsis and multi-organ failure

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. Systemic antibiotics may be necessary

SUPPORTIVE MEASURES—patients should be managed in a burn unit or ICU, as electrolyte abnormalities, renal failure, and pulmonary edema may occur

SPECIFIC ENTITIES

ERYTHEMA MULTIFORME

- **PATHOPHYSIOLOGY**—immune-mediated hypersensitivity reaction involving the skin and VERY LIMITED mucous membranes
- **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 lesions. Palms, soles, forearms, legs most commonly affected
- **TREATMENTS**—discontinue offending drugs. Treat suspected HSV infection with appropriate antivirals

IMPETIGO

- **PATHOPHYSIOLOGY**—intra-epidermal infection by *Staphylococcus aureus* or β-hemolytic streptococci
- **CLINICAL FEATURES**—in bullous form, flaccid, pus-filled lesions often found in intertriginous areas. More commonly found in children

SPECIFIC ENTITIES (CONT'D)

- **TREATMENTS**—antibiotics (cefazolin, cephalexin)

BULLOUS PEMPHIGOID

- **PATHOPHYSIOLOGY**—autoimmune disease with IgG binding to subepidermal proteins, leading to separation of epidermis from dermis
- **ASSOCIATIONS**—furosemide, captopril, thiazide, spironolactone, penicillamine, phenothiazines, tricyclic antidepressants, benzodiazepines
- **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's sign negative
- **TREATMENTS**—discontinue offending drugs. Treat with antiinflammatories and immunosuppressants, including tetracycline and niacinamide. *Prednisone* 1–2 mg/kg PO daily. Methotrexate, azathioprine and cyclosporine

PEMPHIGUS VULGARIS

- **PATHOPHYSIOLOGY**—autoimmune disease with IgG binding to intraepidermal proteins, leading to separation of keratinocytes in epidermis
- **ASSOCIATIONS**—penicillamine, malignancies (paraneoplastic)
- **CLINICAL FEATURES**—acute onset of multiple flaccid blisters. Mucous membranes usually affected first, with spread to scalp, face, chest, and groin. Nikolsky's sign positive. Lesions prone to rupture and infections. May be life-threatening. May be paraneoplastic
- **TREATMENTS**—discontinue offending drugs. Consider burn unit admission. *Prednisone* 1–2 mg/kg PO daily. Azathioprine, cyclosporine, mycophenolate mofetil, 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
- **TREATMENTS**—acyclovir, valacyclovir, famciclovir

VARICELLA ZOSTER VIRUS (VZV)

- **CLINICAL FEATURES**—crops of vesicles over entire body (varicella) or specific dermatone with reactivation (zoster, also known as shingles)
- **TREATMENTS**—acyclovir, valacyclovir, famciclovir. Amitriptyline, gabapentin, and opioids may be useful for post-herpetic neuralgia

Ulcers

DIFFERENTIAL DIAGNOSIS OF ULCERS

VENOUS HYPERTENSION
- **STASIS**—immobility, CHF, incompetent valves, pregnancy
- **DVT**

ATHEROSCLEROTIC

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

TUMOR—squamous cell carcinoma, basal cell carcinoma, melanoma, Kaposi's sarcoma

TRAUMA

INVESTIGATIONS

BASIC
- **LABS**—CBCD, lytes, glucose, urea, Cr, HbA1C
- **MICROBIOLOGY**—wound Gram stain, AFB, C&S, TB culture
- **ANKLE BRACHIAL INDEX**—<0.8 indicates arterial origin
- **IMAGING**—doppler ultrasound, venous plethysmography

SPECIAL
- **PYODERMA GANGRENOSUM**
  - **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, 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. Twice daily if infected). Diuretics (decrease leg edema). Antbiotics 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 necrosis
- **RISK FACTORS**—atherosclerosis, peripheral artery disease, diabetes mellitus, obesity, smoking, rheumatic disease, Buerger's disease, and 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
- **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. 54)

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

SPECIFIC ENTITIES (CONT'D)

- **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 syndrome, 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, 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. ESR may be elevated. Classically worsens with attempted biopsy or debridement
- **TREATMENTS**—treat underlying causes where possible. Immunosuppressive and immunomodulator therapy such as high dose oral or IV glucocorticoids (*prednisone* 60–80 mg PO daily, *pulse methylprednisolone* 1 g IV daily $\times$3 day), cyclosporine, and TNF α blockade and *IVIG* 400 mg/kg IV daily $\times$5 day or 1 g/kg IV daily $\times$2 day have been effective. Other options include sulfasalazine, sulfones, minocycline, and dapsone. Topical and intralesional steroids and tacrolimus have also been used

NEJM 2002 347:18

Melanoma and Skin Tumors

NEJM 2005 353:21; NEJM 2004 351:10; NEJM 2001 344:13

DIFFERENTIAL DIAGNOSIS OF PIGMENTED LESIONS

BENIGN—nevus (congenital, acquired), freckle, seborrheic keratosis, cafe-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, 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

PATHOPHYSIOLOGY (CONT'D)

- **ACRAL LENTIGINOUS**—most common melanoma in pigmented patients. 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's, hypercalcemia, neurological

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A MOLE OR A MELANOMA?
CHECKLIST ★ABCD★—Asymmetry, **B**order irregularity, **C**olor variegation, **D**iameter >6 mm (sens 92–100%, spc 98% depending on how many criteria

CLINICAL FEATURES (CONT'D)

used). **E**volution (change) in lesion is also an important feature

REVISED 7-POINT CHECKLIST—change in size, change in color/irregular color, change in shape/irregular shape, presence of inflammation, diameter $\geq$7 mm, crusting or bleeding, sensory change (sens 79–100%, spc 30–37%, depending on how many criteria used)

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"

JAMA 1998 279:9

INVESTIGATIONS

BASIC

- **EXCISIONAL BIOPSY**—all lesions suspicious for melanoma should be biopsied with caution to obtain the total depth of the melanoma. Breslow depth is the most important prognostic indicator for patients

SPECIAL

- **LABS**—CBC, lytes, urea, Cr, LDH, AST, ALT, ALP, bilirubin as part of staging workup after pathology confirmation
- **IMAGING**—CXR as part of staging workup after pathology confirmation

DIAGNOSTIC AND PROGNOSTIC ISSUES

CLARK'S LEVELS (LIMITED UTILITY FOR SMALL LESIONS)

Level	TNM	5-year survival
I	Intraepidermal (in situ)	100%
II	Invasion into papillary dermis	85%
III	Extensive invasion of papillary dermis	65%
IV	Invasion into reticular dermis	50%
V	Invasion into subcutaneous tissue	15%

TNM STAGING 2009

T STAGE (Breslow depth/thickness)

- **T1** $\leq$1 mm
  - **T1a**=without ulceration and mitosis $<1/mm^2$
  - **T1b**=with ulceration or mitosis $\geq 1/mm^2$
- **T2**=1.01–2 mm
  - **T2a**=without ulceration
  - **T2b**=with ulceration
- **T3**=2.01–4 mm
  - **T3a**=without ulceration
  - **T3b**=with ulceration

DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **T4** >4 mm
  - **T4a**=without ulceration
  - **T4b**=with ulceration

N STAGE

- **N1**=1 LN
  - **N1a**=micronodal
  - **N1b**=macronodal
- **N2**=2–3 LN
  - **N2a**=micronodal
  - **N2b**=macronodal
  - **N2c**=in-transit metastasis/satellite without metastatic nodes
- **N3** $\geq$4 nodes, or matted nodes, or in transit metastasis/satellites with metastatic nodes

M STAGE (lungs, bone, liver, skin, and essentially any organ. Biologically heterogeneous with variable course)

- **M1a**=distant skin, subcutaneous, or nodal metastasis with normal LDH
- **M1b**=lung with normal LDH
- **M1c**=visceral organs or elevated LDH

STAGE GROUPINGS

Stage	TNM @=any	10-year survival
IA	T1aN0M0	95%
IB	T1b–T2aN0M0	85%
IIA	T2b–3aN0M0	70%
IIB	T3b–4aN0M0	60%
IIC	T4bN0M0	40%
III	T@N1–3M0	
IIIA	T1a–4aN1aM0, T1a–4aN2aM0	70%
IIIB	T1b–4bN1aM0, T1b–4bN2aM0, T1a–4aN1bM0, T1a–4aN2bM0, T1–4aN2cM0	45%
IIIC	T1b–4bN1bM0, T1b–4bN2bM0, T1–4bN2cM0, T@N3M0	25%
IV	T@N@M1	10%

SENTINEL LYMPH NODE BIOPSY—usually done if primary melanomas 1–4 mm thick or ulcerated

PROGNOSIS BY SITE OF METASTASIS—**M1a**=62% 1-year survival, **M1b**=53% 1-year survival, **M1c**=33% 1-year survival

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, 2 cm for

MANAGEMENT (CONT'D)

lesions 1–4 mm thick, ≥3 cm for lesions >4 mm thick). **Sentinel lymph node biopsy** for lesions >1 mm thick. If palpable node or sentinel LN positive, consider **lymph node dissection** and **adjuvant high-dose interferon α2b** (5 days/week IV ×4 weeks, then 3 days/week SC ×48 weeks). If extranodal extension or LN >3 cm, consider **adjuvant radiation**. For locoregional recurrence, consider re-excision. **Follow-up** of these patients should include a complete review of systems including headache, visual changes, cough, lymph node examination, and for patients with deep melanomas an LDH and imaging to rule out metastasis. Patients should continue skin examinations at least semi-annually for new lesions as patients have a 3–5% chance of developing another melanoma

STAGE IV—palliative chemotherapy (dacarbazine with response rate 15–20% and median duration of response 4–6 months. Consider temozolomide if CNS metastases). **Palliative radiation** (if localized pain). **Excision** of solitary brain or lung metastasis is occasionally done

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
  - **MORPHEAFORM 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 history, immunosuppression, fair complexion, and red hair
- **TREATMENTS**—usually treated by either excision or electrodessication and curettage. However, if superficial they may be treated with topical imiquimod

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 skin cancer
- **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'S 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
  - **VERRUCOUS CARCINOMA**—clinically and histologically resembles a wart
- **TREATMENTS**—surgical excision is the treatment of choice

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

SPECIFIC ENTITIES (CONT'D)

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 which 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

SPECIFIC ENTITIES (CONT'D)

- **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, UV light

Cutaneous Lupus Erythematosus

DIFFERENTIAL DIAGNOSIS OF PHOTOSENSITIVITY

IATROGENIC (DRUGS)

- **AMIODARONE**
- **DIURETICS**—hydrochlorothiazide, loop
- **ANTIBIOTICS**—tetracycline
- **NSAIDs**
- **ANTINEOPLASTIC**—methotrexate, vincristine, 5-fluorouracil

INFLAMMATORY—SLE, dermatomyositis

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
- **DISCORD 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

CLINICAL FEATURES (CONT'D)

- **BULLOUS LESIONS**—photosensitivity
- **LIVEDO RETICULARIS**—see SPECIFIC DISORDERS
- **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**—CBCD, ANA, ENA, dsDNA

SPECIAL

- **SKIN BIOPSY**
- **PORPHYRIA WORKUP**—porphyrin, urine porphyrin

MANAGEMENT

TREATMENT UNDERLYING CAUSE—sun protection. Topical steroid ointments. Topical immunosuppressants (tacrolimus). Antimalaria (hydroxychloroquine). Systemic immunosuppressants

Related Topics
Systemic Lupus Erythematosus (p. 279)
Porphyria (p. 421)

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

SPECIFIC ENTITIES (CONT'D)

LIVEDO RETICULARIS

- **CAUSES**—**vascular** (polyarteritis, SLE, livedo vasculitis, cryoglobulinemia, antiphospholipid antibody syndrome, atherosclerosis, syphilis, TB), **hyperviscosity** (polycythemia, thrombocytosis, macroglobulinemia), **congenital**, **cerebrovascular disease** (Sneddon's 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
- **TREATMENTS**—avoid exacerbating factors (alcohol, estrogens, iron supplements, drugs). Phlebotomy. Chloroquine, hydroxychloroquine

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, barbiturates
- **ANTIINFLAMMATORIES**—NSAIDs, ASA photosensitivity
- **DIURETICS**—hydrochlorothiazide, loop
- **ANTIBIOTICS**—tetracycline
- **ANTINEOPLASTICS**—methotrexate, vincristine, 5-fluorouracil)

ERYTHEMA MULTIFORME, STEVENS–JOHNSON SYNDROME ★4A'S★

- **ALLOPURINOL**
- **ANTIBIOTICS**—sulfonamides, penicillins, cephalosporins
- **ANTICONVULSANTS**—phenytoin, carbamazepine, phenobarbital
- **ANTIINFLAMMATORIES**—NSAIDs

CONTACT DERMATITIS—neomycin, benzocaine, paraben, ethylenediamine, formaldehyde, para-aminobenzoic acid

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**—CBCD (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, maculopapular rash almost always found on the

SPECIFIC ENTITIES (CONT'D)

trunk and extremities, which may be very pruritic. Usually lasts 1–2 weeks

- **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. **Nonallergic 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 radiocontrast
- **TREATMENTS**—cessation of the offending drug. Antihistamines and oral steroids may be used. For acute, life-threatening reactions, ABC, O_2, ***epinephrine*** 0.5 mL of 1:1000 (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
- **TREATMENTS**—typically resolve 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 hypersensitivity reaction (delayed cell mediated, T-cell activated)
- **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)
- **TREATMENTS**—identify and avoid causative agent(s)

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, maculopapular rash, biopsy including arteriole and venule. Need three of five criteria (sens 71%, spc 84%)
- **TREATMENTS**—discontinue offending drug

Related Topics
Antibiotics (p. 254)
Penicillin Allergy (p. 257)

Erythema Nodosum

DIFFERENTIAL DIAGNOSIS OF PAINFUL NODULES

PANNICULITIS—erythema nodosum, erythema induratum, Weber–Christian disease (relapsing febrile nodular panniculitis)
INFECTIONS—bacteria, fungi

DIFFERENTIAL DIAGNOSIS OF PAINFUL NODULES (CONT'D)

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, Behcet's
- **INFILTRATIVE**—sarcoidosis, Hodgkin's
- **IATROGENIC**—oral contraceptive pills, omeprazole, montelukast
- **IDIOPATHIC**

CLINICAL FEATURES

TYPICAL PRESENTATION—painful, erythematous nodules on the anterior surfaces of both legs and sometimes thighs, trunk, and upper extremities. May evolve into bruise-like lesions that resolve without scarring over a 2–8-week period. Other symptoms include polyarthralgias, fever, and malaise. Presence of GI symptoms and/or hilar adenopathy may help in narrowing differential

INVESTIGATIONS

BASIC

- **LABS**—CBCD, antistreptolysin-O titer, ANA
- **MICROBIOLOGY**—wound C&S, throat C&S (for *Streptococcus*), TB skin test
- **IMAGING**—CXR

SPECIAL

- **DEEP INCISIONAL BIOPSY**

MANAGEMENT

SYMPTOM CONTROL—**NSAIDs**, **potassium iodide**, **glucocorticoids** (beware of TB)

TREAT UNDERLYING CAUSE

Related Topics
Tuberculosis (p. 250)
Fungal Infections (p. 265)
Sarcoidosis (p. 420)

Clubbing

DIFFERENTIAL DIAGNOSIS

RESPIRATORY—lung cancer, lung abscess, bronchiectasis, cystic fibrosis, empyema, mesothelioma, idiopathic pulmonary fibrosis, asbestosis
CARDIAC—cyanotic heart disease, congenital, subacute endocarditis
GI—colon cancer, esophageal cancer, inflammatory bowel disease, celiac disease, cirrhosis
OTHERS—hyperthyroidism, 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's 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)

CLINICAL FEATURES (CONT'D)

PALPATION—floating nail bed elicited by rocking the distal and proximal nail back and forth
APPROACH—"the profile angle and phalangeal depth ratio can be used as quantitative indices to assist in identifying clubbing. In individuals without clubbing, values for these indices do not exceed 192°, and 1.0, respectively. Inter-observer agreement by clinicians is highly variable (κ values 0.39–0.90). Because of the lack of an objective diagnostic standard, accuracy of physical examination for clubbing cannot be determined. The accuracy of clubbing as a marker of specific underlying disease has been determined for lung cancer (LR+ 3.9 with phalangeal depth ratio >1.0) and for inflammatory bowel disease (LR+ 2.8 and 3.7 for active Crohn's disease and ulcerative colitis, respectively)"

JAMA 2001 286:3

INVESTIGATIONS

BASIC

- **IMAGING**—CXR

SPECIAL

- **CARDIAC WORKUP**—ECG, echocardiogram
- **OTHER ETIOLOGY WORKUP**—CBCD, 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. 124)
Inflammatory Bowel Disease (p. 120)
Lung Cancer (p. 185)

Dupuytren's Contracture

DIFFERENTIAL DIAGNOSIS

DIABETIC CHEIROARTHROPATHY (usually all four fingers)
INTRINSIC JOINT DISEASE
DUPUYTREN'S CONTRACTURE
VOLKMANN'S ISCHEMIC CONTRACTURE
TRAUMATIC SCARS
PALMAR FASCIITIS—malignancy (usually bilateral)

PATHOPHYSIOLOGY

RISK FACTORS—alcoholism, smoking, diabetes, repetitive hand motions/vibrations, reflex sympathetic dystrophy
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. Surgery or radiation for severe disease

Notes

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GERIATRICS

Section Editor: Dr. Fiona Lawson

Geriatric-Specific Issues

THE FRAIL ELDERLY

THE CONCEPT OF FRAILTY—frailty is a "weakened" or "precarious" state resulting in heightened susceptibility to stressors. While no standard definition for frailty exists, it is associated with (1) limited function, (2) multiple medical conditions, and (3) one of the geriatric syndromes (dementia, delirium, depression, falls $\geq$1 per month, osteoporosis, failure to thrive, and urinary incontinence). Frailty predisposes patients to functional and cognitive decline, particularly in the presence of precipitants/stressors. While age can be a factor in choosing treatments due to altered pharmacokinetics, frailty is a more important treatment-modifying factor. In general, less aggressive (and sometimes more palliative) treatments are offered to frail patients. Clinical outcomes for frail seniors can be improved with various interventions, such as comprehensive geriatric assessment and exercise programs

POTENTIAL PRECIPITANTS—acute illness, infections, infarction, medications, social stress, environmental changes, and surgical intervention. Patients with frailty are at higher risk of complications, such as increased mortality, morbidity, and rates of institutionalization when faced with these precipitants

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:

FUNCTIONAL HISTORY—activities of daily living (ADLs, dressing, bathing, eating, hygiene, toileting, mobility), instrumental activities of daily living (IADLs, transportation, shopping, phoning, laundry, cooking, accounting, housekeeping, medications), falls (number, causes, fractures), mobility prior to admission (how many steps)

GERIATRIC SYNDROMES/GIANTS—presence/absence and severity of dementia, delirium, depression, falls ($\geq$1/month), osteoporosis with spontaneous fractures, neglect and abuse, failure to thrive, incontinence

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

COMPREHENSIVE GERIATRICS ASSESSMENT (CONT'D)

POLYPHARMACY—number of medications, potential medications that can cause delirium and other significant side effects, adherence, assistance with medications, drug interactions (p. 385)

NUTRITION RISK—dietary intake, calorie intake

SOCIAL HISTORY—living situation, education, work, family, caregivers at home, financial stability, access to transportation, personal directives

COGNITIVE EXAMINATION—mini-mental status exam, clock face drawing, dementia (apraxia; aphasia; agnosia; abstraction similarities, proverb; executive-safety situational questions), CAM score (see DELIRIUM p. 380), language (4-legged animals in 1 min. Abnormal $<$12), frontal assessment battery (abnormal $<$13), EXIT, cognistat

FUNCTIONAL EXAMINATION—timed up and go test (subjects asked to rise from chair, walk 10 ft, turn and return to chair; $<$20 s correlates with independence in ADLs, $>$20 s abnormal), Tinetti's gait assessment (score $<$20/28 predictive of recurrent falls)

COMPREHENSIVE GERIATRIC MANAGEMENT

INTERPROFESSIONAL TEAMS—often require interdisciplinary teams consisting of geriatricians, nurses, social workers, physiotherapists, occupational therapists, pharmacists, registered dieticians, speech-language therapists, recreational therapists, psychologists, and family

Discipline	Task
Dieticians	Nutrition and diet
Nurses	Education and assistance with ADLs, IADLs
Occupational therapists	Cognitive and functional assessments, ADL training
Pharmacists	Medication use
Physiotherapists	Training to ↑ ROM, strength, endurance, coordination, mobility

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_13,

COMPREHENSIVE GERIATRIC MANAGEMENT (CONT'D)

Discipline	Task
Recreational therapists	Maintenance of social roles
Social workers	Counseling, evaluation, and disposition within community
Speech-language therapists	Training in communication and therapy for swallowing disorders

HEALTH CARE AND FINANCIAL PROXY

ADVANCE DIRECTIVE (living will)—a document that is created when patient is competent. Allows direction of their care in future (e.g. regarding tube feeding, resuscitation status) when they are no longer capable of expressing their own wishes

PERSONAL DIRECTIVE—agent assigned when patient competent so that if they become incompetent, agent can act on patient's behalf regarding decisions for personal care and accommodation

POWER OF ATTORNEY—agent assigned when patient competent so that if they become incompetent, agent can act on patient's behalf regarding finances

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—suspect incapacity, risk, undue influence

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 ADLs, finances, medical condition, living will. Are they consistent in their choices? Do they understand and appreciate the consequences of their actions?

INFORM AND ACT

Dementia and Cognitive Impairment

DIFFERENTIAL DIAGNOSIS

PRIMARY PROGRESSIVE DEMENTIA

- **ALZHEIMER'S**—slow insidious cognitive decline but otherwise no physical findings, mini-mental status examination globally low, CT may show white matter change, mostly a diagnosis of exclusion, but accounting for 60% of dementias
- **VASCULAR**—acute stepwise or slow progressive decline, focal neurological deficits, mini-mental status examination patchy, CT may show white matter change, pure vascular dementia uncommon, more frequently occurs with Alzheimer's-like dementia (mixed vascular)
- **PARKINSON'S**—Parkinsonian symptoms for a long time, slow decline, Parkinson's patients have 6× increased risk for dementia
- **LEWY BODY**—Parkinsonism, persistent visual hallucinations, progressive decline, fluctuating cognition especially attention/alertness, marked adverse hypersensitivity to typical antipsychotic medications, supportive features include syncope, delusions, and sleep disturbance
- **FRONTOTEMPORAL**—prominent impairment in executive function, 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, MMSE may be normal, abnormal clock drawing, CT frontal temporal atrophy
- **PRION DISEASE**—Creutzfeldt–Jakob disease

POTENTIALLY REVERSIBLE DEMENTIA (<1%)

- **METABOLIC**—alcoholism, vitamin B12, hypothyroidism
- **STRUCTURAL**—NPH, subdural hemorrhage, neoplastic, vascular
- **INFECTIONS**—chronic meningitis, HIV, neurosyphilis, Whipple's
- **INFLAMMATORY**—vasculitis, Hashimoto encephalitis, multiple sclerosis

DEMENTIA MIMICS—depression, delirium, developmental disorder, age-associated memory impairment

PATHOPHYSIOLOGY

DEMENTIA—acquired, progressive, global decline in cognition resulting in impairment in function. Learning and memory impairment are present, plus ≥1 of the following: aphasia, agnosia, apraxia, impairment of executive function. Deficits result in impaired function. Disorientation and impairment in regulation of emotion and aggression may also be present

PATHOPHYSIOLOGY (CONT'D)

MILD COGNITIVE IMPAIRMENT—predominant memory complaints with other cognitive domains largely intact and preservation of functional independence; 10–15% of patients progress to Alzheimer's annually

CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN VARIOUS TYPES OF DEMENTIA

	Alzheimer's	Vascular	Fronto-temporal
Physical findings	Relatively normal	Focal neurological deficits	Disinhibited or passive Primitive reflexes
MMSE	Globally low	Patchy changes Early executive loss	Early executive loss
CT	White matter changes	White matter changes	Frontal temporal atrophy

Related Topics
Delirium (p. 380)
Parkinson's disease (p. 320)
Stroke (p. 299)
Vitamin B12 deficiency (p. 405)

CLINICAL FEATURES (CONT'D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE DEMENTIA?

MINI-MENTAL STATE EXAMINATION (MMSE)—orientation to place (5), time (5), immediate and delayed recall (6), spell "WORLD" backward (5), 3 step commend (3), name 2 objects (2), close your eyes (1), repeat sentence "No, if's, and's, or but's" (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

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	0.13–0.710

APPROACH—"to detect cognitive impairment of at least moderate severity, consider the mini-mental state examination. The Hopkins Verbal Learning Test or the Word List Acquisition Test may be used to screen for mild impairment in highly educated patient. 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"

JAMA 2007 297:21

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, creatinine, glucose, Ca, TSH, vitamin B12
- **IMAGING**—head CT

SPECIAL

- **FURTHER DEMENTIA WORKUP**—AST, ALT, ALP, bilirubin, RBC folate, VDRL, HIV serology, urine collection for heavy metals

DIAGNOSTIC ISSUES

DSM IV CRITERIA FOR DEMENTIA

A. Short-term memory loss
B. One of agnosia, aphasia, apraxia, executive dysfunction (abstraction, planning)
C. Functional/social decline
D. Rule out depression or delirium

MINI-MENTAL STATE EXAMINATION (MMSE)—adjusted based on age and education. An abnormal test may indicate the presence of dementia, delirium, or depression. Traditional threshold for MMSE ≤ 23 suggests dementia (LR+ 6–8) in the absence of delirium. Newer thresholds: ≤ 20 rules in dementia (LR+ 14.5, sens 39–69%, spc 93–99%), ≥ 26 rules out dementia (LR+ 0.1), 21–25 inconclusive (LR+ 2.2)

HACHINSKI ISCHEMIC SCORE

- **SCORING**—abrupt onset (2), stepwise progression (1), fluctuating course (2), nocturnal confusion (1), relative preservation of personality (1), depression (1), somatic complaints (1), emotional incontinence (1), history of hypertension (1), history of strokes (2), evidence of associated atherosclerosis (1), focal neurological symptoms (2), focal neurological signs (2)

DIAGNOSTIC ISSUES (CONT'D)

- **UTILITY**—if score <4, likely Alzheimer's disease; if >7, likely vascular dementia

CLOCK DRAWING—a test of constructional apraxia with many technical variants. Wolf–Klein method provides patient with paper and preprinted circle (4 in. in diameter) and instructions to "draw a clock." "Normal" clock has numbers clockwise in correct order and near 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 CT HEAD—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)

CMAJ 1999 160:12; Canadian Consensus Conference on Dementia

MANAGEMENT

RISK REDUCTION—**anti-hypertensive** (see HYPERTENSION p. 57), **dyslipidemia treatment** (see DYSLIPIDEMIA p. 62)

DISEASE MANAGEMENT—**anticholinesterase** may be considered for Alzheimer's disease and include *donepezil* 5–10 mg PO qhs, *rivastigmine* 1.5–6 mg PO BID, and *galantamine* ER 8–24 mg daily. Avoid if seizures, cardiac conduction problems, significant asthma, COPD, or recent GI bleed. *Memantine* 5–10 mg PO BID may be used as a single agent or as add-on therapy to cholinesterase inhibitor

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)

MANAGEMENT (CONT'D)

SPECIFIC ENTITIES

SEQUENCE OF SYMPTOMS IN ALZHEIMER'S DISEASE—mood changes, cognitive decline, loss of functional autonomy, neuropsychiatric manifestations, parkinsonism

LESS COMMON CAUSES OF DEMENTIA

- **NORMAL PRESSURE HYDROCEPHALUS (NPH)**
  - **PATHOPHYSIOLOGY**—inflammation and fibrosis of the arachnoid granulations → decreased absorption of CSF → hydrocephalus → normal 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'S-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'S 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

Delirium NEJM 2006 354:11

DIFFERENTIAL DIAGNOSIS

★DIMS★
DRUGS ★ABCD★

- **ALCOHOL**—intoxication, withdrawal, Wernicke–Korsakoff
- **ANTICHOLINERGICS**—atropine, benztropine, scopolamine
- **ANTIDEPRESSANTS**—SSRIs, TCA

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **ANTICONVULSANTS**—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**
- **CARDIAC**—amiodarone, β-blockers, digoxin, diuretics
- **DOPAMINE AGENTS**—amantadine, bromocriptine, levodopa

INFECTIOUS—pneumonia, UTI, meningitis, encephalitis, abscess, sepsis

METABOLIC

- **ORGAN FAILURE**—hepatic, azotemia, hypothyroidism, hypoxia, hypercapnia, hypothermia, hypertensive
- **ELECTROLYTE IMBALANCE**—ketoacidosis, glucose (hypo, hyper), hyponatremia, hypernatremia, hypomagnesemia, hypercalcemia

STRUCTURAL

- **HEMORRHAGE**—subarachnoid, epidural, subdural, intracerebral

DIFFERENTIAL DIAGNOSIS (CONT'D)

- **STROKE**—basilar
- **TUMOR**
- **ABSCESS**

SEIZURES

PATHOPHYSIOLOGY

HOSPITALIZATION—hospitalized patients, particularly the elderly, are at high risk of developing delirium. The prevalence of delirium in geriatric patients on admission to hospital is 14–24%. The estimated incidence is up to 40% on the medical ward, 7–26% for general surgery, 29–42% for vascular surgery, 8–42% for cardiac surgery, and 16–62% for orthopedic surgery

FRAILTY IN ELDERLY—limited reserve so easily tipped over by any event, leading to delirium

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	Usually 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. A majority of patients with delirium fall under this category
- **HYPOACTIVE 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 also prolongs hospitalization and is associated with a poor prognosis and caregiver distress

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**★

1. **ACUTE ONSET AND FLUCTUATING CONFUSION**—abnormal behaviors come and go, ↑/↓ severity

CLINICAL FEATURES (CONT'D)

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 mini-mental status examination (useful for monitoring)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, Ca, urinalysis
- **IMAGING**—CXR, head CT
- **MICROBIOLOGY**—urine C&S, blood C&S (if any fever)

SPECIAL

- **METABOLIC WORKUP**—TSH if suspect thyroid disease, AST, ALT, ALP, bilirubin, INR, PTT, NH_4 if suspect liver disease, Mg, PO_4
- **CARDIAC WORKUP**—ECG, CK, troponin if suspect ACS
- **SEIZURES WORKUP**—EEG

INVESTIGATIONS (CONT'D)

- **DRUG OVERDOSE WORKUP**—medication serum levels (e.g. digoxin, phenytoin salicylate, acetaminophen), alcohol level, osmolality
- **MENINGITIS WORKUP**—lumbar puncture

DIAGNOSTIC ISSUES

PERSISTENT DELIRIUM—if delirium persists despite basic workup, think through differential diagnosis again (VERY CAREFULLY). Also consider dehydration, depression, urinary/fecal retention, abscess

MANAGEMENT

PREVENTION—ensure adequate O_2, fluid and electrolyte balance, pain management, reduction in use of psychoactive drugs, bowel and bladder function, nutrition, early mobilization, prevention of postop complications, appropriate environmental stimuli, and treatment of symptoms of delirium

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 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)

MANAGEMENT (CONT'D)

PHARMACOLOGICAL MEASURES—**neuroleptics** for agitated patient (*haloperidol* 0.5–2 mg PO/IV/SC q4–6h and q1h PRN, *loxapine* 2.5–5 mg PO/SC BID and q6h PRN, *risperidone* 0.25 mg PO BID PRN, *olanzapine* 2.5–5 mg PO daily PRN, *quetiapine* 25 mg PO BID PRN), **benzodiazepines** may precipitate or worsen delirium and should generally be avoided except for patients with alcohol or benzodiazepine withdrawal (*lorazepam* 0.5–1 mg PO/SL daily-QID PRN)

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. 105)
Hypercalcemia (p. 353)
Meningitis (p. 241)
Metabolic Acidosis (p. 77)
Overdose (p. 102)

Falls

JAGS 2000 48:8; NEJM 2003 348:1

DIFFERENTIAL DIAGNOSIS

SYNCOPE—neurogenic, cardiogenic, neurocardiogenic
DROP ATTACKS—transient vertebrobasilar insufficiency
POSTURAL HYPOTENSION
CONFUSION—delirium
DIZZINESS—vertigo, dysequilibrium
FALLS—accidental, imbalance

PATHOPHYSIOLOGY

PREDISPOSITION TO FALLS IN ELDERLY—multifactorial 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

PATHOPHYSIOLOGY (CONT'D)

- **SOMATOSENSORY SYSTEM**—decreased sensation, proprioception, vibration perception
- **MUSCULOSKELETAL SYSTEM**—weakness
- **GAIT INCOORDINATION**—Parkinson's, cerebellar ataxia, stroke, normal pressure hydrocephalus
- **MEDICATIONS** (strongest risk factor for falls)—SSRIs, TCAs, neuroleptics, anticonvulsants, benzodiazepines, class IA antiarrhythmics
- **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, long lies (risk for dehydration, pressure sores, pneumonia, rhabdomyolysis), and death

CLINICAL FEATURES

HISTORY—★**SPLAT**★ **S**ymptoms associated with fall (circumstances, onset, frequency), **P**revious falls, **P**ast medical history, **L**ocation, **A**ctivity preceding fall, **T**oxin (meds), and **T**rauma

PHYSICAL—vitals (postural HR and BP, temperature), cardiovascular (murmurs, rhythm, volume status), respiratory (adventitious sounds), 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)

PERFORMANCE-ORIENTED EVALUATION OF GAIT AND BALANCE

- **TIMED UP AND GO TEST**—rise from chair, walk 10 ft, turn, and return to chair. Should finish in less than 10 s. If takes >20 s, further evaluation required
- **TINETTI'S PERFORMANCE-ORIENTED ASSESSMENT**—easy to administer, incorporates gait, and balance scales to identify high risk of falls, score ≤20/28 predictive of recurrent falls

RATIONAL CLINICAL EXAMINATION SERIES: WILL MY PATIENT FALL? RISK FACTORS FOR FALLS

	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

CLINICAL FEATURES (CONT'D)

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 problems are at higher risk of future falls"

JAMA 2007 297:1

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, glucose, TSH, CK, ESR, urinalysis
- **IMAGING**—head CT

SPECIAL

- **CARDIAC WORKUP**—ECG, Holter monitor if suspect arrhythmia
- **SEIZURES WORKUP**—EEG if suspect seizures
- **NEUROLOGIC WORKUP**—EMG/NCS if significant weakness thought to be related to peripheral lesion

MANAGEMENT

PREVENTION—**education** (proper shoes, avoid hot tubs, drink 1.5–2 L/day, getting up slowly). **Exercise** (balance and gait training, 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)

Osteoporosis

See OSTEOPOROSIS (p. 354)

Urinary Incontinence

CMAJ 1997 157:8; 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

DIFFERENTIAL DIAGNOSIS OF CHRONIC URINARY INCONTINENCE (CONT'D)

STRESS (small volumes with ↑ abdominal pressure)

- **URETHRAL HYPERMOBILITY**—childbirth, menopausal
- **SPHINCTER WEAKNESS**—TURP

OVERFLOW (over-distended bladder, small volumes but continuous leakage, incomplete emptying)

- **BLADDER OUTLET OBSTRUCTION**—BPH, prostate cancer

DIFFERENTIAL DIAGNOSIS OF CHRONIC URINARY INCONTINENCE (CONT'D)

- **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)

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, 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)

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"

JAMA 2008 299:12

INVESTIGATIONS

BASIC

- **LABS**—lytes, urea, Cr, glucose, Ca, urinalysis
- **MICROBIOLOGY**—urine C&S

SPECIAL

- **URODYNAMIC STUDIES**

MANAGEMENT OF CHRONIC URINARY INCONTINENCE

GENERAL MEASURES

- **ABSORPTIVE PADS**—incontinence pad or adult diapers (depends)
- **CATHETERIZATION/DIAPERS**—indwelling catheter, condom catheter, timed collection, intermittent self-catheterization

URGE INCONTINENCE—**behavioral modification, anticholinergic** (↓ detrusor contraction, ↑ bladder volume; *oxybutynin* 2.5–5 mg PO BID–TID or *XL* 5–30 mg PO daily; *tolterodine* 1–2 mg PO BID or *LA* 2–4 mg PO daily). **TCA** (*imipramine* 25–100 mg PO qhs; associated with significant adverse effects, particularly in the elderly). **Estrogen**

STRESS INCONTINENCE—**bladder** training (30–50 pelvic floor exercises/day). **Weight loss** if obesity. **SSRI** (duloxetine hydrochloride). **Intravaginal pessaries/tampons** to exert pressure to provide urethral support

OVERFLOW INCONTINENCE—**α1-antagonist** (only if BPH; *tamsulosin* 0.4–0.8 mg PO daily; *terazosin* 1–10 mg PO qhs; *doxazosin* 1–5 mg PO qhs). **5α reductase inhibitor** (only if BPH; *finasteride* 5 mg PO daily)

OVERFLOW WITH NEUROGENIC BLADDER—**acetylcholine agonist** (↑ bladder contractility; *bethanechol* 10–30 mg PO BID–QID for short term only, may require clean intermittent catheterization)

RESTRICTED MOBILITY—bedside urinal/commode, call bell, prompted voiding

Hearing Impairment

See HEARING IMPAIRMENT (p. 317)

Pharmacological Issues in the Elderly

Lancet 2007 370:9582;
BMJ 2008 336:7644

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-recognitionof 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 dosing)

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—list of 33 drugs that should **always** be avoided (e.g. meperidine, barbiturates, chlorpropamide), drugs that are **rarely appropriate** (e.g. diazepam, cyclobenzaprine), and drugs with **some indications** but are often misused (e.g. indomethacin, amitriptyline, oxybutynin)

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's disease

COMMON ADVERSE DRUG REACTIONS AND DRUG–DRUG INTERACTIONS

CHARACTERISTIC SIDE EFFECTS OF DRUGS FREQUENTLY USED IN THE ELDERLY

Drugs	Adverse effects
α1 blockers (doxazosin)	Falls, orthostatic hypotension, dry mouth
Anticholinergics (diphenhydramine)	Delirium, urinary retention, constipation, dry mouth, blurred vision, postural hypotension
Benzodiazepines (lorazepam)	Falls, confusion
NSAIDs (indomethacin)	Gastrointestinal irritation and hemorrhage, renal impairment, hypertension, heart failure
Sulfonylureas (chlorpropamide)	Hypoglycemia
Tricyclic antidepressants (amitriptyline)	Falls, orthostatic hypotension, sedation, delirium, arrhythmias

COMMON ADVERSE DRUG REACTIONS AND DRUG–DRUG INTERACTIONS (CONT'D)

WARFARIN INTERACTIONS—many medications implicated in increasing bleeding risk (↑ INR) with warfarin. Most severe interactions described with trimethoprim–sulfamethoxazole, erythromycin, amiodarone, propafenone, ketoconazole, fluconazole, itraconazole, metronidazole. Antibiotics, acetaminophen, steroids, and ginkgo biloba may also increase bleeding risk

COMMON ADVERSE DRUG REACTIONS AND DRUG–DRUG INTERACTIONS (CONT'D)

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

Notes

Notes

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PALLIATIVE CARE

Section Editors:
Dr. Sriram Yennurajalingam and Dr. Eduardo Bruera

Palliative Care-Specific Issues

INTRODUCTION

DEFINITION—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."

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, particularly at the end of life, inevitably involves variable degrees of physical, psychosocial, and existential suffering

REFERRAL TO PALLIATIVE CARE—while palliative care is commonly associated with end-of-life care, it is

INTRODUCTION (CONT'D)

most effective when incorporated early in the disease trajectory of life-limiting illnesses. Timely incorporation of palliative care principles can help to optimize symptom management, improve psychosocial interventions, enhance coordination of care, and facilitate patients' transition from active treatment to end-of-life care. Thus, patients living with incurable life-threatening conditions, such as advanced cancer, COPD, end-stage cardiac failure, stage V chronic kidney disease, progressive liver failure, and AIDS would benefit from palliative care involvement

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 symptom 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%

JPSM 2006 31:1

SYMPTOM COMPLEX AND ASSESSMENT (CONT'D)

COMPREHENSIVE PALLIATIVE CARE ASSESSMENT—given the intricate nature of interaction between physical, psychosocial, and existential, it is important to perform regular screening to accurately assess and manage the symptoms

- **SYMPTOM BATTERY**—Edmonton Symptom Assessment Scale (ESAS, Likert scale of 1–10 for 10 symptoms including pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, and sleep), global assessment scale
- **PAIN**—Edmonton Pain Classification System
- **DELIRIUM**—Mini-Mental State Examination, Memorial Delirium Assessment Scale

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_14,

SYMPTOM COMPLEX AND ASSESSMENT (CONT'D)

- **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 decision making at the end of life (e.g. discharge location, initiation, or termination of treatment)

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

TREATMENTS—**expressive/supportive therapy**, **antidepressants** (*mirtazapine* 15–45 mg PO qhs, *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 patients' 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 and the emotional burden of seeing their loved ones suffer. Moreover, many patients develop delirium close to the end of life, necessitating substitute decision making

INTERVENTIONS FOR CAREGIVERS—specific interventions may include (1) educating caregivers regarding signs and symptoms of dying so they can be more prepared, (2) supportive-expressive counseling for family members during split visits, (3) family meetings to help update all parties involved and to define goals of care, (4) bereavement counseling and support groups

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. 399) covers a number of basic techniques in breaking bad news. For further information, readers

COMMUNICATION IN THE PALLIATIVE SETTING (CONT'D)

are referred to a recent 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

Cancer 2008 113:7

DECISION MAKING IN THE PALLIATIVE SETTING

Patients with advanced disease have to face many difficult decisions which 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

SPIRITUAL NEEDS OF THE DYING

- **SEARCH FOR MEANING OF LIFE**—provide time for personal reflection, reminiscing, and life review
- **TO DIE APPROPRIATELY**—allow for interpretation of death, explore beliefs about pain and suffering
- **TO FIND HOPE THAT EXTENDS BEYOND THE GRAVE**—explore religious or other belief systems in order to give the reassurance of immortality, religious ritual

FACILITATION—listen, acknowledge, explore, reflect, integrate

SPIRITUAL HISTORY ★SPIRIT★

- **S**piritual belief system
- **P**ersonal spirituality
- **I**ntegration with a spiritual community
- **R**itualized practices/restrictions
- **I**mplications for medical care
- **T**erminal events planning

PITFALLS—try to solve patient's problems or resolve unanswerable questions, go beyond physician's

SPIRITUALITY IN THE PALLIATIVE SETTING (CONT'D)

expertise and role, or imposing own religious beliefs, provide premature reassurance

RESOURCES—caregivers, spiritual counselors, chaplains, faith community

JAMA 2006 296:11

DIAGNOSIS OF DYING

CHALLENGE—clinicians 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 dying can be made, knowing that there may still be a small chance of recovery in some patients

FEATURES OF DYING PATIENTS

- **CANCER**—bed bound, semicomatose, only able to take sips of fluid, unable to take oral drugs
- **HEART FAILURE**—previous admissions with worsening heart failures, no identifiable reversible precipitant, medications optimized, deteriorating renal function, failure to respond within 2–3 days to

DIAGNOSIS OF DYING (CONT'D)

appropriate changes in diuretic or vasodilator drugs. The diagnosis of dying is particularly difficult to make because worsening heart failure may be associated with secondary causes and could potentially be reversible once treated

OVERALL—no specific criteria for diagnosis of dying, but based on overall clinical impression. Helpful if other members of the inter-professional team agree that the patient is going to die soon

MEDICATION ADMINISTRATION IN THE PALLIATIVE SETTING

SUBCUTANEOUS ROUTE—preferred over intravenous route because it is associated with greater comfort, fewer complications, less maintenance, and medications can be given at home. Disadvantages include less rapid onset of medication effects. This route may not be suitable for certain medications

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)

SOMATIZATION

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—about 80% experience some form of pain during their course of illness; 80% due to tumor; 20% due to cancer therapy, and >5% due to other unrelated diseases

TOLERANCE—normal pharmacophysiological effect in which increasing doses of opioids are required to provide the same analgesic effect over time

PATHOPHYSIOLOGY (CONT'D)

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 opioid dose is required to prevent withdrawal symptoms

ADDICTION—abnormal psychopathological compulsion to use a substance affecting daily function. Although the great 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 for developing opioid dependence/addiction. These individuals may be prescribed an ever escalating dose of opioid, without adequate pain control. It is important to minimize use of opioids and to emphasize the use of analgesics to maintain function rather than to treat pain

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, TCAs, antiepileptics, venlafaxine

PATHOPHYSIOLOGY (CONT'D)

CAUSES OF INTRACTABLE CANCER PAIN—disease progression, neuropathic pain, bone pain, breakthrough pain, delirium, substance use, delirium, depression/anxiety, and somatization (i.e. psychosocial/existential distress)

MANAGEMENT

FIRST LINE (non-opioids)—*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 postoperative pain. Consider ceiling dose effect. Common side effects include gastritis, gastric ulcer, 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

SECOND LINE (weak opioids)—*codeine* 30–60 mg PO q4h, *acetaminophen/codeine* 325 mg/30 mg 1–2 tabs PO q4h, *acetaminophen/hydrocodonè* 325 mg/5–10 mg PO q4h, *tramadol* 50–100 mg PO q4–6 h

THIRD LINE (strong opioids)—*morphine* 5 mg PO q4h and 2.5 mg q1h PRN, *hydromorphone* 2 mg PO q4h and 1 mg q1h PRN, *oxycodone* 5 mg PO q4h and 2.5 mg q1h PRN, fentanyl (only if pain stable), methadone

PROCEDURES—surgical interventions (celiac plexus/splanchnic block, subarachnoid block, cordotomy, epidural/intrathecal infusion, vertebroplasty) may be added to any line as needed

ADJUVANT THERAPIES

- **MEDICATIONS MITIGATING ADVERSE EFFECTS OF OPIOIDS**—start bowel protocol (*senna* 2 tab PO qhs) and anti-nausea (*metoclopramide* 10 mg PO q4h) at the same time of opioids. *Methylphenidate* 5–10 mg PO qAM and 5–10 mg qnoon may be used for opioid sedation
- **TRICYCLIC ANTIDEPRESSANTS** (neuropathic pain)—*nortriptyline* 25 mg PO qhs initially, increase by 25 mg/day every week if tolerated, target 75 mg PO qhs-BID
- **ANTICONVULSANTS** (neuropathic pain, opioid-induced myoclonus)—*gabapentin* 100–300 mg PO TID, *pregabalin* 100 mg PO TID, *carbamazepine* 100 mg PO BID, *phenytoin* 100 mg PO TID
- **ANTISPASMODICS**—*baclofen* 10 mg PO TID muscle for spasms
- **ANTINEOPLASTIC TREATMENTS** (cancer pain)—chemotherapy, radiation (external beam radiation for focal tumor infiltration, Strontium^{89}, or Samarium^{153} 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

MANAGEMENT (CONT'D)

- **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). Need to increase scheduled dose if $\geq$3 breakthroughs/day
- **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
- **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 nausea, somnolence, dry mouth, pruritus, and constipation. While these side effects generally 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, cognitive impairment, and respiratory depression. Long-term side effects include hypogonadism, sexual dysfunction, osteoporosis, immunosuppression, altered renal function, and peripheral edema. Methadone is also associated with QT prolongation at high doses
- **TREATMENT OF OPIOID TOXICITIES**—ensure adequate hydration, opioid rotation, exclude underlying aggravating metabolic factors (uremia, liver failure, hypercalcemia), and symptom management (e.g. treat nausea and constipation)

TREATMENT ISSUES (CONT'D)

OPIOID ROTATION—if severe side effects (sedation, nightmares, hallucinations, myoclonus), switch to another opioid with a 25–50% dose reduction. If poor analgesic response, switch without dose reduction

EQUIANALGESIC TABLE

	Ratio[a]	Starting	q1h PRN	Route
Codeine[b]	0.1	30–60 mg q4h PRN	–	PO/PR
Hydrocodone[c]	0.5–1	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
Oxycodone[d]	1.5	5 mg q4h	2.5 mg	PO/PR/SC
Fentanyl drip	100	10–50 μg/hr	25 μg	IV
Methadone	2–20[e]	5 mg q8–12 h	–	PO/PR/IV

[a] Higher number indicates greater potency
[b] Tylenol #1–3 = acetaminophen plus codeine with or without caffeine
[c] Vicodin, Lortab, Norco = acetaminophen plus hydrocodone
[d] Percocet = acetaminophen plus oxycodone
[e] See methadone conversion table below

TREATMENT ISSUES (CONT'D)

FENTANYL DURAGESIC CONVERSION

Fentanyl TD (μg/h)	Morphine PO (mg)
25	45–134
50	135–224
75	225–314
100	315–404
125	405–494
150	495–584

- **CONVERSION BETWEEN FENTANYL PATCH (IN μG/H) AND ORAL MORPHINE (IN MG/DAY)**—consider using a ratio of 3.6, e.g. fentanyl patch of 25 μg/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 mg/day	2:1
30–99 mg/day	4:1
100–299 mg/day	8:1
300–499 mg/day	12:1
500–999 mg/day	15:1
>1000 mg/day	20:1 or greater

TREATMENT ISSUES (CONT'D)

2. **DETERMINE THE SCHEDULE**

	Day 1	Day 2	Day 3	Day 4
Morphine (MS)	66% TDD	33% TDD	0% TDD	0% TDD
Methadone (ME)	33% TDD	66% TDD	100% TDD	100% TDD
Break through	10% w/morphine	10% w/morphine	10% w/morphine	10% w/methadone

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 everyday. Due to its complex pharmacology, methadone should only be prescribed by clinicians familiar with this drug

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 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)
- **NEUROPATHIC PAIN**—opioids are effective against neuropathic pain. Methadone is theoretically more useful because of its NMDA antagonist activity. Also consider use of non-opioids such as gabapentin, pregabalin, carbamazepine, venlafaxine, and TCAs

Delirium

See DELIRIUM (p. 380)

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**
- **THROBBING PAIN**
- **HEAD**—depression, anxiety
- **ELECTROLYTES**—Na, K, Mg, Ca
- **NUTRITIONAL FAILURE**—anorexia–cachexia
- **INACTIVITY**
- **COMORBIDITIES**—cardiac/pulmonary failure, hepatic/renal failure, neurologic/endocrine failure such as 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. Note that fatigue has not been well studied in other palliative care settings, although the underlying pathophysiology and treatments are similar to cancer-related fatigue

PATHOPHYSIOLOGY (CONT'D)

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, 75% with metastatic disease, and >90% at the end of life. It is also underdiagnosed 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**—CBCD, lytes, urea, Cr, glucose, TSH, Mg, Ca, albumin

MANAGEMENT

NON-PHARMACOLOGIC—exercise for at least 30 min/day (strongest evidence), psychosocial interventions, nutritional counseling, sleep therapy

PHARMACOLOGIC—*methylphenidate* 5 mg PO qAM and noon, and 5 mg q4h PO PRN, up to 20 mg/day; *modafinil* 200 mg PO daily, corticosteroids (*dexamethasone* 4 mg PO BID)

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

DIFFERENTIAL DIAGNOSIS OF ACUTE DYSPNEA (CONT'D)

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 may not correlate with physical findings, such as tachypnea, wheezing, cyanosis, and O_2 saturation

INVESTIGATIONS

BASIC

- **LABS**—CBCD, 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 (particularly effective if add cool cloth to fan), open windows, relaxation techniques, distraction therapy
PHARMACOLOGICAL—supplemental **O_2** if hypoxemic, **opioids** (similar for pain control, although the starting doses are usually lower, e.g. 5–10 mg PO. If already on opioids, may increase dose by 25%. No difference shown between q4h dose and infusion), **corticosteroids** (*dexamethasone* 4–8 mg PO BID), **bronchodilators**, **diuretics** (furosemide SC if HF), **non-invasive positive pressure ventilation** (BIPAP) may be beneficial for patients with significant muscle weakness. **Palliative sedation** as a last resort
PROCEDURES—if significant pleural effusion, consider thoracentesis, pleurodesis, or PleurX 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

TREATMENT ISSUES (CONT'D)

- **INDICATIONS**—when suffering (delirium/agitation, dyspnea, pain) persists despite all other means; not to be confused with euthanasia. Must ensure detail discussion with patient (if possible), family, and palliative care team prior to initiation of treatment
- **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)

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 *glycopyrrolate* 0.2 mg SC q4–6h or 0.4–1.2 mg/day SC/IV, or *hyoscine hydrobromide/scopolamine* 0.8 mg SC initially, then 0.2–0.6 mg SC q1h PRN, total 0.8–2 mg/day (note: *hyoscine hydrobromide/Scopolamine* is frequently confused with hyoscine butylbromide/Buscopan, which is used to relieve GI/bladder spasms and is dosed very differently)
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 midbrain 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

BLOOD TESTS—CBCD, lytes, urea, Cr, glucose, Ca, Mg, PO_4, cortisol
URINE TESTS—urinalysis
MICROBIOLOGY—urine C&S
IMAGING—CXR, AXR (rule out bowel obstruction and constipation)

Related Topic
Nausea and Vomiting (p. 111)

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** (more D2 blockade)—switch *metoclopramide* to SC infusion 60–120 mg/day. Also consider adding *haloperidol* 1–2 mg SC q8–12h and q1h PRN
- **FURTHER OPTIONS**
  - **H1 BLOCKADE**—*dimenhydrinate* 50 mg PO/SC/IV q4h or *diphenhydramine* 50 mg PO/SC/IV q4h
  - **STEROIDS**—*dexamethasone* 4–10 mg PO/SC/IV BID
  - **NEUROLEPTICS**—*methotrimeprazine* 5–25 mg PO TID, *chlorpromazine* 10–25 mg PO q4h
  - **CANNABINOID AGONISTS**—*nabilone* 1 mg PO daily may also be considered
  - **5HT3 ANTAGONISTS**—*ondansetron* 8 mg PO daily-TID for chemotherapy-induced nausea and vomiting
  - **PROMOTILITY AGENTS**—*domperidone* 10 mg PO TID-QID, *cisapride* 10 mg PO TID–QID (special release)

SPECIFIC ENTITIES

BOWEL OBSTRUCTION IN THE PALLIATIVE SETTING

- **PATHOPHYSIOLOGY**—3% of all advanced cancers, particularly ovarian (11–42%), colorectal (5–24%), gastric, endometrial, prostate, and bladder. If inoperable, median survival is only 2 months
- **CAUSES**—**intraluminal** (mass, constipation, intussusception), **luminal** (carcinomatosis causing dysmotility, bowel infarction), and **extraluminal** (compression, adhesions)
- **CLINICAL FEATURES**—nausea and vomiting, abdominal distension and pain, obstipation, absent bowel sounds
- **DIAGNOSIS**—AXR
- **MANAGEMENT**
  - **SUPPORTIVE MEASURES**—intravenous fluids, bowel rest, pain control (opioids, hyoscine butylbromide/buscopan), antiemetics, NG suction (clump when output $<$100 cc/day and ensure no further N&V before removal). Consider venting PEG tube insertion sooner than later
  - **ANTI-SPASMODIC/ANTISECRETORY AGENTS**—antimuscarinic agents (*hyoscine butylbromide* 10–20 mg PO/IV/IM TID, atropine), somatostatin analogues (*octreotide* 10 μg/h IV or 50 μg SC q8h)
  - **BYPASS OBSTRUCTION**—surgery, stent placement, venting gastrostomy, corticosteroids to decrease local inflammation

Constipation in the Palliative Setting

DIFFERENTIAL DIAGNOSIS

★DUODENUM★

DIET—low fiber, dehydration

ψSYCHIATRY—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's, 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

PATHOPHYSIOLOGY (CONT'D)

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—based on flat abdominal X-ray. Divide into 4 quadrants (ascending, transverse, descending, and rectosigmoid colon). Rate amount

DIAGNOSTIC ISSUES (CONT'D)

of stool in each quadrant from 0 to 3. A total score >6/12 suggests constipation

Related Topic
Constipation (p. 126)

MANAGEMENT

PREVENTION IS KEY—a prescription for laxatives (e.g. *senna* 1–2 tabs PO qhs 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**—in order of increasing potency: *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 *Golytely* 4 L PO/NG ×1 for severe constipation
- **μ-OPIOID RECEPTOR ANTAGONISTS**—indicated for patients with opioid-induced constipation despite at least 3 days of laxatives. *Methylnaltrexone* 12 mg SC ×1 d, repeat every other day as needed. These antagonists are peripheral acting, and thus do not affect pain control which happens centrally
- **MANUAL DISIMPACTION**—as last resort. 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

TREAT UNDERLYING CAUSE—stop potentially constipation-causing medications if possible. Methadone and fentanyl *may be* less constipating than other opioids (controversial)

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's

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. 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)

CONTRIBUTORS OF WEIGHT LOSS—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

DIFFERENTIAL DIAGNOSIS (CONT'D)

REACTIVE DEPRESSION
EVACUATION—constipation
XEROSTOMIA—taste change
IATROGENIC—chemotherapy, radiation to esophagus
ILLNESS—underlying disease
ACID RELATED—GERD

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, Ca, PO_4, 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

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 occult blood, 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 things they enjoy in small and frequent portions, without have having to worry too much about their nutritional content. Dietician 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, but not quality of life or survival. However, it is associated with increased thromboembolic risk, swelling, impotence, and GI upset). **Serotonin antagonists**

ANTICATABOLIC AGENTS (antimetabolic and anticytokine)—less effective than steroids and megestrol and/or not enough evidence

ANABOLIC AGENTS (primarily hormonal)—less effective and/or not enough evidence

CANNABINOIDS—not helpful in cancer patients but may be useful in chronic inflammatory conditions such as HIV/AIDS

OTHER POTENTIAL AGENTS—melatonin, mirtazapine, thalidomide, lenalidomide are considered investigational at this time

TREATMENT OF CONTRIBUTORS—consider treatment of nausea with antiemetics, mucositis with lidocaine vicous 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

TREATMENT ISSUES FOR ANOREXIA–CACHEXIA

MEGESTROL ACETATE VS. CORTICOSTEROIDS—megestrol 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 should be taken into consideration. Corticosteroids may be useful for short- term (i.e. days to weeks) use, particularly if other symptoms (e.g. pain, nausea) are present. Long-term use of steroid should be avoided due to side effects. Investigational agents include *melatonin* 6–20 mg PO daily which has been shown to be effective in preventing and treating cancer cachexia in open-labeled trials

Related Topics
Nausea and Vomiting (p. 111)
Supplemental Nutrition (p. 406)

Communication Issues

COMMUNICATION TECHNIQUES

1. **ASSESS PATIENT'S UNDERSTANDING** of their disease and their expectations before sharing information
2. **"ASK-TELL-ASK" APPROACH**—if information is sensitive, ask for patient's permission before starting, then share information tailored to her intellectual comprehension and emotional resilence and assess her 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

DISCUSSING RESUSCITATION STATUS

The following overview is based on JCO 2001 19:5, with a number of citations from the article

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 more ill?"
- "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?"
- "So, what you are saying is you want to be as comfortable as possible when the time comes."
- "What I hear you saying is you do not want us to 'call a code' if it would not do any good."
- "What you have said is 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."

DISCUSSING RESUSCITATION STATUS (CONT'D)

- "Tell me more about how you are feeling."
- "You seem angry."

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/ 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. Please help us to determine what guidelines will be for deciding whether to remain on life support or not if you were not able to participate in the discussion at that time."

JCO 2001 19:5

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 worry 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 matter to discuss. Do you feel ready for this discussion?"

BREAKING BAD NEWS—THE GENTLE ART OF TRUTH TELLING (CONT'D)

- "Would you like me to tell you everything? Or would you prefer a more general overview?"
- "Some people like a whole lot of details, others do not. What do you like?"

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."

BREAKING BAD NEWS—THE GENTLE ART OF TRUTH TELLING (CONT'D)

- "Many people feel frustrated and sad... Is this your experience?"
- "I'd like to check so I know where you're at."

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 with any questions."

Oncologist 2000 5:4

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 patients are defined as predicted survival 3–12 months; far advanced cancer patients are defined as predicted survival <3 months

PROGNOSTIC FACTORS

CLINICIAN PREDICTION OF SURVIVAL—clinician estimation of survival (generally 2–5$\times$ overestimation)

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
Death and Dying (p. 391)
Discussing Prognosis (p. 400)

PROGNOSTIC TOOLS

PALLIATIVE PROGNOSTIC SCORE (PaP)

- **CLINICIAN PREDICTION OF SURVIVAL**—$>$12 weeks=0, 11–12 weeks=2, 7–10 weeks=2.5, 5–6 weeks=4.5, 3–4 weeks=6, 1–2 weeks=8.5
- **KARNOFSKY PERFORMANCE STATUS**—$\geq$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
- **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**—$\geq$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%

PROGNOSTIC TOOLS (CONT'D)

PALLIATIVE PERFORMANCE SCALE (PPS)

PPS	Mobility	Activity and evidence of disease	Self-care	Intake	LOC
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	Minimal to sips	Full or drowsy ± confusion
20%	Totally bed bound	Unable to do any activity Extensive disease	Total care	Mouth care only	Full or drowsy ± confusion
10%	Totally bed bound	Unable to do any activity Extensive disease	Total care		Drowsy or coma ± confusion
0%	Dead	–	–	–	–

J Pall Care 2007 23:4

Notes

15
NUTRITION

Section Editor: Dr. Raj Padwal

Obesity

NEJM 2007 356:21; NEJM 2008 358:18

COMPLICATIONS AND ASSOCIATED DISORDERS

ENDOCRINE

- **INSULIN RESISTANCE**—hyperinsulinemia, prediabetes, type 2 diabetes
- **REPRODUCTION**—irregular menses, anovulatory cycles, infertility

CARDIOVASCULAR—hypertension, dyslipidemia (↑ chol, ↑ LDL or normal with small, dense particles, ↑ VLDL, ↑ TGL, ↓ HDL), coronary artery disease, heart failure, stroke

RESPIRATORY

- **SLEEP APNEA**
- **OBESITY-ASSOCIATED HYPOVENTILATION SYNDROME** ($PaCO_2 \geq 45$ mmHg)—↓ 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

GU—incontinence, kidney stones, glomerulopathy

MSK—osteoarthritis

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'S LYMPHOMA**
- **MULTIPLE MYELOMA**

PSYCHOSOCIAL—↓ education, ↓ employment, depression

PATHOPHYSIOLOGY

BODY MASS INDEX (BMI, weight/height^2)—underweight <18.5 kg/m^2, normal 18.5–24.9 kg/m^2, overweight 25–29.9 kg/m^2, obesity $\geq$30–39.9 kg/m^2, severe or morbid obesity ≥ 40 kg/m^2

PATHOPHYSIOLOGY (CONT'D)

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.]

Use Europid cutoff points for South and Central American, sub-Saharan African, Eastern Mediterranean, and Middle Eastern populations until more specific data are available

BASAL ENERGY EXPENDITURE—approximately 22 kcal/kg/day [10 kcal/lb/day] is required for weight maintenance (e.g. 1540 kcal is the basal energy need for a 70 kg [154 lb] adult)

INVESTIGATIONS

BASIC

- **LABS**—CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, albumin, fasting glucose, fasting lipid profile, HbA1C

SPECIAL

- **CARDIAC WORKUP**—after history and physical, consider ECG. Stress test if indicated
- **SLEEP APNEA WORKUP**—sleep study if symptoms of obstructive sleep apnea
- **OBESITY HYPOVENTILATION WORKUP**—ABG and PFT to demonstrate hypercarbia

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 minimal initial goal, as this correlates with improvement in comorbidities. Failing that, weight maintenance (no change from baseline weight) is the goal. Consult **dietitian** for dietary/behavior modification. **Exercise** (at least 150 min of physical activity/week). Consult **psychologist** if psychological issues

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_15,

MANAGEMENT (CONT'D)

(depression, abuse, binge eating) are major barriers to weight loss success

DRUG THERAPY—consider for patients with BMI >30 kg/m^2 or BMI >27 kg/m^2 if comorbid conditions. Aim to reduce at least >2 kg [>4.4 lbs] in first month, and >5% of initial body weight in 3–6 months. **Pancreatic lipase inhibitor** reduces fat absorption (*orlistat* 120 mg PO TID ac meals). **NE/5HT reuptake inhibitor** induces satiety (*sibutramine* 10–15 mg PO daily). If drug therapy successful, indefinite use should be considered

SURGERY—consider for patients with BMI ≥40 kg/m^2 or BMI ≥35 kg/m^2 if comorbid conditions. Surgery is the only treatment demonstrated to reduce mortality (**NEJM 2008 375:8**). **Gastric restriction procedures** (gastric banding (adjustable band squeezes and restricts upper gastric area), gastroplasty (stapling the stomach to reduce size). **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)

RISK REDUCTION—**lipid control** (see HYPERLIPIDEMIA p. 61). **Blood pressure control** (see HYPERTENSION p. 57). **Glycemic control** (see DIABETES p. 337)

TREATMENT ISSUES

OVERALL APPROACH

1. Identify overweight or obese adults
2. If BMI >25 kg/m^2, conduct clinical and laboratory investigations (heart rate, blood pressure, fasting glucose, lipid profiles), screen for depression, eating and mood disorders, and treat comorbidities and other health risks if present
3. Assess readiness to change behaviors
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)

TREATMENT ISSUES (CONT'D)

- **NUTRITION**—reduce energy intake by 500–1000 kcal/day
- **PHYSICAL ACTIVITY**—initially 30 minutes of moderate intensity 3–5×/week. Eventually ≥60 min on most days
- **COGNITIVE BEHAVIORAL THERAPY**

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/m^2 plus risk factors or BMI ≥30 kg/m^2. Consider if patient has not lost 0.5 kg/week [1.1 lb/week] by 3–6 months of lifestyle changes
   - **BARIATRIC SURGERY**—if BMI ≥35 kg/m^2 plus risk factors or BMI ≥40 kg/m^2. Consider if other weight loss attempts have failed. Requires lifelong monitoring

Canadian Clinical Practice Guidelines 2006
CMAJ 2006 176:8

PREDICTIVE FACTORS FOR LONG-TERM WEIGHT CONTROL FROM THE NATIONAL WEIGHT CONTROL REGISTRY IN THE USA—low fat diet, regular self-monitoring of food intake and weight, physical activity (35 min of jogging per day or 80 min of brisk walking per day). Long-term follow-up and close patient–physician relationship important

Related Topics
Cardiovascular Disorders (p. 25)
Diabetes Mellitus (p. 337)
Hyperlipidemia (p. 61)
Hypertension (p. 57)
Fatty Liver (p. 128)
Sleep Apnea (p. 17)

Malabsorption Syndromes

See MALABSORPTION SYNDROMES (p. 125)

Anorexia–Cachexia

See ANOREXIA–CACHEXIA (p. 397)

Vitamin B12 Deficiency

DIFFERENTIAL DIAGNOSIS

DIET—strict vegans
GASTRIC—pernicious anemia, gastrectomy, gastritis, achlorhydria
PANCREATIC—insufficiency
SMALL BOWEL—malabsorption syndromes, ileal resection, Crohn's blind loops, bacterial overgrowth
DRUGS—neomycin, metformin, proton pump inhibitors, N_2O

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. 146)
Malabsorption (p. 125)
Vitamin Deficiencies (p. 126)

CLINICAL FEATURES

HISTORY—anemia, dyspnea, chest pain, fatigue, weight loss, dementia, paresthesia, weakness, falls, diet history, past medical history (gastritis, IBD, pancreatic disorders, bowel resection, alcoholism), medications
PHYSICAL—weight loss, lemon-colored skin tone (anemia and jaundice), dementia, decreased visual acuity, optic atrophy, Lhermitte's 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

CLINICAL FEATURES (CONT'D)

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**—CBCD (megaloblastic anemia), peripheral smear (hypersegmented neutrophils), pancytopenia, bilirubin (↑), LDH (↑), vitamin B12, RBC folate

SPECIAL

- **SERUM ANTI-INTRINSIC FACTOR ANTIBODY**—sens 50–70%
- **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
- **SHILLING'S TEST**—not usually performed but may help to sort out etiology
  - **FIRST STAGE**—administer radiolabeled cyanoCbl 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 possibilities 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 achlorydria will be unable to split Cbl from food proteins and urinary excretion of Cbl will be <10%

MANAGEMENT

TREAT UNDERLYING CAUSE—diet adjustment. ***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. Hematologic parameters improve within days to weeks; neurological

MANAGEMENT (CONT'D)

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

INTRODUCTION

This chapter provides an overview of nutritional assessment, hospital diet types, enteral feeds, and supplemental parenteral nutrition

GENERAL ADVICE—for patients with significant under-nourishment or at risk of developing malnourishment (e.g. ICU patients, head and neck or esophageal cancer patients), consult dieticians for nutritional assessment and guidance regarding supplemental nutrition

NUTRITIONAL ASSESSMENT

FACTORS INFLUENCING ENERGY REQUIREMENTS—age, previous nutritional status, comorbidities (sepsis, obesity), activity

IDEAL BODY WEIGHT CALCULATIONS

- ♂ **IBW** (kg)=(height in cm – 152 cm)×1.1+ 48.2 kg or in lbs=(height in inches – 60 in.)×6+106 lbs
- ♀ **IBW** (kg)=(height in cm –152 cm)×0.9+45.5 kg or in lbs=(height in inches – 60 in.)×5+100 lbs

DAILY ENERGY REQUIREMENTS

- **14 KCAL/KG [6.4 KCAL/LB] BODY WEIGHT**—BMI >40 kg/m^2
- **21 KCAL/KG [9.5 KCAL/LB] BODY WEIGHT**—BMI 30–39 kg/m^2
- **25 KCAL/KG [11.4 KCAL/LB] BODY WEIGHT**—single organ failure, heavily sedated
- **30 KCAL/KG [13.6 KCAL/LB] BODY WEIGHT**—multi-organ failure, sepsis, trauma, postop major surgery

DAILY PROTEIN REQUIREMENTS

- **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, hepatic encephalopathy
- **1.2–1.4 G/KG [0.55–0.64 G/LB] BODY WEIGHT**—multi-organ failure, hemodialysis, sepsis, major trauma/surgery, closed head injury, malnutrition
- **1.4–2.0 G/KG [0.64–0.91 G/LB] (IDEAL) BODY WEIGHT**—multiple surgeries, trauma, severe burns, long bone fractures. If BMI >30 kg/m^2, 1.5 g/kg [0.68 g/lb] IBW

DAILY LIPID REQUIREMENTS

- **0.8–1 G/KG [0.36–0.45 G/LB] (IDEAL) BODY WEIGHT**

NUTRITIONAL ASSESSMENT (CONT'D)

DAILY CARBOHYDRATE REQUIREMENTS

- **2–4 MG/KG/MIN** (start low and go slow if concern regarding refeeding syndrome)

HOSPITAL DIET TYPES

STANDARD—regular, full fluid, clear fluid

THERAPEUTIC—heart healthy, diabetic, renal (predialysis, hemodialysis, peritoneal dialysis), sodium restricted (2 g Na, 4 g Na), fiber restricted, high protein/calorie

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

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 and immunologically favorable compared to total parenteral nutrition

CONTRAINDICATIONS—hemodynamically unstable, severe ileus, bowel obstruction, UGI bleed, distal anastomosis, NG output >1 L/24 h, uncontrollable nausea, vomiting and/or diarrhea, short gut, radiation enteritis

ROUTES FOR ENTERAL FEEDS

NASOGASTRIC/KAOFEED/OROGASTRIC TUBE—<6 weeks. Risk of aspiration

NASOJEJUNAL TUBE—<6 weeks. Less chance of aspiration/pneumonia

GASTROSTOMY TUBE—>6 weeks. Risk of aspiration

JEJUNOSTOMY TUBE—>6 weeks. Decreased aspiration risk

ADMINISTRATION OF ENTERAL FEEDS

CONTINUOUS—usually given over 24 h. Compared to bolus feed, decreased aspiration risk, and better

ADMINISTRATION OF ENTERAL FEEDS (CONT'D)

glycemic control. Start full strength formula at 25 mL/h, increase by 25 mL q4h to goal rate. 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

BOLUS/INTERMITTENT—for patients more mobile. More physiologic. Start with 1 can (250 mL) over 30–60 min 4×/day

ENTERAL NUTRITION FORMULAS

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

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. Used for patients with malabsorption problems, severe diarrhea

PULMOCARE—1.5 kcal/mL, 0.063 g protein/mL. Low carbohydrate to lower CO_2 production. For patients with COPD or CO_2 retention

ADDITIONS TO ENTERAL FEEDS

PECTIN—20 mL BID. Soluble fiber to aid in 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, medications, gastroenteritis, *Clostridium difficile*

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

COMPLICATIONS OF ENTERAL FEEDS (CONT'D)

agents 30 min before feeding (*metoclopramide* 10 mg PO QID), ensure bowel routine

PARENTERAL NUTRITION OVERVIEW

TOTAL PARENTERAL NUTRITION (TPN)

- **INDICATIONS**—unusable GI tract for at least 5–7 days. Severe pancreatitis, bowel resection/obstruction/fistula without distal feeding access, intractable diarrhea/malabsorption/vomiting, acute GI bleed, failure of enteral nutrition to meet nutritional feeds, short gut, prolonged ileus
- **CONTRAINDICATIONS**—GI tract usable within 3–5 days/dependence on TPN <5 days, well-nourished patient with minimal stress or trauma where GI tract usable in <7 days, non-survivable injury/illness, aggressive support not desired, risks of TPN outweigh benefits
- **COMPLICATIONS**—no GI tract mucosal growth, no maintenance of gut barrier, metabolic disturbances if overfeeding (hyperglycemia, cholestasis/hepatic steatosis, electrolyte imbalances), line sepsis

PERIPHERAL PARENTERAL NUTRITION (PPN)—short-term use only as nutritionally inadequate; addition of low-dose heparin and hydrocortisone to prevent line thrombosis; must be <1000 mOsm

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

ELECTROLYTES—Na (60–150 mmol/day), K (30–80 mmol/day), Ca (5–15 mmol/day), Mg (4–8 mmol/day), PO_4 (15–30 mmol/day)

MICRONUTRIENTS—multivitamin solution (10 mL/day), vitamin K (10 mg/week) as required, trace element solution (1 mL/day), acetate as required

REFEEDING SYNDROME

RISK FACTORS—severe malnutrition, anorexia nervosa, cancer, alcoholism, severe unintentional weight loss

MECHANISM—carbohydrate administration leading to a sudden shift from fat to carbohydrate metabolism → ↑ insulin secretion → stimulates cellular uptake of phosphate → ↓ Mg, ↓ PO_4, ↓ K

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, PO_4 daily ×3 days sand replete PRN), monitor glycemic control

Notes

16
OBSTETRIC MEDICINE

Section Editor: Dr. Winnie Sia

Preeclampsia/Eclampsia/HELLP Syndrome

DIFFERENTIAL DIAGNOSIS OF HYPERTENSION IN PREGNANCY

PREECLAMPSIA—new onset or worsening hypertension, ± proteinuria (≥300 mg/day or ≥30 mg/mmol spot urine protein to creatinine ratio), ± adverse clinical signs or symptoms or abnormal labs. A disease >20 weeks gestation

ECLAMPSIA—preeclampsia with generalized tonic clonic seizures

HELLP SYNDROME—a variant of preeclampsia with **H**emolysis (i.e. microangiopathic hemolytic anemia), **E**levated **L**iver enzymes (i.e. RUQ or epigastric pain), and **L**ow **P**latelets

PREEXISTING HYPERTENSION—BP >140/90 mmHg prior to 20th week of gestation, complicates 3–5% of pregnancies, 20% risk of developing preeclampsia

PREECLAMPSIA SUPERIMPOSED UPON PREEXISTING HYPERTENSION—new-onset proteinuria in women with preexisting hypertension or worsening of blood pressure despite 3 antihypertensive medications

GESTATIONAL HYPERTENSION—hypertension ≥20 weeks without proteinuria without adverse effects

Related Topics
Hypertension (p. 57)
Proteinuria (p. 74)
Seizures (p. 309)

PATHOPHYSIOLOGY

DEFINITION OF HYPERTENSION IN PREGNANCY—diastolic BP ≥90 mmHg

RISK FACTORS—age ≥40, nulliparity, multiple gestations, prior preeclampsia, obesity, chronic hypertension, diabetes mellitus, chronic kidney disease, antiphospholipid antibodies, and inter-pregnancy interval ≥10 years

CLINICAL FEATURES

HISTORY—inquire about headaches, visual disturbances, epigastric or RUQ pain, and swelling. Adverse events include seizures, Δ level of consciousness, pulmonary edema, heart failure, renal failure, liver failure, oligohydramnios, IUGR, abnormal uterine or cord dopplers, and fetal demise

CLINICAL FEATURES (CONT'D)

PHYSICAL—check vitals (BP in both arms) and look for retinal vasospasm, heart failure, edema (facial, limbs), RUQ tenderness, hyperreflexia, and clonus

CAUSES OF DEATH—maternal cause of death is cerebral hemorrhage in developing countries and fluid overload in developed countries

INVESTIGATIONS

BASIC

- **LABS**—CBCD, Cr, spot urine for protein to creatinine ratio, AST, ALT, albumin, uric acid

SPECIAL

- **BLOOD TESTS**—peripheral smear, lytes, urea, bilirubin, INR, LDH if indicated
- **FETAL EFFECTS**—biophysical profile and fetal U/S

MANAGEMENT

ACUTE—ABC, O_2 to keep sat >95%, IV with judicious fluid volume

ACUTE LOWERING OF SEVERE HYPERTENSION (SBP ≥160 mmHg or DBP ≥110 mmHg)—*labetalol* (start with 20 mg IV, repeat 20–80 mg IV q10–30min, or infusion 1–2 mg/min, max 300 mg), *nifedipine short-acting capsule* 5–10 mg PO q30min, or *nifedipine PA tablet* 10 mg PO q45min, max 80 mg/day, avoid SL tab) or *hydralazine* (start with 5 mg IV, repeat 5–10 mg IV q20–30min, max 20 mg). Severe cases may require continuous infusion. Consider urgent delivery if not controlled

CHRONIC MANAGEMENT OF NON-SEVERE HYPERTENSION (SBP 140–159 mmHg or DBP 90–109 mmHg)—target BP at 130–140/80–90 mmHg if renal disease, diabetes, cardiovascular disease, or cerebrovascular disease. Otherwise target BP 130–155/80–105 mmHg. *Methyldopa* 250–1000 mg PO BID–TID, max 3 g/day, *labetalol* 100–800 mg PO BID–TID, max 2400 mg/day, *nifedipine PA tablet* 10–20 mg PO TID, max 180 mg/day, or *nifedipine XL* 20–60 mg PO daily, max 120 mg/day are good choices. Avoid ACE inhibitors, ARBs, and atenolol. Other β-blockers, clonidine, hydralazine are alternatives

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_16,

MANAGEMENT (CONT'D)

SEIZURE PREVENTION AND TREATMENT—$MgSO_4$ 4 g IV bolus, then 2 g/h (contraindicated in myasthenia gravis)

DELIVERY—the cure for preeclampsia, eclampsia, and HELLP. Administer steroids to promote fetal lung maturation prior to 34 weeks if early delivery

MANAGEMENT (CONT'D)

RECURRENCE—recurrence rate of preeclampsia is 18–66% in subsequent pregnancies. Rule out antiphospholipid syndrome if preeclampsia or placental insufficiency <34 weeks. ASA 81 mg/day before and during next pregnancy is recommended

Pulmonary Diseases in Pregnancy

ASTHMA

ASTHMA—treatments similar to non-pregnant patients. β-Agonists, anticholinergics, and glucocorticoids (inhaled, systemic) are all safe. Leukotriene antagonists only if refractory to above. Keep O_2 sat >95% at all times. Stress dose steroids during delivery if patient required moderate systemic steroids for >3 weeks in the preceding year

VENOUS THROMBOEMBOLISM

PATHOPHYSIOLOGY—increased risk of DVT/PE due to ↑ factors II, VII, X, and fibrin, as well as ↓ protein S and fibrinolytic activity, especially during T3. Also stasis due to ↓ venous tone and flow. Similar risk of DVT/PE in each trimester but highest post-partum; 90% of DVT in pregnancies are left sided

DIAGNOSIS—if suspect venous thromboembolism, consider initiation of LMWH while waiting for investigations. For DVT workup, perform compression U/S; if pelvic vein DVT suspected, consider MRV pelvis (without gadolinium in pregnancy), doppler study, or (post-partum) CT of pelvic veins. Otherwise, repeat compression U/S in 5–7 days if still symptomatic. For PE workup, rule out other etiologies by performing a CXR. If PE still suspected, consider initial low-dose perfusion (Q) scan and proceed with CT chest if abnormal. CT chest is associated with lower fetal radiation exposure than V/Q scan in T1–2, but higher risk of maternal breast cancer

RADIATION RISKS—fetal exposure of <5 cGy [5 rad] accumulatively in each pregnancy is acceptable, but oncologic effects controversial (e.g. childhood leukemia). Consider proximity of fetus to radiations site (i.e. radiation from CT chest > V/Q scan in T3)

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)

VENOUS THROMBOEMBOLISM (CONT'D)

Imaging	Estimated fetal radiation exposure (rad)
CT chest (PE protocol)	0.0003–0.002 (T1) 0.0008–0.0077 (T2) 0.005–0.013 (T3)
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. 8)

TREATMENTS—LMWH (monitor anti-Xa level). LMWH is contraindicated for 12–24 h prior to neuraxial analgesia, so switch to unfractionated heparin for ≥24 h prior to labor or cesarean delivery. Switch to warfarin post-delivery and continue for a minimum of 6 months after an acute clot. Rule out thrombophilia. IVC filters may be considered if prolonged interruption of anticoagulation is unsafe. In regard to DVT prophylaxis for future pregnancies, give low-dose SC LMWH during pregnancy and 6 weeks post-delivery. Warfarin is teratogenic (deformities, fetal hemorrhage). Thrombolysis is generally contraindicated as risk of fetal demise

NEJM 2008 359:19

AMNIOTIC FLUID EMBOLISM

PATHOPHYSIOLOGY—can occur during labor and delivery or with uterine manipulation. Risk factors include older age and multiparity

DIAGNOSIS—clinical diagnosis. Differential diagnosis includes septic shock, pulmonary embolism, aspiration pneumonia, uterine rupture, abruptio placentae, and venous air embolism

TREATMENTS—supportive. ICU admission. Rapid delivery of the fetus

AMNIOTIC FLUID EMBOLISM (CONT'D)

COMPLICATIONS—10% of maternal mortality, 25–50% of which die within the first hours of onset of the disease. Patients who survive are at high risk for DIC and ARDS

Cardiac Diseases in Pregnancy

PATHOPHYSIOLOGY

PHYSIOLOGIC CHANGES DURING PREGNANCY—↑ cardiac output and ↓ peripheral vascular resistance. Risk of cardiac decompensation highest in 28–32 weeks (maximum increase in maternal blood volume), labor (hemodynamic changes), and post-partum (fluid shifts)

HIGH-RISK CARDIOPULMONARY CONDITIONS—generally advise against pregnancy in following conditions: tetralogy of Fallot with severe cyanosis, Eisenmenger's syndrome, severe pulmonary hypertension, functional limitation NYHA 3 or 4, recent cardiac transplantation with high-dose immunosuppression, Marfan's syndrome with aortic root >40 mm [1.6 in.], interstitial pulmonary fibrosis, lymphangioleiomyomatosis, and active lung cancer

Related Topics
Endocarditis (p. 52)
Heart Failure (p. 33)
Valvular Disorders (p. 51)

VALVULAR DISORDERS

REGURGITANT VALVULAR HEART DISEASE—may improve during pregnancy due to ↓ systemic vascular resistance. Avoid Valsalva maneuver. Assist second stage with forceps

STENOTIC VALVULAR HEART DISEASE—may worsen during pregnancy. Consider β-blockers to decrease HR in mitral stenosis. Supportive measures with aggressive pain control during labor. Avoid fluid overload

PROSTHETIC HEART VALVE—for metal valves, continue oral anticoagulation until conception, can switch to LMWH before 6th week and continue throughout first trimester and possibly throughout pregnancy (aim for higher anti-Xa level). Warfarin, which crosses the placenta and may cause fetal bleeds, may be considered during 2nd and 3rd trimesters for more thrombogenic valves until 36th week, and then switch back to unfractionated heparin in preparation for delivery. Preconception counseling should be emphasized

VALVULAR DISORDERS (CONT'D)

ENDOCARDITIS PROPHYLAXIS—normally not required for vaginal delivery and cesarean sections; optional for high-risk lesions (complex congenital heart disease, prosthetic heart valve, cardiac transplant recipients with valvuloplasty, previous endocarditis)

MYOCARDIAL DISORDERS

PERIPARTUM CARDIOMYOPATHY—T3 to 5 months post-partum. One-third recovers spontaneously. May treat with diuretics, β-blockers (except atenolol), nitrates, hydralazine, and digoxin. Avoid ACE inhibitors and ARBs. Anticoagulate as risk of thromboembolism. Patients with residual left ventricular dysfunction are at high risk of progression or death with future pregnancies and should be counseled to avoid future pregnancies

ISCHEMIC HEART DISEASE—may become more common in pregnancy. Stress echocardiogram (preferred), exercise stress test, MIBI, and angiograms (radiation) can be done

RHYTHM DISORDERS

PALPITATIONS—sinus tachycardia and ectopic beats 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, but fetal monitoring devices should be removed first. CPR can be performed on pregnant woman, but pull uterus to left side to decrease IVC compression and improve venous return

Hepatic Diseases in Pregnancy

DIFFERENTIAL DIAGNOSIS

NOTE: GESTATIONAL AGE HELPS WITH DIAGNOSIS

HYPEREMESIS GRAVIDARUM (T1–2, incidence 0.3–1%)—**nausea, vomiting,** mild jaundice, weight loss, ↑ ALT>AST, N bili

INTRAHEPATIC CHOLESTASIS OF PREGNANCY (T2–3, incidence 0.1–0.2%)—functional disorder of bile formation with severe **pruritus**. Jaundice in 20–60% 1–4 weeks after pruritus starts. ↑ ALT, ↑ AST, ↑ bilirubin (less common), ↑↑ **bile acids**. Resolves following delivery without hepatic sequelae. Fetus at risk for sudden death especially with bile acids >40 μmol/L [16 μg/mL]

DIFFERENTIAL DIAGNOSIS (CONT'D)

DIFFERENTIAL DIAGNOSIS (CONT'D)

ACUTE FATTY LIVER OF PREGNANCY (T3, incidence 0.008%)—may be associated with preeclampsia. Characterized by **severe liver dysfunction** (encephalopathy, hypoglycemia, coagulopathy) and commonly jaundice. ↑↑ ALT, ↑↑ AST, ↑ bilirubin, ↑ WBC, ↑ PT, ↑ **uric acid**. U/S is often normal (microvesicular fat on biopsy) and CT shows a lowdensity liver. May progress to acute hepatic failure and DIC in >75%. Increased maternal and fetal mortality

PREECLAMPSIA/ECLAMPSIA (T2–3, incidence 5–10%)—see section under preeclampsia. May progress to HELLP (4–12%), DIC (7%), jaundice (5–14%) later

HELLP SYNDROME (T3, incidence 0.1%)—preeclampsia symptoms. ↑ ALT, ↑ AST, ↑ bilirubin, ↓ platelets, ↑ LDH. May progress to DIC (30%)

OTHER CONDITIONS—drug-induced hepatitis, ascending cholangitis, acute cholecystitis, malignancy, HBV, and HCV

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**—CBCD, 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), LDH, fibrinogen (DIC), TSH

INVESTIGATIONS (CONT'D)

- **MICROBIOLOGY**—HBV and HCV serology
- **IMAGING**—U/S abd

SPECIAL

- **LIVER BIOPSY**—if not coagulopathic

MANAGEMENT

HYPEREMESIS GRAVIDARUM—rule out molar pregnancy and hyperthyroidism. Supportive fluids. Metoclopramide, dimenhydrinate, and diclectin acceptable. Consider ondansetron if refractory. Continuous metoclopramide infusion if severe

INTRAHEPATIC CHOLESTASIS OF PREGNANCY—ursodeoxycholic acid or cholestyramine, increase fetal monitoring, consider early delivery as risk of fetal demise if high bile acids

ACUTE FATTY LIVER OF PREGNANCY—vitamin K if coagulopathic, early delivery

HELLP—anti-hypertensive, $MgSO_4$, early delivery

HEPATITIS B OR C—no proven treatment during pregnancy (but risk of vertical transmission especially if co-infection with HIV)

SPECIFIC ENTITIES

OTHER GI DISORDERS

- **GERD**—very common during pregnancy. 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 safest during 2nd trimester

Related Topics
Acute Liver Failure (p. 128)
Dyspepsia (p. 113)

Infectious Diseases in Pregnancy

URINARY TRACT INFECTIONS

ASYMPTOMATIC BACTERIURIA—occurring in 2–7% of pregnancies, associated with pre-term birth, low birth weight, and perinatal mortality. 30–40% will develop symptomatic UTI if untreated, and therefore should be treated (depending 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

URINARY TRACT INFECTIONS (CONT'D)

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 qhs [risk of hemolytic anemia] or *cephalexin* 250–500 mg PO qhs) for remainder of pregnancy as recurrent pyelonephritis occurs in 6–8% of women without prophylaxis

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

ANTEPARTUM CARE—determine HIV symptoms, infections, immunization status, and perform ophthalmologic examination if CD4 $<50/mm^3$. Baseline testing include CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, CD4 count, viral load, TB skin test, toxoplasma, VDRL, pap smear, cervical swabs for gonorrhea and chlamydia, CMV, HBV, and HCV serologies. Counsel regarding perinatal transmission (30% without treatment, <1% with optimal and effective combination therapy), contraceptive use during pregnancy (condoms), and mode of delivery. If on HAART already, continue as combination therapy which should contain AZT. For pregnant women not already on HAART, consider zidovudine from 2nd trimester onwards. Prophylaxis for opportunistic infections same as in non-pregnancy patients. Amniocentesis or other invasive procedures may increase vertical transmission risk

INTRAPARTUM CARE—upon onset of labour or rupture of membranes, give *zidovudine* 2 mg/kg IV over 1 h, then 1 mg/kg until delivery (even if on HAART already). For cesarean section, start infusion at least 3 h before procedure. Consider use of cesarean delivery if viral load >1000/mL. Avoid invasive monitoring, use of instruments to assist delivery, and prolonged interval between rupture of membranes and delivery

POSTPARTUM CARE—treat newborn with zidovudine for 6 weeks, to be followed by PJP prophylaxis. Determine HIV status at 1–2 days, 2 weeks, 1–2 months, and 3–6 months. Avoid breast feeding. Ensure good support system for mother. Counsel regarding contraceptive use

NEJM 2002 346:24

TORCHES INFECTIONS

INFECTIONS ASSOCIATED WITH BIRTH DEFECTS ★TORCHES★—TOxoplasma, **R**ubella, **C**MV, **HE**rpes, and **S**yphilis infections during pregnancy are associated with birth defects

TUBERCULOSIS

MANAGEMENT—treat patient as risk of infection to fetus is greater than risk of medications. Use isoniazid, rifampin, and ethambutol for 9 months minimum. Breastfeeding is safe. *Pyridoxine* 25 mg PO daily is recommended for all pregnant or breastfeeding women taking isoniazid

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, streptomycin, fluoroquinolones

Related Topics
HIV (p. 259)
Tuberculosis (p. 250)
Urinary Tract Infections (p. 244)

Endocrine Disorders in Pregnancy

DIABETES IN PREGNANCY

RISK FACTORS FOR GESTATIONAL DIABETES—previous history of gestational diabetes, prior delivery of macrosomic infant, ethnic group (Aboriginal, Hispanic, Asian, African), maternal age ≥35, obesity, PCOS, polyhydramnios, multiple gestation, fetal macrosomia (>4000 g or >90th percentile) or unexplained stillbirth, family history of diabetes, corticosteroid use

DIAGNOSIS OF GESTATIONAL DIABETES

- **Step 1: Gestational Diabetes Screen (GDS) 50 g oral glucose and draw blood after 1 h**
  - If blood glucose ≥10.3 mmol/L [≥185 mg/dL], diagnosis of GDM can be made
  - If blood, glucose ≥7.8 mmol/L [≥140 mg/dL], perform 2 hr OGTT
  - If blood glucose is <7.8 mmol/L [<140 mg/dL], then no GDM but re-test if continued at high risk or high suspicion (e.g. macrosomia, polyhydramnios)

DIABETES IN PREGNANCY (CONT'D)

- **Step 2: 2 h Oral Glucose Tolerance Test (OGTT) 75 g glucose after overnight fast**
  - Abnormal if fasting blood glucose ≥5.3 mmol/L [≥95 mg/dL]
  - Or 1 h blood glucose ≥10.6 mmol/L [≥190 mg/dL]
  - Or 2 hour blood glucose ≥8.6 mmol/L [≥155 mg/dL]
- **Step 3: Diagnosis based on OGTT**
  - If 1 value abnormal, then impaired glucose tolerance of pregnancy (IGTP)
  - If ≥2 values abnormal, then GDM

MONITORING—monitor blood glucose ac all meals for type 1 diabetics (goal <5.3 mmol/L [<95 mg/dL]), 1 h post all meals (goal <7.8 mmol/L [<140 mg/dL]), and qhs (goal <6 mmol/L [<108 mg/dL]). Hyperglycemia during the 1st trimester is a teratogen. Check urine ketones every morning

Related Topics
Diabetes Mellitus (p. 337)
Hyperthyroidism (p. 344)
Hypothyroidism (p. 343)

DIABETES IN PREGNANCY (CONT'D)

TREATMENTS—diabetic diet and exercise. Ensure excellent glycemic control with normal HbA1C prior to and throughout pregnancy. Increase bedtime snack portion if ketonuria in morning

- **TYPE 1 DIABETICS**—insulin injections and insulin pump equally effective
- **TYPE 2 DIABETICS**—switch oral hypoglycemics to insulin, preferably preconception
- **GESTATIONAL DIABETES**—insulin (Insulin Lispro or Aspart TID ac meals and Humulin N or NPH qhs) required if hyperglycemia persists. Glyburide acceptable if mild
- **INTRAPARTUM**—during labor (and induction), monitor blood glucose q1–2h and check urine ketones q2h. IV fluids and insulin sliding scale may be required
- **POSTPARTUM**—insulin rarely required for GDM postpartum. Test for diabetes several weeks postpartum with 2 h OGTT

COMPLICATIONS—maternal complications include preeclampsia, polyhydramnios, preterm labor, progression of existing diabetic retinopathy and nephropathy. Fetal complications include macrosomia, shoulder dystocia, malformations, intrauterine death, cardiomyopathy, polycythemia, hypoglycemia, hypocalcemia and hyperbilirubinemia

http://www.diabetes.ca/files/cpg2008/cpg-2008

HYPOTHYROIDISM IN PREGNANCY

PATHOPHYSIOLOGY—may be due to ↑ thyroid-binding globulin, ↑ volume of distribution of T4, and ↑ destruction of T4 by placental deiodinases. There is also increased metabolic demand during pregnancy

TREATMENTS—levothyroxine can be safely given during pregnancy. Dose may need to be increased in pregnancy. Take levothyroxine separate from vitamins, which decrease its absorption

COMPLICATIONS—untreated hypothyroidism can lead to neurodevelopmental abnormalities in the child

HYPERTHYROIDISM IN PREGNANCY

PATHOPHYSIOLOGY—during T1, total T4 ↑ (secondary to βhCG ↑) and thyroid-binding globulin ↑, fT4 remains same and TSH ↓/N. Hyperthyroidism may be associated with hyperemesis gravidarum

GRAVES DISEASE—most common cause of hyperthyroidism in pregnancy (95%). TSH receptor antibodies can cross placenta to cause thyrotoxicosis in fetus and fetal goiter. Exacerbations may happen in T1 and postpartum. Improvement may happen in T3. Classically improves in pregnancy

POSTPARTUM THYROIDITIS—clinically just like subacute thyroiditis, but autoimmune in origin and goiter is painless. Usually begins with a hyperthyroid phase followed by a hypothyroid phase. If patient has postpartum depression, consider this diagnosis and perform thyroid uptake study. Nursing mothers who had the radioactive uptake study should pump and dump breast milk for 72 h before refeeding

DIAGNOSIS—once hyperthyroidism is diagnosed during pregnancy (high free T4, low TSH), the cause may be difficult to establish. Postpartum follow-up may help. Thyroid radionuclide scan is contraindicated in pregnant women. Consider anti-TSH receptor antibody if suspect Graves disease

TREATMENTS

- **GRAVES' DISEASE**—β-blockers (avoid atenolol) can be safely used in pregnancy and lactation. PTU is the anti-thyroid agent of choice before and during the first trimester (as methimazole is associated with fetal abnormalities during this period), while methimazole should be used for the remainder of the pregnancy. Use the lowest dose of PTU possible. Graves' generally improves in pregnancy. β-Blockers may lead to bradycardia, hypoglycemia, and IUGR
- **POSTPARTUM THYROIDITIS**—may not require treatment if mild symptoms. For significant hyperthyroidism symptom, give β-blocker. For hypothyroidism, give *L-thyroxine* 50–100 μg PO daily ×8–12 weeks and then reassess
- **COMPLICATIONS**—decreased fertility, ↑ miscarriage, premature labor, thyroid storm (especially during labor and delivery), IUGR, and perinatal mortality

Other Disorders in Pregnancy

SEIZURES IN PREGNANCY

PATHOPHYSIOLOGY—for women with known epilepsy, 25% will have ↑ frequency, 25% will have ↓ frequency, and 50% will not change in pregnancy. It is important to be seizure free, ideally off medications, for at least 6 months prior to conception to ensure good outcome. Risk of seizures in offspring is

SEIZURES IN PREGNANCY (CONT'D)

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,

SEIZURES IN PREGNANCY (CONT'D)

carbamazepine, and phenobarbital are all teratogenic but may be used if indicated and after appropriate counseling. Lamotrigine seems to have reasonable data in pregnancy. *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. *Vitamin K* may be recommended during the last month of pregnancy to reduce the risk of hemorrhagic complications in newborns

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 renal failure, preeclampsia, and maternal death. Children of patients with anti-SSA and anti-SSB are at increased risk for congenital heart block and neonatal lupus. Patients with antiphospholipid antibodies are at increased risk of preeclampsia, miscarriage, and possibly thrombosis

BREAST CANCER IN PREGNANCY

DIAGNOSIS—staging workup similar to non-pregnant women. Use MRI (without gadolinium) or U/S 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 2nd and 3rd trimesters, but not in 1st trimester 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

ACCEPTABLE—acetaminophen, opioids

CONTRAINDICATED—NSAIDs in T3 (may use in T1 or T2)

THROMBOCYTOPENIA IN PREGNANCY

GESTATIONAL THROMBOCYTOPENIA (T3)—asymptomatic and resolves after pregnancy. May be difficult to distinguish from ITP except platelet count usually higher ($>70\times10^9$/L) in gestational thrombocytopenia. Follow platelet counts regularly

THROMBOCYTOPENIA IN PREGNANCY (CONT'D)

ITP (T1–3)—may use prednisone and IVIG in pregnancy. Platelet transfusion if acute. Monitor closely. Splenectomy is last resort (safest in T2). Epidural is generally performed if platelet $>80\times10^9$/L. Cesarean delivery safe if platelet $>50\times10^9$/L; 5% of newborns may also have thrombocytopenia, requiring close monitoring in first few days

HELLP (T2–3)—supportive, early delivery, steroids for lung maturity if delivered <34 weeks (see earlier sections)

TTP/HUS—plasma exchange, dialysis as needed

OTHERS—DIC, bone marrow disease, vitamin B12 deficiency, drugs, autoimmune diseases, and hypersplenism

ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN PREGNANCY

PATHOPHYSIOLOGY—antibody against phospholipids or cell surface proteins bound to anionic phospholipids. These include lupus anticoagulants, anticardiolipin antibody (false-positive VDRL), and anti-β2GP1 antibody → most lead to hypercoagulable state, some may inhibit coagulation

CLINICAL FEATURES—venous and arterial thrombosis and rarely hemorrhage affecting the lungs, heart, CNS, GI, kidneys, skin, and eyes. Also thrombocytopenia (via ITP, TTP), Raynaud's phenomenon, ↑ risk of preeclampsia/eclampsia, recurrent fetal losses or >10-week losses 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 consecutive T1 losses, or 1 or more unexplained morphologically normal T2 loss, or <34-week preeclampsia/eclampsia/placental insufficiency; *plus* laboratory criteria of elevated anticardiolipin antibodies, or lupus anticoagulant, or anti-β2GP1 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. For women with APS associated with VTE, same antenatal treatment plus anticoagulation prophylaxis postpartum for 6 weeks (see p. 157 for more details on ANTIPHOSPHOLIPID ANTIBODY SYNDROME)

Related Topics

Antiphospholipid Antibody Syndrome (p. 157)
Breast Cancer (p. 189)
Lupus (p. 279)
Thrombocytopenia (p. 151)
Seizures (p. 309)

Notes

17
GENERAL INTERNAL MEDICINE

Section Editor: Dr. Peter Hamilton

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 and helps to rule **out** disease

SPECIFICITY ★SPIN★

$= d/(b+d)$

= out of 100 people without disease, how many have a negative test result? Independent of prevalence and helps to rule **in** disease

POSITIVE PREDICTIVE VALUE (PPV)

$= a/(a+b)$

= out of 100 patients with a positive test result, how many actually have disease? Dependent on prevalence of disease

NEGATIVE PREDICTIVE VALUE (NPV)

$= d/(c+d)$

= out of 100 patients with a negative test result, how many do not have disease? Dependent on prevalence of disease

LIKELIHOOD RATIOS (LR)—indicate how much a given diagnostic test result will change the pretest probability of the disorder under investigation:

- LR+ 1.0 means pre-test probability = post-test probability

DIAGNOSTIC TESTS (CONT'D)

- LR+ >1.0 increases the probability the disorder is present. A test with LR+ >10 is particularly useful
- LR+ <1.0 decreases the probability the disorder is present. A test with LR+ <0.1 is particularly useful

POSITIVE LIKELIHOOD RATIO (LR+)

= (positive test in disease)/(positive test in no disease)

= sensitivity/(1 − specificity)

NEGATIVE LIKELIHOOD RATIO (LR−)

= (negative test in disease)/(negative test in no disease)

= (1 − sensitivity)/specificity

ACCURACY

$= (a+d)/(a+b+c+d)$

= how often is test correct in predicting true positive and false negative

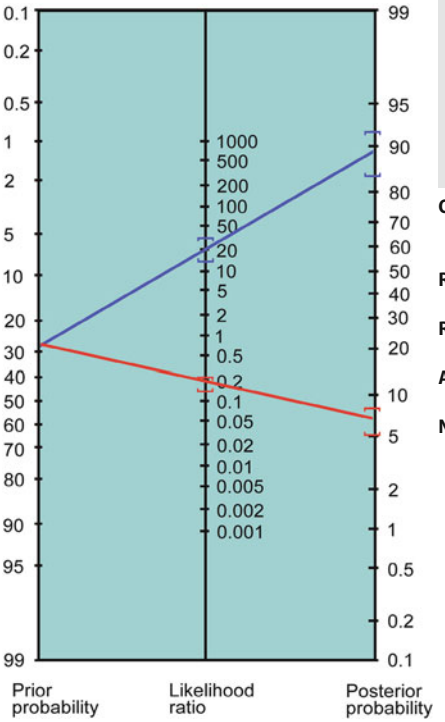
TO CALCULATE THE POST-TEST PROBABILITY OF A DIAGNOSIS AFTER A TEST

- **PRE-TEST PROBABILITY**
  = probability of disease just 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 × likelihood ratio
- **POST TEST PROBABILITY** = (post-test odds)/(1 + post-test odds)

FAGAN NOMOGRAM—easily converts from pre-test probability to post-test probability using LR (alleviating tedious calculations above)

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_17,

DIAGNOSTIC TESTS (CONT'D)



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THERAPEUTIC INTERVENTIONS

2×2 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) – case control study
= *ad*/*bc*. Odds ratio approximates RR if the disease is relatively rare

RELATIVE RISK (RR) – cohort study
$= [a/(a+b)]/[c/(c+d)]$

RELATIVE RISK REDUCTION (RRR)
$= [a/(a+b) - c/(c+d)]/[c/(c+d)]$

ABSOLUTE RISK REDUCTION (ARR)
$= a/(a+b) - c/(c+d)$

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

Smoking Cessation

NEJM 2002 346:7; NEJM 2008 359:19

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's disease

RESPIRATORY DISEASES—COPD, pneumonia

METABOLIC—diabetes mellitus, infertility, premature menopause, osteoporosis

COAGULOPATHY

PATHOPHYSIOLOGY OF SMOKING

NICOTINE ADDICTION—related to the combination of the following: (1) the pleasurable effects of nicotine such as relief of anxiety and arousal; (2) the pleasurable effects of associated environmental triggers such as coffee and meals; and (3) the unpleasureable effects of nicotine withdrawal such as dysphoria, anxiety, irritability, insomnia, decreased concentration, increased appetite and over the long-term increased weight

PATHOPHYSIOLOGY OF SMOKING (CONT'D)

LUNG CANCER—cigarette smoke contains numerous carcinogenic substances. In particular, *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. The 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 and cigar smoking. Smokers have a 10–30× increased risk of developing lung cancer.

PATHOPHYSIOLOGY OF SMOKING (CONT'D)

The risk the lung cancer returns close to baseline (i.e. 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

MANAGEMENT OF SMOKING CESSATION

COUNSELING—identify smoking cues and 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 to quit at the same time, or other substances). **Coping** (inform family/friends/co-workers about quitting and seek support, plan strategies such as gum, stress management)

DRUG THERAPY—**nicotine replacement** (nicotine gum, *nicotine transdermal* 21 mg daily ×6 weeks, then 14 mg daily ×2 weeks, then 7 mg daily ×2 weeks). ***Bupropion SR*** (150 mg PO daily ×3 days, then BID ×7–12 weeks, stop smoking after 6–7 days of treatment). **Nicotinic acetylcholine receptor partial agonist** (*Varenicline* 0.5 mg PO daily for d1–3, then 0.5 mg PO BID d4–7, then 1 mg PO BID for weeks 2–12)

TREATMENT ISSUES

APPROACH TO COUNSELING

1. **SCREENING**—identification of smokers at every visit and explore willingness to quit
2. **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"
3. **IF PATIENT READY TO QUIT WITHIN 30 DAYS**—offer counseling (quit date, what worked, what did not, express confidence, strategies) and aid (nicotine replacement, bupropion)
4. **IF PATIENT WANTS TO QUIT BUT NOT NOW**—explore smoker barriers to smoking cessation (nicotine dependence, fear of failure, lack of social support, lack of self-confidence, concern about weight gain, depression, substance abuse). Explore reasons to quit (health, social, financial). Set quit date. Follow-up
5. **IF PATIENT NOT READY TO QUIT**—avoid argument. Explore smoker's view of pros/cons of smoking and cessation and correct misperceptions. Discuss risks of passive smoking for family and friends. Advise no-smoking policy at home. Offer to help the smoker when ready to quit

TREATMENT ISSUES (CONT'D)

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 to months
- **PSYCHOLOGICAL**—smoking is a learned behavior/ritual

SIDE EFFECTS OF SMOKING CESSATION METHODS

- **NICOTINE GUM**—mouth irritation, sore jaw, dyspepsia, hiccups, and damage to dental work
- **NICOTINE PATCH**—skin irritation and insomnia. Contraindications include unstable angina or MI <2 weeks and pregnancy
- **BUPROPION SR**—insomnia, dry mouth, agitation, increased risk of seizure <0.1%
- **VARENICLINE**—nausea, vomiting, insomnia, abnormal dreams, headaches, constipation, diarrhea, flatulence, and dyspepsia. Contraindicated in pregnancy

PROGNOSTIC ISSUES

CESSATION RATE

- **WITHOUT HELP**—<10%
- **COMBINE DRUG THERAPY WITH COUNSELING**—40–60% at the end of drug treatment, 25–30% at 1 year. The use of drug therapy (either nicotine replacement or bupropion) increases success rate by 2–3× compared to placebo

Related Topics
Coronary Artery Disease (p. 26)
Esophageal cancer (p. 195)
Lung cancer (p. 185)

Multisystem Disorders

SELECTED MULTISYSTEM DISORDERS

INFECTIONS
- **BACTERIAL**—endocarditis, TB, Whipple's
- **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. Among the North American population of European descent, approximately 10% are heterozygous and 0.3% are homozygous for hemochromatosis

PATHOPHYSIOLOGY—mutation of HFE C282Y (normally forms a complex with transferrin receptor to decrease its affinity for transferrin) → ↑ absorption of Fe → iron deposition in organs

CLINICAL FEATURES—**skin** (bronze), **joints** (destructive arthritis, classically 2nd and 3rd MCP), **heart** (arrhythmia, heart failure), **pancreas** ("bronze" diabetes), **thyroid** (hypothyroidism), **liver** (↑ LFT, cirrhosis, hepatocellular carcinoma 200× ↑ risk, cholangiocarcinoma rare), **gonads** (hypogonadism, impotence), **pituitary** (hypopituitarism)

DIAGNOSIS—transferrin % saturation (=serum iron/TIBC ×100%, ↑, most useful for screening), Fe (↑), TIBC, ferritin (↑), liver biopsy (hepatic iron index), HFE genotype testing

TREATMENTS—**alcohol cessation**, **phlebotomy** (remove 1–2 U weekly until ferritin <50 ng/mL)

NEJM 2004 350:23

SARCOIDOSIS

PATHOPHYSIOLOGY—cause unknown but may involve antigen exposure → activation of T-cell immunity → non-caseating granuloma formation

CLINICAL FEATURES—**constitutional** (fatigue, weight loss, fever), **pulmonary** (staged according to CXR. Stage 0=no CXR changes, stage I=hilar adenopathy, stage II=hilar adenopathy with parenchymal opacities, stage III=parenchymal opacities without hilar adenopathy, stage IV=advanced fibrosis with evidence of honey-combing, hilar retraction, bullae, cysts, and emphysema. Stages are not necessarily

SARCOIDOSIS (CONT'D)

chronological), **cardiac** (arrhythmia especially conduction blocks, HF), **GI tract** (rarely ulcers, obstruction), **renal** (interstitial nephritis), **neurologic** (cranial nerve palsies especially CN VII, pituitary dysfunction, peripheral neuropathy, neuromuscular, transverse myelitis), **ocular** (uveitis), **endocrine** (hypercalcemia), **lymphatics** (lymphadenopathy, hypersplenism), **joints/bone** (arthritis of knees, ankles, elbows, wrists, small joints of hands and feet, bone pain), and **skin** (erythema nodosum, lupus pernio). **Lofgren's syndrome** is an acute presentation characterized by bilateral hilar lymphadenopathy, erythema nodosum, arthritis, fever, ±uveitis (50%). It is associated with a good prognosis with >80% remission in 2 years

INVESTIGATIONS—**blood tests** (CBCD, lytes, urea, Cr, Ca, PO_4, AST, ALT, ALP, bilirubin, serum ACE level), **urine tests** (urinalysis), **imaging** (CXR, CT chest), **special** (TB skin test, ECG, PFT, LP if neurological symptoms, BAL, biopsy). Diagnosis is made by clinical findings plus biopsy (except if Lofgren's syndrome)

PROGNOSIS—poor prognostic factors include age at onset >40, black race, progressive pulmonary sarcoidosis, neurological or cardiac involvement, chronic uveitis, lupus pernio, chronic hypercalcemia, and nephrocalcinosis

TREATMENTS
- **LUNG INVOLVEMENT**—observation only if asymptomatic, minimal parenchymal changes, Lofgren's syndrome, or stage I lung disease as high chance of spontaneous remission. Inhaled steroids for mild disease and systemic steroid (*prednisone* 1 mg/kg PO daily) for moderate/severe disease
- **SKIN AND EYE INVOLVEMENT**—topical steroid
- **JOINT INVOLVEMENT**—NSAIDs/colchicine
- **CARDIAC OR NEUROLOGIC INVOLVEMENT OR ANY OTHER PROGRESSIVE DISEASE**—*prednisone* 0.5–1 mg/kg PO daily, methotrexate, azathioprine, cyclophosphamide and infliximab

NEJM 2007 357:21

AMYLOIDOSIS

PATHOPHYSIOLOGY—soluble amyloid precursor protein (AL=Ig light chain variable region in myeloma, AA=serum amyloid A in chronic inflammatory conditions, ATTR=derived from mutant transthyretin protein, Aβ=Aβ protein precursor in Alzheimer's) → insoluble fibrils in anti-parallel β-pleated sheet configuration → deposition in different organs

CLINICAL FEATURES—**constitutional** (fatigue, weight loss), **renal** (nephrotic range proteinuria, distal RTA, nephrogenic diabetes insipidus), **cardiac** (HF, cardiomyopathy, arrhythmia, heart block, MI),

AMYLOIDOSIS (CONT'D)

neurologic (peripheral neuropathy, autonomic neuropathy), **GI tract** (GI bleed, malabsorption, pseudoobstruction), **hepatic** (hepatomegaly), **hematologic** (bruising, factor X deficiency, binding of Ca-dependent factors to amyloid), **endocrine** (adrenal insufficiency, hypothyroidism), **soft tissues** (shoulder pad sign, nail dystrophy, alopecia, macroglossia which is specific to AL, occurring in 20%)

DIAGNOSIS—serum and urine protein electrophoresis, biopsy of involved organ, subcutaneous fat, rectal tissue, and bone marrow biopsy. Immunofixation electrophoresis (AL), immunohistochemical staining for specific amyloid protein (AA). Amyloid stains red with Congo red dye and shows "apple-green" birefringence under polarized light

PROGNOSIS—median survival is 1–2 years for AL, but only 6 months if cardiac involvement. Up to 15 years in ATTR. Prognosis is dependent on underlying disease in AA

TREATMENTS—supportive (dialysis if renal failure), chemotherapy for AL amyloidosis

NOTE—amyloidosis usually involves λ light chain, whereas light chain deposition disease involves κ light chain

NEJM 1997 337:13

CRYOGLOBULINEMIA

PATHOPHYSIOLOGY—chronic immune stimulation resulting in production of immunoglobulin, i.e. cryoglobulin (type I=monoclonal IgG/IgM/IgA/free light chains, produced by Waldenstrom's macroglobulinemia or myeloma; type II=monoclonal IgM/IgA against polyclonal Ig, may be essential or due to persistent viral infections [HCV/HIV]; type III=polyclonal Ig against polyclonal Ig, may be essential or due to connective tissue diseases) → cryoglobulin precipitates with complexes at temperature $<37^{\circ}C$ [$<98.6^{\circ}F$] → deposition in different organs/vessels → systemic inflammation/vasculitis

CLINICAL FEATURES OF TYPE I—skin (livedo reticularis, purpura), **hyperviscosity/thrombosis** (Raynaud's phenomenon, digital ischemia)

CLINICAL FEATURES OF TYPE II/III—constitutional (fatigue, weight loss, arthralgia, myalgia), **neurologic** (peripheral neuropathy), **renal** (proteinuria, hematuria, MPGN, RPGN), **pulmonary** (small airway disease), **rheumatologic** (Sjogren's, Raynaud's), splenomegaly, lymphadenopathy

DIAGNOSIS—laboratory (↑ cryoglobulin level >800 μg/L or cryocrit >1% over 3–6 months, hypocomplementemia, ↑ ESR/CRP), **clinical** (vasculitis, thrombosis), **pathological** (biopsy of affected organ), **secondary causes** (serum protein electrophoresis, ANA, RF, HCV, HBV, HIV serology)

CRYOGLOBULINEMIA (CONT'D)

PROGNOSIS—10-year survival 50%. Death usually due to infection or cardiovascular disease

TREATMENTS—treat underlying cause. For severe disease, consider steroids, plasmapheresis, and cytotoxic agents

PORPHYRIA

INHERITANCE—mainly autosomal dominant with incomplete penetrance

PATHOPHYSIOLOGY—enzymatic defect in the heme synthesis pathway → continued production of toxic heme precursors by liver and RBC → accumulation in neurovisceral organs (acute porphyrias) and/or skin (cutaneous porphyrias), with specific symptoms related to the nature of precursors. There are seven types of porphyria representing defects at each of the seven steps of the pathway

CLINICAL FEATURES OF ACUTE PORPHYRIAS—acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria. Preceded by anxiety, restlessness, and insomnia → **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 sometimes **CNS symptoms** (confusion, hallucinations, seizures) → usually decline within a week. Occasionally may progress to diffuse muscle weakness with respiratory muscle paralysis

CLINICAL FEATURES OF CUTANEOUS PORPHYRIAS—variegate porphyria, hereditary coproporphyria, and porphyria cutanea tarda. Chronic photosensitive skin symptoms include excessive fragility, blistering and scarring, particularly on the back of hands, hypertrichosis, and hyperpigmentation of face

DIAGNOSIS—24 h urinary porphobilinogen, urinary ALAD, urinary porphyrins, fecal porphyrins. Ideally collect samples during acute attack. Other tests include erythrocyte porphyrins, plasma fluorescence spectrum, enzyme activity, DNA analysis, and skin biopsy

TREATMENTS—for acute porphyria, **avoid precipitating** medications, alcohol and infections if possible, with mostly supportive treatments during an episode. High-dose carbohydrate (400 g/day) diet is recommended acutely and exogenous heme infusions (*hematin* 4 mg/kg IV q12h) should be considered. For cutaneous porphyria, **avoidance of sun** is the only preventative strategy

Lancet 2005 365:241

WHIPPLE'S DISEASE

PATHOPHYSIOLOGY—*Tropheryma whipplei* (Gram-positive bacillus, non-acid-fast, periodic acid-schiff positive) → infiltration of various organs without significant inflammatory response → accumulation of organisms eventually causing organ failure. White male predominance, mean age 50

CLINICAL FEATURES—**GI** (diarrhea, abdominal pain, malabsorption with weight loss and iron deficiency, GI bleed, abdominal mass), **joints** (polyarthritis, polyarthralgia. Joint symptoms may precede others for years), **CNS** (delirium, dementia, seizures, coma, hypothalamic pituitary axis dysfunction, cerebellar ataxia, meningitis, myelopathy), **eyes** (supranuclear vertical gaze palsy, oculomasticatory myorhythmia, and oculo-facial–skeletal myorhythmia are pathognomonic), **skin** (hyperpigmentation, subcutaneous nodules, purpura), **cardiac** (myocarditis, pericarditis, culture negative endocarditis), pulmonary (interstitial fibrosis, pleural effusion, hilar lymphadenopathy), **hematologic** (anemia, lymphadenopathy), **constitutional** (fever, weight loss)

DIAGNOSIS—small bowel or tissue biopsy (PAS-positive macrophages). RT-PCR

TREATMENTS—antibiotics (*ceftriaxone* 2 g IV daily ×2–4 weeks, then *trimethoprim–sulfamethoxazole* DS 1 tab PO BID ×1–2 years), nutritional supplement (protein, iron, folate)

NEJM 2007 356:1

Related Topics
Chronic Liver Disease (p. 132)
Glomerulonephritis (p. 70)
Hepatitis C (p. 131)
Monoclonal gammopathy (p. 179)

Perioperative Assessment for Non-cardiopulmonary Surgery and Postoperative Complications

ACC guidelines 2007

PERIOPERATIVE CARDIAC RISK ASSESSMENT

ACC/AHA PERIOPERATIVE SUMMARY

- **ACTIVE CARDIAC CONDITIONS**
  - **UNSTABLE CORONARY SYNDROMES**—unstable or severe angina* (CCS class III or IV), recent MI decompensated heart failure (NYHA functional class IV; worsening or new-onset heart failure)
  - **SIGNIFICANT ARRHYTHMIAS**—high-grade AV block, Mobitz II AV block, 3rd degree AV block, symptomatic ventricular arrhythmias, supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate >100 bpm at rest, symptomatic bradycardia, newly recognized ventricular tachycardia
  - **SEVERE VALVULAR DISEASE**—severe aortic stenosis (mean pressure gradient >40 mmHg, aortic valve area <1.0 cm^2, or symptomatic), symptomatic mitral stenosis (progressive dyspnea on exertion, exertional presyncope, or heart failure)
- **PROCEDURE RISK**
  - **VASCULAR** (cardiac risk >5%)—aortic and other major vascular surgery, peripheral vascular surgery
  - **INTERMEDIATE** (cardiac risk 1–5%)—intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopedic surgery, prostate surgery
  - **LOW** (cardiac risk <1%)—endoscopic procedures, superficial procedure, cataract surgery, breast surgery, ambulatory surgery

PERIOPERATIVE CARDIAC RISK ASSESSMENT (CONT'D)

- **METABOLIC EQUIVALENT**
  - **1 MET**—ADLs (eat, dress, use toilet)
  - **2–3 MET**—walk indoors, walk one to two blocks on level ground at 3.2–4.8 km/h [2–3 mi/h]
  - **4 METS**—climb 1 flight of stairs, light housework such as dusting or washing dishes
  - **5–9 METS**—recreational activities, walk on level ground at 6.4 km/h [4 mi/h], run a short distance, heavy housework such as scrubbing floors or lifting heavy furniture
  - **10 METS**—strenuous sports such as swimming, tennis, football, basketball, skiing
- **OVERALL ALGORITHM**
  1. **Need for emergency non-cardiac surgery?** Yes=proceed to operation with perioperative surveillance and postoperative risk stratification and risk factor management; no=proceed to step 2
  2. **Active cardiac conditions (see above)?** Yes=proceed to evaluation and treatment per ACC/AHA guidelines; no=proceed to step 3
  3. **Low-risk surgery?** Yes=proceed with planned surgery; no=proceed to step 4
  4. **Functional capacity greater than or equal to four METs without symptoms?** Yes=proceed with planned surgery; no or unknown=proceed to step 5
  5. **Determine clinical risk factors**. If no clinical risk factors, proceed to with planned surgery; if

PERIOPERATIVE CARDIAC RISK ASSESSMENT (CONT'D)

one to two risk factors, proceed to step 6; if three or more risk factors, proceed to step 7

6. One to two clinical risk factors: **For both vascular surgery and intermediate risk surgery**, proceed with planned surgery with HR control or consider noninvasive testing if it will change management
7. Three or more clinical risk factors: **Is vascular surgery planned?** Yes=consider testing if it will change management; no=proceed with planned surgery with HR control or consider noninvasive testing if it will change management

- **ALGORITHM FOR PATIENTS WHO REQUIRE PERCUTANEOUS CORONARY INTERVENTION PRIOR TO SUBSEQUENT SURGERY**
  1. For patients with acute MI, high-risk ACS or high-risk cardiac anatomy, **what is the bleeding risk of surgery?** Low=stent and continue dual-antiplatelet therapy; not low=proceed to step 2
  2. **What is the timing of planned surgery?** 14–29 days=perform balloon angioplasty; 30–365 days =use bare metal stent; >365 days=use drug eluting stent
- **ALGORITHM FOR PATIENTS WITH PREVIOUS PERCUTANEOUS CORONARY INTERVENTION**
  1. What was the type of PCI performed? Balloon angioplasty=proceed to step 2; bare-metal stent=proceed to step 3; drug-eluting stent=proceed to step 4
  2. Greater than 14 days between balloon angioplasty and planned surgery? Yes=proceed to the operation room with aspirin; no=delay for elective or non-urgent surgery
  3. Greater than 30–45 days between bare metal stent insertion and planned surgery? Yes=proceed to the operation room with aspirin; no=delay for elective or non-urgent surgery
  4. Greater than 365 days between drug eluting stent insertion and planned surgery? Yes=proceed to the operation room with aspirin; no=delay for elective or non-urgent surgery
- **ACUTE** (cardiac risk >5%)—aortic and other major vascular surgery, peripheral vascular surgery
- **INTERMEDIATE** (cardiac risk 1–5%)—intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopedic surgery, prostate surgery
- **LOW** (cardiac risk <1%)—endoscopic procedures, superficial procedure, cataract surgery, breast surgery, ambulatory surgery

Circulation 2007 116:e418–e499

LEE CRITERIA (REVISED CARDIAC RISK INDEX)

- **HIGH-RISK SURGERY**—thoracic surgery, intraperitoneal surgery, suprainguinal vascular surgery

PERIOPERATIVE CARDIAC RISK ASSESSMENT (CONT'D)

- **CAD**—any MI, current angina, current nitrate use, positive exercise stress test, Q in ECG
- **HF**—history of HF, PND, pulmonary edema, S3, crackles, vascular redistribution on CXR
- **CVD**—history of stroke or TIA
- **DIABETES**—using insulin
- **RENAL FAILURE**—creatinine >175 μmol/L [1.9 mg/dL]
- **RISK OF MAJOR CARDIAC COMPLICATIONS**—**0/6** =0.5% (0.4–0.5%), **1/6**=1% (0.9–1.3%), **2/6** =5% (4–7%), ≥**3/6**=10% (9–11%)

PERIOPERATIVE PULMONARY RISKS

PATIENT—age >70, COPD, asthma, smoking (>40 pack year), poor general health status (ASA >2, see below). Note obesity is not a risk factor

PROCEDURE—nasogastric tube insertion perioperatively, upper abdominal, thoracic, and abdominal aortic aneurysm surgery, surgery >3 h, intraoperative pancuronium, general anesthesia

AMERICAN SOCIETY OF ANESTHESIOLOGISTS (ASA) CLASSIFICATION

- **1**—healthy patient with no disease outside of surgical process (<0.03% mortality)
- **2**—mild to moderate systemic disease caused by the surgical condition or other diseases, medically well controlled (0.2% mortality)
- **3**—severe disease process which limits activity but is not incapacitating (1.2% mortality)
- **4**—severe incapacitating disease process that is a constant threat to life (8% mortality)
- **5**—moribund patient not expected to survive 24 h with or without an operation (34% mortality)
- **E**—suffix for emergency surgery for any class

INVESTIGATIONS FOR PERIOPERATIVE PATIENTS

BASIC—CBCD, lytes, urea, Cr, INR, PTT, X-match

CARDIAC

- **ECG**—should be obtained in most patients
- **NON-INVASIVE TESTING** (exercise stress test, stress MIBI, dobutamine stress echocardiogram, radionuclide ventriculography)—consider if high or intermediate clinical predictors, high-risk surgical procedures, and/or poor functional capacity (<4 METs). See ACC/AHA summary for more details
- **ANGIOGRAPHY**—indicated if high risk based on non-invasive testing, equivocal non-invasive test results in patients at high clinical risk undergoing high-risk surgery, angina unresponsive to medical treatment, unstable angina, especially if intermediate/high-risk surgery

PULMONARY

- **ABG**—for patients undergoing CABG, upper abdominal surgery, or lung resection with underlying lung disease or unexplained dyspnea. Provides baseline but not useful for risk stratification

INVESTIGATIONS FOR PERIOPERATIVE PATIENTS (CONT'D)

- **CXR**—should be obtained if age >60 or suspect/known lung pathologies
- **PULMONARY FUNCTION TESTS**—patients undergoing thoracic or upper abdominal surgery with unexplained dyspnea and for those with COPD or asthma where clinical evaluation cannot determine if airflow obstruction has been optimally reduced
- **LUNG RESECTION WORKUP**—patients with preoperative FEV1 >2 L can probably tolerate pneumonectomy. Patients with FEV1 <2 L but predicted postoperative FEV1 >800 mL can probably tolerate lung resection. DLCO <40% suggests high postoperative risk. Patients with VO_2max >15 mL/kg/min during cardiopulmonary exercise testing will likely tolerate surgery

NEJM 1999 340:12

MANAGEMENT OF PERIOPERATIVE PATIENTS

1. **REASON FOR CONSULT**—determine the reason for surgery and try to answer specific questions from the referring physician. Next, explore the 8 key domains of Perioperative assessment
2. **CARDIAC RISK OPTIMIZATION**
   - **OPTIMAL TIMING**—**myocardial infarction** (wait 4–6 weeks if small to moderate MI. Wait >3 months if severe MI or LV dysfunction). **Angioplasty** (see ACC/AHA algorithm for patients with previous PCI). **CABG** (wait at least 1 month)
   - **OVERALL ELIGIBILITY**—if no acute MI, acute HF, severe mitral or aortic stenosis, severe arrhythmia will likely be able to go for surgery
   - **PREOPERATIVE**—**β-blockers** (for Lee score ≥2, give *atenolol* 10 mg IV over 15 min prior to surgery, then *atenolol* 50–100 mg PO daily or *bisoprolol* 5–10 mg PO daily, titrate to HR 50–60 for a total of 1 month). α2 agonists (*clonidine* 0.1 mg PO BID). **CABG** (indications include poorly controlled angina despite maximal medical therapy, >50% stenosis of left main coronary artery, >70% stenosis of 2- or 3-vessel coronary artery disease with involvement of proximal LAD, easily induced myocardial ischemia on preoperative stress testing, and left ventricular systolic dysfunction). **Angioplasty** (see ACC/AHA algorithm for patients who require PCI prior to subsequent surgery). **Valvular surgery** (e.g. symptomatic aortic stenosis. If indicated should be done before elective non-cardiac surgery. If urgent surgery and severe aortic or mitral stenosis, consider balloon valvuloplasty)
   - **POSTOPERATIVE**—daily ECG and troponin ×3 days if high-risk and patient unable to communicate angina

MANAGEMENT OF PERIOPERATIVE PATIENTS (CONT'D)

3. **BACTERIAL ENDOCARDITIS PROPHYLAXIS**—only given to patients with the highest risk of developing endocarditis, which include the following
   - **HIGH-RISK CARDIAC CONDITIONS**
     - **PROSTHETIC**—prosthetic cardiac valve, prosthetic material used for cardiac valve repair
     - **CYANOTIC CONGENITAL HEART DISEASE**—unrepaired, completely repaired but with residual defects at the site or adjacent to the site of the prosthetic device
     - **CARDIAC TRANSPLANT RECIPIENTS WITH VALVULOPATHY**
     - **PREVIOUS ENDOCARDITIS**
   - **PROCEDURES**
     - **ORAL CAVITY**—manipulation of gingival or periapical region of teeth, perforation of oral mucosa
     - **RESPIRATORY TRACT**—tonsillectomy, adenoidectomy, bronchoscopy with a rigid bronchoscope, or flexible bronchoscopy if biopsied
     - **GI/GU TRACT**—generally not recommended
   - **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, *cephalexin* 2 g PO, *clindamycin* 600 mg PO/IM/IV, *azithromycin* 500 mg PO, *clarithromycin* 500 mg PO

AHA Guidelines 2007

4. **PULMONARY RISK OPTIMIZATION**
   - **PREOPERATIVE**—smoking cessation for >8 weeks. Manage obstructive lung diseases (*ipratropium* 0.25 mg INH QID for all COPD patients, *salbutamol* 2.5 mg INH q4h PRN for all COPD/asthma patients with wheezing, and steroids if exacerbations). Antibiotics and delay surgery if respiratory infection is present. Patient education regarding lung expansion maneuvers
   - **INTRA-OPERATIVE**—**limit duration** of surgery to <3 h. **Avoid general anesthetics** (use spinal or epidural anesthesia). **Avoid pancuronium**. **Laparoscopic procedures** when possible. **Substitute** less ambitious procedure for upper abdominal or thoracic surgery when possible
   - **POSTOPERATIVE**—**deep-breathing exercises** or **incentive spirometry**. **CPAP** if needed. **Pain control** (consider epidural analgesia or intercostal nerve blocks)
5. **MEDICATION MANAGEMENT**
   - **CARDIOVASCULAR AGENTS**—**β-blockers** (continue up to and including day of surgery. If prolonged NPO, substitute with IV labetalol, propanolol, metoprolol, or esmolol). **α-Agonists** (continue up to and including day of surgery. If prolonged NPO, substitute with TD clonidine or IV methyldopa). **Calcium channel blockers** (continue up to and including day of surgery. If prolonged NPO, no IV substitute unless poor hemodynamics). **ACE**

MANAGEMENT OF PERIOPERATIVE PATIENTS (CONT'D)

inhibitor/ARB (continue up to and including day of surgery if for hypertension, but stop day of surgery if for HF. If prolonged NPO, use IV β-blocker if hypertension and hydralazine/nitrate if HF). **Diuretics** (continue up to day before surgery but stop day of surgery. If prolonged NPO, use IV form on PRN basis). **ASA** (vascular protective effect thus should not stop unless high-risk of bleed, e.g. CNS surgery. If so, hold 7–10 days before surgery and restart 6 h postop). **Dipyridamole** (similar to ASA in terms of indications for stopping. If stop, hold 2 days before surgery)

- CARDIOVASCULAR AGENTS—**clopidogrel and ticlopidine** (dependent on indication: often standard to hold 7–10 days before surgery. If used following angioplasty, continue for at least 6 weeks before stopping. Continue combination clopidogrel+ASA for at least 1 month for bare-metal stents and 12 months for drug-eluting stents. Premature discontinuation of dual antiplatelet therapy increases risk of perioperative cardiac death 5–10×, incidence 30%. Combination clopidogrel+ASA increases absolute risk of major perioperative bleeding by 0.4–1% compared to ASA alone. Generally, most surgeries can be performed without discontinuing antiplatelet therapy for recent coronary stenting, except neurosurgery or posterior chamber eye surgery). **NSAIDs** (some vascular protective effect but also potential renal failure. Hold 3 days before surgery, substitute with acetaminophen desired). **Statins** (continue up to and including day of surgery). **Fibrates/niacin/cholestyramine** (continue up to day before surgery but stop day of surgery)
- ANTICOAGULATION—elective surgery should be delayed till at least 1 month after treatment of venous or arterial thromboembolism. If low perioperative bleeding risk, maintain INR <2 with warfarin. If high perioperative bleeding risk, keep INR <1.5 by stopping warfarin 4–7 days preoperatively. If high-risk of thrombosis (<1 month of any thrombosis, some valvular heart diseases, mechanical valves), start patient on IV heparin until 4 h preop and then restart within 24 h postop (once hemostasis achieved). Start warfarin postoperatively when there is no contraindication to anticoagulation (as early as day of operation, depending on surgery type), and stop IV heparin when INR >2
- 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 anaesthetic), 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 $\times 24$ hours, 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 $\times 24$ h, then 25 mg q8h $\times 24$ h, then resume maintenance)
- DIABETIC AGENTS—key principle is to avoid hypoglycemia and hyperglycemia. **Oral hypoglycemics** (continue up to day before surgery and discontinue AM dose on day of surgery. If prolonged NPO or hyperglycemia, substitute with insulin sliding scale). **Insulin** (decrease nighttime insulin dose by half the night prior to surgery and omit morning insulin the day of surgery. For short procedures, may give 1/3 to 1/2 long-or intermediate-acting insulin dose. For complicated procedures, type 1 diabetics, or volatile sugar levels in type 2 diabetics, consider insulin drip)
- THYROID AGENTS—**thyroxine** (T4) should be given IV or IM (80% of PO dose) if oral intake cannot be resumed in 5–7 days. Otherwise, can miss a few days without effect
- NEUROLOGIC AGENTS—**antiepileptics** (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)

6. **DVT PROPHYLAXIS**—early ambulation, intermittent pneumatic compression, low-dose heparin, LMWH, coumadin
7. **BLEEDING RISK ASSESSMENT**—inquire about any recurrent bleeding tendencies and bleeding complications from past surgeries. Review Hb, platelets, INR, and PTT
8. **ANESTHETIC RISK ASSESSMENT**—inquire about past surgeries and family history of malignant hyperthermia
9. **DELIRIUM RISK ASSESSMENT**—inquire about alcohol and illicit drug use, and diagnosis of dementia to assess the risk of postperative delirium

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★

- **W**ound—infection
- **W**ind—pulmonary (pneumonia, atelectasis, PE)
- **W**eins—DVT/PE

POSTOPERATIVE COMPLICATIONS (CONT'D)

- **W**ater—UTI
- **W**onder drugs
- **W**hat the heck—sepsis
- **W**hat else—thyroid storm

POSTOPERATIVE DELIRIUM ★DIMS★ (see p. 380 for more details)

- **D**rugs—alcohol withdrawal, benzodiazepines, pain (i.e. lack of appropriate drugs)
- **I**nfections—pneumonia, UTI, sepsis
- **M**etabolic—myocardial infarction, hypoxia (pulmonary embolism), electrolyte abnormalities
- **S**tructural—stroke, intracranial hemorrhage

POSTOPERATIVE HYPERTENSION (see p. 57 for more details)

- **PHYSIOLOGIC**—pain, bladder distension, confusion/agitation, thyroid storm
- **PATHOLOGIC**—infections, stroke
- **DRUGS**—alcohol withdrawal, withdrawal of antihypertensive medications, neuroleptic malignant syndrome, malignant hyperthermia

POSTOPERATIVE ACUTE RENAL FAILURE (see p. 68 for more details)

- **PRE-RENAL**—blood loss, fluid loss, ACE inhibitors, NSAIDs, cyclosporin

POSTOPERATIVE COMPLICATIONS (CONT'D)

- **RENAL**—ATN (ischemic, contrast, aminoglycosides), AIN (penicillins, cephalosporins), microvascular (cholesterol emboli)
- **POST-RENAL**—urinary retention

POSTOPERATIVE BLEEDING (see p. 153 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. 151 for more details)

- **PSEUDOTHROMBOCYTOPENIA**—platelet clumping
- **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)

Medical Fitness to Drive

GENERAL PRINCIPLES

DRIVER'S LICENSING AUTHORITY—responsible for issuing/revoking licenses

PHYSICIANS—responsible for reporting unfit drivers. In some jurisdictions, it is mandatory to report. The physicians can be 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 it and inform the Ministry of Transportation

BALANCE—interest of public has priority over rights of individual driver

LICENSE TYPE—class 1–4=professional vehicles, 5=private vehicle, class 6=motorcycle

DURATION OF NO DRIVING FOR SPECIFIC DISORDERS

	Private driver	Professional driver
First seizure	3 months	12 months
EtOH withdrawal seizures	6 months (EtOH and seizure free and completed rehabilitation)	
Epilepsy	6 months (seizure free on meds)	5 years (seizure free on/off meds)
MI	1 month	3 months
PTCA	48 h	7 days
CABG	1 month	3 months
Arrhythmias	If no symptoms	If no symptoms
Pacemaker	1 week	1 month
Heart failure	No if NYHA ≥IV	No if NYHA ≥II, EF <35% or >3 VT on Holter
AAA	No if >5 cm [>2 in.]	No if >5 cm [>2 in.]
TIA	If no symptoms	If no symptoms
Stroke	1 month	1 month

GENERAL PRINCIPLES (CONT'D)

	Private driver	Professional driver
Vision	No if poor vision <20/50, hemianopsia, or diplopia	No if poor vision <20/40, hemianopsia, or diplopia
Diabetes	No if hypoglycemia ≤6 months	No if unstable insulin regimen, hypoglycemia, ≤6 months, neuropathy, retinopathy
COPD	No if on home O_2 (need road test)	No if on home O_2

NOTE: regulations for specific jurisdiction 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 (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 Issues

ETHICS JUDGMENT

MORAL JUDGMENT—the decision-making process is based on both ethics principles and facts

- **ETHICS 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 he/she wants 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 (CONT'D)

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 (p. 377)

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
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 (bioethicist), 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

EUTHANASIA

EXAMPLE—ALS patient asks for active euthanasia

TYPES—active euthanasia is direct involvement of killing a patient (e.g. injection of KCl), while passive euthanasia is providing the means for the patient to kill himself (e.g. preparing KCl)

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, but passive/active euthanasia not allowed based on intention and causation

RESOURCE ALLOCATION

EXAMPLE—selection of organ transplant recipients

FACTORS TO CONSIDER—justice

RESOURCE ALLOCATION (CONT'D)

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 on the basis of 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 pizza 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 to prevent secondary gain from dominating or appearing to dominate professional decisions or choices

Hospital Admission and Discharge Issues

PRINCIPLES OF MEDICAL MANAGEMENT

★THE 5Cs★

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**

CONSULT—seek advice from other disciplines when indicated (physiotherapy, dietician, specialists)

CONTINUITY—provide appropriate follow-up

REASONS FOR ADMISSION

MEDICAL—diagnostic workup, monitoring, IV therapy (hydration, antibiotics, chemotherapy), surgery

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

REHABILITATION CRITERIA

Not demented
Not depressed
Medically stable
Possibility for improvement
Discharge plan after rehabilitation

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, subacute, rehabilitation, psychiatry

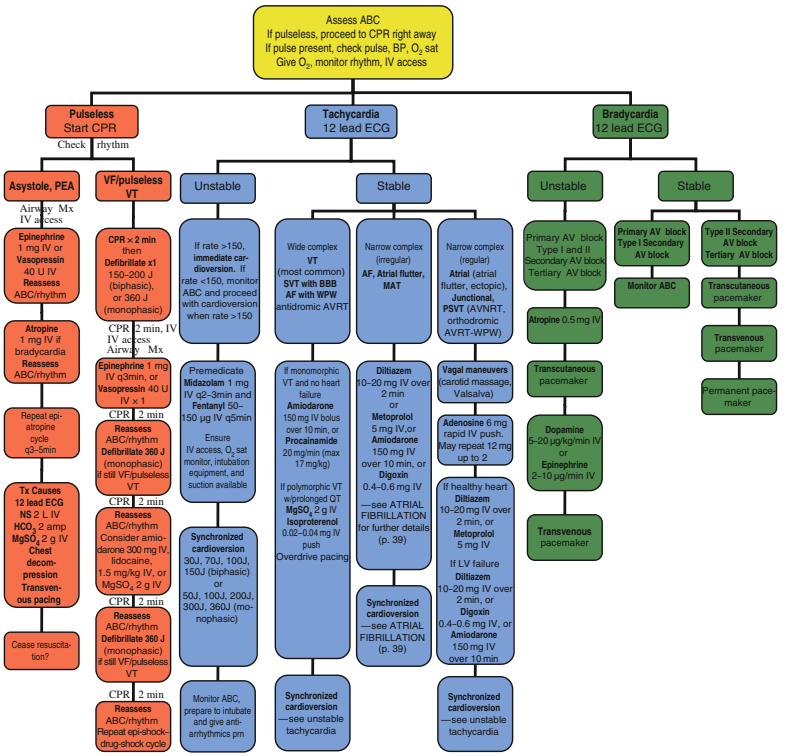
PALLIATIVE CARE—palliative care unit, hospice

Notes

Appendix A

ADVANCED CARDIAC LIFE SUPPORT

American Heart Association (AHA), European Resuscitation Council (ERC), and International Liaison Committee on Resuscitation (ILCOR) 2005 Guidelines. *Circulation 2005; 112[Suppl I]:IV1-211*



Asystole/PEA DDx
Hypovolemia hypoxia
Hypothermia hyper/hypoK
H^+ (acidosis)
Tablets
Tamponade
Tension pneumothorax
Thrombosis CAD
Thrombosis PE

Asystole/PEA drugs
Epinephrine 1 mg IV push, q3–5min, or 2–2.5 IV dose down endotracheal tube in 10 mL of NS followed by hyperventilation if IV not available
Atropine 1 mg IV push, q3–5min, max total 0.04 mg/kg (approximately 3 doses), 2–2.5 IV dose down endotracheal tube in 10 mL NS if needed

VF/pulseless VT drugs
Epinephrine 1 mg IV push, q3–5min
Vasopressin 40 U IV push 1 dose
Amiodarone 1st dose 300 mg IV push, 2nd dose 150 mg, max total 2.2 g/24 h
Lidocaine 1.5 mg/kg IV push, and repeat 0.5–0.75 mg/kg q5–10min to max 3 mg/kg
Procainamide 50 mg/min IV

$MgSO_4$ 2 g IV if torsades de pointes or suspect hypo-Mg
HCO_3 2 amp IV push if hyperkalemia, metabolic acidosis, TCA overdose, barbiturate overdose, ASA daily, etc. Avoid if respiratory acidosis

Tachycardia drugs
Amiodarone 150 mg IV bolus over 10 min, then 1 mg/min (60 mg/h) for 6 h, followed by 0.5 mg/min (30 mg/h) for 18 h. Maximum total 2.2 g/24 h
Procainamide 20–30 mg/min IV, maximum infusion at 17 mg/kg, maintenance at 1–4 mg/min. Indicated particularly for WPW with AF (wide complex irregular tachycardia). Administer until maximum dose reached, dysrhythmia suppressed, QRS widens >50%, or hypotension occurs

Adenosine 6 mg rapid IV push, 2nd dose 12 mg, 3rd dose 12 mg. Indicated in PSVT. Avoid if WPW with AF
Amiodarone 150 mg IV bolus over 10 min, q10–15min. Alternatively, infusion 360 mg over 6 h, then 540 mg over 18 h. Maximum total 2.2 g/24 h. Good for most SVT

β-Blocker: Metoprolol 5 mg IV q5min, may repeat 2. Maximum total 15 mg, **Labetalol** 10 mg IV q10min. Maximum total 150 mg
Calcium channel blocker: Diltiazem 0.25 mg/kg (10–20 mg) IV over 2 min, 2nd dose 0.35 mg/kg (25 mg), then infusion at 5–10 mg/h. **Verapamil** 2.5–5 mg IV over 2 min, repeat 15–30 min. Avoid if WPW with AF
Digoxin 0.4–0.6 mg IV, then 0.1–0.3 mg q6–8h. Then 0.125–0.5 mg IV/PO daily

Bradycardia drugs
Atropine 0.5–1 mg IV repeat q3–5min, max total 0.04 mg/kg (approximately 3 doses), 2–2.5 IV dose down endotracheal tube in 10 mL NS if needed. Unlikely beneficial in third degree or Mobitz type II block
Dopamine 5–20 µg/kg/min IV, after max dose of atropine
Epinephrine 2–10 µg/min IV, if severe bradycardia with hypotension

Important Principles
CPR—ensure good compressions by allowing chest to recoil fully and minimizing interruptions. Aim for 100 compressions per minute for 2 min each cycle. Continue until regain pulse. The focus for initial resuscitation should be on performing high-quality CPR. Frequent pulse check, intubation, central line insertion, and medications may sometimes distract the team from this important task
Airway—avoid hyperventilation as this could increase intrathoracic pressure. Initial use of oropharyngeal airway with bag-valve mask is reasonable, with 2 breaths given after every 30 CPR compressions. Once switched to advanced airway (laryngeal mask airway, combitube, or endotracheal tube), breaths should be given every 6 s
Access—the preferred route is through a peripherial intravenous (IV) line, which can usually be established easily. The intraosseous (IO) route represents a second choice, while central lines and endotracheal tube should be the last resort for medication access

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_18,

Appendix B
LIST OF COMMON ABBREVIATIONS

% sat	Percentage saturation
5-FU	5-Fluorouracil
5-HIAA	5-Hydroxyindoleacetic acid
5HT	Serotonin
AAA	Abdominal aortic aneurysm
ABC	Airway, breathing, circulation
Abd	Abdomen
ABG	Arterial blood gas
ABPA	Allergic bronchopulmonary aspergillosis
ABx	Antibiotics
ACE	Angiotensin-converting enzyme
ACR	American College of Rheumatology
ACS	Acute coronary syndrome
ACTH	Adrenocorticotropic hormone
ADL	Activity of daily living
ADP	Adenosine diphosphate
AF	Atrial fibrillation
AFB	Acid fast bacilli
AFP	Alpha fetoprotein
AG	Anion gap
AIDS	Acquired immunodeficiency syndrome
AIN	Acute interstitial nephritis
AJR	Abdominal jugular reflex
AKI	Acute kidney injury
ALI	Acute lung injury
ALL	Acute lymphoblastic lymphoma
ALND	Axillary lymph node dissection
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
AMA	Antimitochondrial antibody
AML	Acute myelogenous leukemia
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
ANCA	Anti-neutrophilic cytoplasmic antibody
AP	Anterior–posterior
APA	Antiphospholipid antibody
APACHE	Acute physiology and chronic health evaluation
APC	Adenomatosis polyposis coli
APS	Antiphospholipid antibody syndrome
ARB	Angiotensin receptor blocker
ARDS	Acute respiratory distress syndrome
ARR	Absolute risk reduction
AS	Aortic stenosis
ASA	Acetylsalicylic acid, American Society of Anesthesiologists
ASD	Atrial septal defect
ASO	AntiStreptolysin-*O*
AST	Aspartate aminotransferase
ATC	Around the clock
ATN	Acute tubular necrosis
AV	Atrioventricular or arteriovenous
AVM	Arteriovenous malformation
AVNRT	Atrioventricular nodal reentry tachycardia
AXR	Abdominal X-ray
BAC	Bronchioloalveolar carcinoma
BAL	Bronchoalveolar lavage
BID	Twice per day
Bili	Bilirubin
BIPAP	Bilevel positive airway pressure
BL	Burkitt's lymphoma
BMD	Bone mineral density
BMI	Body mass index
BMT	Bone marrow transplant
BNP	B-type natriuretic peptide
BOOP	Bronchiolitis obliterans organizing pneumonia
BP	Blood pressure
BRBPR	Bright red blood per rectum
BRCA	Breast cancer gene
BSA	Body surface area
BSE	Breast self-examination
C&S	Culture and sensitivity
Ca	Calcium
CA 125	Cancer antigen 125
CA 15.3	Cancer antigen 15.3
CA 19-9	Cancer antigen 19-9
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAH	Congenital adrenal hyperplasia
CA-MRSA	Community-acquired methicillin-resistant *Staphylococcus aureus*
CAP	Community-acquired pneumonia
CBC	Complete blood count
CBCD	Complete blood count and differential
CBE	Clinical breast examination
Cbl	Cobalamin
CCB	Calcium channel blocker
CCP	Cyclic citrullinated peptides
CCS	Canadian Cardiovascular Society
CEA	Carcinoembryonic antigen
CHF	Congestive heart failure
Chol	Cholesterol
CK	Creatine kinase
CKD	Chronic kidney disease
CKMB	Creatine kinaseMB
Cl	Chloride
CLL	Chronic lymphocytic leukemia
CMA	Canadian Medical Association
CMC	Carpometacarpal joint
CML	Chronic myelogenous leukemia
CMML	Chronic myelomonocytic leukemia
CMV	Cytomegalovirus
CN	Cranial nerve, cyanide
CNS	Central nervous system
CO	Carbon monoxide
COP	Cryptogenic organizing pneumonia
COPD	Chronic obstructive pulmonary disease
COX	Cyclooxygenase
CPAP	Continuous positive airway pressure
CPR	Cardiopulmonary resuscitation
CR	Controlled release

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_19,

CrCl	Creatinine clearance
CRF	Chronic renal failure
CRH	Corticotropin-releasing hormone
CRP	C-reactive protein
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CVA	Cerebral vascular disease, costovertebral angle
CVD	Cerebral vascular disease
CVP	Central venous pressure
CVVHD	Continuous veno-venous hemodialysis
CXR	Chest X-ray
D5W	5% dextrose water
DAT	Direct antiglobulin test
DBP	Diastolic blood pressure
DC	Direct current
DCIS	Ductal carcinoma in situ
DDAVP	Desmopressin acetate
DEXA	Dual-energy X-ray absorptiometry
DHEA	Dehydroepiandrosterone
DHEAS	Dehydroepiandrosterone sulfate
DI	Diabetes insipidus
DIC	Disseminated intravascular coagulation
DIP	Distal interphalangeal joint
DKA	Diabetic ketoacidosis
DLBCL	Diffuse large B-cell lymphoma
DLCO	Diffusion capacity of lung for carbon monoxide
DM	Diabetes mellitus
DM1	Type 1 diabetes mellitus
DM2	Type 2 diabetes mellitus
DMARDs	Disease-modifying agents of rheumatoid disease
DOT	Directly observed treatment
DPI	Dry powder inhaler
DPT	Diphtheria, pertussis, tetanus
dsDNA	Double-stranded DNA
DT	Delirium tremens
DVT	Deep vein thrombosis
Dx	Disease
EBV	Epstein–Barr virus
ECG	Electrocardiogram
EEG	Electroencephalography
EF	Ejection fraction
EGFR	Epidermal growth factor receptor
EHEC	Enterohemorrhagic *Escherichia coli*
EIEC	Enteroinvasive *Escherichia coli*
EMG	Electromyography
ENA	Extractable nuclear antigen
EPO	Erythropoietin
ER	Estrogen receptor, emergency room
ERCP	Endoscopic retrograde cholangiopancreatography
ESAS	Edmonton symptom assessment scale
ESBL	Extended spectrum β-lactamase
ESR	Erythrocyte sedimentation rate
ESRD	End-stage renal disease
ET	Essential thrombocytosis
ETEC	Enteropathogenic *Escherichia coli*
FAP	Familial adenomatous polyposis
Fe	Iron
FEV1	Forced expiratory volume (1 second)
FFP	Fresh frozen plasma
FH	Family history
FHF	Fulminant hepatic failure
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FNA	Fine needle aspirate
FNH	Focal nodular hyperplasia
FOB	Fecal occult blood
FSGS	Focal segmental glomerulosclerosis
FSH	Follicle-stimulating hormone
FTA-ABS	Fluorescent treponemal antibody-absorption
FUO	Fever of unknown origin
FVC	Forced vital capacity
G6PD	Glucose-6-phosphate dehydrogenase deficiency
GBM	Glomerular basement membrane, glioblastoma multiforme
GBS	Guillain–Barre syndrome
GCS	Glasglow coma scale
GCSF	Granulocyte colony-stimulating factor
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
Gm	Gram stain
GN	Glomerulonephritis
GU	Genitourinary
GVHD	Graft vs. host disease
GYN	Gynecological
H&N	Head and neck
Hb	Hemoglobin
HBV	Hepatitis B virus
HCL	Hairy cell leukemia
HCO_3	Bicarbonate
Hct	Hematocrit
HCV	Hepatitis C virus
HD	Hemodialysis
HDL	High density lipoprotein
HF	Heart failure
HHV8	Human herpes virus 8
HITT	Heparin-induced thrombocytopenia with associated thrombosis
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
HNPCC	Hereditary non-polyposis colorectal cancer
HR	Heart rate
HSP	Henoch–Schonlein purpura
HSV	Herpes simplex virus
HTLV	Human T-cell lymphoma virus
HU	Hounsfield unit
HUS	Hemolytic uremic syndrome
IADL	Instrumental activities of daily living
IBD	Inflammatory bowel disease
IBS	Irritable bowel syndrome
IBW	Ideal body weight
ICD	Implantable cardioverter-defibrillators
ICH	Intracerebral hemorrhage
ICP	Intracranial pressure
ICU	Intensive care unit
IDU	Injection drug use
IL	Interleukin
INF	Interferon
INH	Inhaler
INR	International normalized ratio
IPF	Idiopathic pulmonary fibrosis
IPI	International prognostic index
IR	Immediate release
ITP	Idiopathic thrombocytopenic purpura
IV	Intravenous
IVC	Inferior vena cava
IVP	Intravenous pyelogram
JVP	Jugular venous pressure
KOH	Potassium hydroxide
KPS	Karnofsky performance status
KUB	Kidney, ureter, and bladder X-ray study
LAA	Left atrial abnormality
LAD	Left anterior descending
LAE	Left atrial enlargement

LAHB	Left anterior hemiblock
LAP	Leukocyte alkaline phosphatase
LBBB	Left bundle branch block
LCIS	Lobular carcinoma in situ
LCX	Left circumflex artery
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LES	Lambert–Eaton syndrome
LFT	Liver function test
LH	Luteinizing hormone
Li	Lithium
LLL	Left lower lobe
LLQ	Left lower quadrant
LLSB	Left lower sternal border
LML	Left middle lobe
LMN	Lower motor neuron
LMWH	Low molecular weight heparin
LN	Lymph node
LOC	Level of consciousness
LPHB	Left posterior hemiblock
LR-	Negative likelihood ratio
LR+	Positive likelihood ratio
LSD	Lysergic acid diethylamide
LTBI	Latent tuberculosis infection
LUL	Left upper lobe
LUQ	Left upper quadrant
LUSB	Left upper sternal border
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVH	Left ventricular hypertrophy
MAC	*Mycobacterium avium* complex
MALT	Mucosa-associated lymphoid tissue
MAO	Monoamine oxidase
MAP	Mean arterial pressure
MCA	Middle cerebral artery
MCD	Minimal change disease
MCL	Mantle cell lymphoma
MCP	Metacarpal joint
MCV	Mean corpuscular volume
MDI	Metered dose inhaler
MDS	Myelodysplastic syndrome
MEDD	Morphine equivalent daily dose
MELD	Model for end-stage liver disease
MEN	Multiple endocrine neoplasia
MF	Myelofibrosis, mycosis fungoides
Mg	Magnesium
MGN	Membranous glomerulopathy
MGUS	Monoclonal gammopathy of uncertain significance
MHA-TP	Microhemagglutination assay for antibody to *Treponema pallidum*
MI	Myocardial infarction
MIBG	Iodine-131-meta-iodobenzylguanidine
MIBI	Methoxyisobutyl isonitrile
MM	Multiple myeloma
MMR	Measles, mumps, and rubella
MMSE	Mini-mental state examination
MPA	Microscopic polyangiitis
MPGN	Membranoproliferative glomerulopathy
MPS	Myeloproliferative syndrome
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MS	Mitral stenosis, multiple sclerosis
MSI	Microsatellite instability
MSK	Musculoskeletal
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MTC	Medullary thyroid cancer
MTP	Metatarsophalangeal joint
MZL	Marginal zone lymphoma
N&V	Nausea and vomiting
Na	Sodium
NAAT	Nucleic acid amplification test
NCS	Nerve conduction studies
NE	Norepinephrine
NEB	Nebulizer
NG	Nasogastric
NMDA	*N*-methyl-D-aspartic acid
NMS	Neuroleptic malignant syndrome
NNT	Number needed to treat
NPH	Normal pressure hydrocephalus, insulin
NPO	Nothing by mouth
NPV	Negative predictive value
NS	Normal saline
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NSIP	Nonspecific interstitial pneumonia
NSTE	Non-ST elevation
NYD	Not yet diagnosed
NYHA	New York Heart Association
O&P	Ovum and parasites
OHS	Obesity hypoventilation syndrome
OHS	Obesity hypoventilation syndrome
OR	Odds ratio
OSA	Obstructive sleep apnea
Osmo	Osmolality
PA	Posterior–anterior
PAC	Paroxysmal atrial contraction
P_aCO_2	Arterial carbon dioxide pressure
PAN	Polyarteritis nodosa
P_aO_2	Arterial oxygen pressure
PAOP	Pulmonary artery occlusion pressure
PaP	Palliative prognostic score
PAP	Pulmonary artery pressure
PBC	Primary biliary sclerosis
PCOS	Polycystic ovarian syndrome
PCR	Polymerase chain reaction
PCWP	Pulmonary capillary wedge pressure
PDA	Patent ductus arteriosus
PE	Pulmonary embolism
PEA	Pulseless electrical activity
PEEP	Positive end expiratory pressure
PEF	Peak expiratory flow
PET	Positron emission tomography
PFO	Patent foramen ovale
PFT	Pulmonary function test
PIP	Proximal interphalageal joint
PJP	*Pneumocystis jirovecii* pneumonia
PML	Progressive multifocal leukoencephalopathy
PMN	Polymorphonuclear neutrophil
PND	Paroxysmal nocturnal dyspnea
PNH	Paroxysmal nocturnal hemoglobinuria
PO	Oral
PPS	Palliative performance scale
PPV	Positive predictive value
PR	Progesterone receptor
PRV	Polycythemia ruba vera
PSA	Prostate-specific antigen
PSC	Primary sclerosing cholangitis
PSI	Pneumonia severity of illness score
PSV	Pressure support ventilation
PTCA	Percutaneous transluminal coronary angioplasty
PTCL	Peripheral T-cell lymphoma
PTH	Parathyroid hormone
PTLD	Post-transplant lymphoproliferative disease
PTP	Post transfusion purpura
PTT	Partial thromboplastin time

PTU	Propylthiouracil
PUD	Peptic ulcer disease
PVC	Paroxysmal ventricular contraction
PVD	Peripheral vascular disease
QID	Four times per day
RA	Rheumatoid arthritis
RAA	Right atrial abnormality
RAE	Right atrial enlargement
RAS	Renal artery stenosis
RBBB	Right bundle branch block
RBC	Red blood cell
RCA	Right coronary artery
RDW	Red blood cell distribution width
RF	Rheumatoid factor
RLL	Right lower lobe
RLQ	Right lower quadrant
RPGN	Rapidly progressive glomerulonephritis
RR	Respiratory rate, relative risk
RRR	Relative risk reduction
RSV	Respiratory syncytial virus
RSVP	Right ventricular systolic pressure
RTA	Renal tubular acidosis
RT-PCR	Reverse transcriptase polymerase chain reaction
RUL	Right upper lobe
RUQ	Right upper quadrant
RUSB	Right upper sternal border
SAH	Subarachnoid hemorrhage
SBP	Systolic blood pressure, spontaneous bacterial peritonitis
SCLC	Small cell lung cancer
SCT	Stem cell transplant
Sens	Sensitivity
SIADH	Syndrome of inappropriate antidiuretic hormone
SIRS	Systemic inflammatory response syndrome
SK	Streptokinase
SLE	Systemic lupus erythematosus
SLL	Chronic lymphocytic lymphoma
Spc	Specificity
SPN	Solitary pulmonary nodule
SR	Slow release
SSRI	Selective serotonin reuptake inhibitor
SSS	Sick sinus syndrome
SSSS	Staphylococcal scalded skin syndrome
STE	ST elevation
SVC	Superior vena cava
SVR	Systemic vascular resistance
SVT	Supraventricular tachycardia
TB	Tuberculosis
TBI	Total body irradiation
TCA	Tricyclic antidepressants
TD	Transdermal
TEE	Transesophageal echocardiogram
TGL	Triglyceride
TIA	Transient ischemic attack
TIBC	Total iron-binding capacity
TID	Three times per day
TIMI	Thrombolysis in myocardial infarction
TIPS	Transjugular intrahepatic portosystemic shunt
TLC	Total lung capacity
TNF	Tumor necrosis factor
TP-EIA	*Treponema pallidum* enzyme immunoassay
TPN	Total parenteral nutrition
TPO	Thyroid peroxidase
TPPA	*Treponema pallidum* particle agglutination assay
TRH	Thyrotropin releasing hormone
TSH	Thyroid stimulating hormone
TST	Tuberculin skin test
TTE	Transthoracic echocardiogram
TTP	Thrombotic thrombocytopenic purpura
TUR	Transurethral resection
TURP	Transurethral resection of prostate
U/A	Urinalysis
UGI	Upper gastrointestinal
UIP	Usual interstitial pneumonia
UMN	Upper motor neuron
UNC	Urine net charge
US	Ultrasound
UTI	Urinary tract infection
UV	Ultraviolet
V/Q	Ventilation/perfusion
VAP	Ventilator-associated pneumonia
VC	Vital capacity
VDRL	Venereal Disease Research Laboratory
VF	Ventricular fibrillation
VHL	Von Hippel–Lindau syndrome
VLDL	Very low density lipoprotein
VRE	Vancomycin-resistant enterococci
VSD	Ventricular septal defect
VT	Ventricular tachycardia
vWD	Von Willebrand disease
VZV	Varicella zoster virus
WBC	White blood cell
WPW	Wolff–Parkinson–White

Appendix C
COMMON LABORATORY VALUES AND UNIT CONVERSION

Note: normal ranges are provided for general reference only. The normal values for individual institution may vary significantly due to assay used and population tested. An excellent resource is the *AMA Manual of Style: A Guide for Authors and Editors*. 10th ed. New York, NY: Oxford University Press; 2007

BLOOD COUNTS	SI units	US units	SI→US ratio	US→SI ratio
Hematocrit				
Male	0.41–0.50	41–50%	100	0.01
Female	0.35–0.45	35–45%	100	0.01
Hemoglobin				
Male	140–175 g/L	14–17.5 g/dL	0.1	10
Female	120–160 g/L	12–16 g/dL	0.1	10
RBC count				
Male	$4.5–5.9\times10^{12}$/L	$4.5–5.9\times10^{6}$/μL	1	1
Female	$4.0–5.2\times10^{12}$/L	$4.0–5.2\times10^{6}$/μL	1	1
Platelet count	$140–440\times10^{9}$/L	$140–440\times10^{3}$/μL	1	1
WBC count	$4.5–11.0\times10^{9}$/L	$4.5–11.0\times10^{3}$/μL	1	1
Neutrophil	$1.7–7.3\times10^{9}$/L	$1.7–7.3\times10^{3}$/μL	1	1
Lymphocyte	$1.0–4.8\times10^{9}$/L	$1.0–4.8\times10^{3}$/μL	1	1
Monocyte	$0.08–0.70\times10^{9}$/L	$0.08–0.70\times10^{3}$/μL	1	1
Eosinophil	$0.04–0.40\times10^{9}$/L	$0.04–0.40\times10^{3}$/μL	1	1
Basophil	$0–0.10\times10^{9}$/L	$0–0.10\times10^{3}$/μL	1	1
CD4 count	$0.64–1.18\times10^{9}$/L	640–1175/mm^3	1000	0.001
CD8 count	$0.34–0.88\times10^{9}$/L	335–875/mm^3	1000	0.001
CD4:CD8 ratio	1.0–4.0	1.0–4.0	1	1
Reticulocyte count	0.005–0.025	0.5–2.5%	100	0.01

COAGULATION STUDIES	SI units	US units	SI→US ratio	US→SI ratio
aPTT	22.1–35.1 s	22.1–35.1 s	1	1
Bleeding time	2–9.5 min	2–9.5 min	1	1
D-dimer	<0.5 mg/L	<0.5 μg/mL	1	1
INR	0.8–1.2	0.8–1.2	1	1
PT	10–13 s	10–13 s	1	1
Thrombin time	16–24 s	16–24 s	1	1

TUMOR MARKERS	SI units	US units	SI→US ratio	US→SI ratio
AFP	<15 μg/L	<15 ng/mL	1	1
β2 microglobulin	0–2 mg/L	0–2 mg/L	1	1
CA 19–9	<37 kU/L	<37 U/mL	1	1
CA 27.29	<32 kU/L	<32 U/mL	1	1
CA 125	<35 kU/L	<35 U/mL	1	1
CEA	<4 μg/L	<4 ng/mL	1	1
HCG	<5 IU/L	<5 mIU/mL	1	1
PSA	<4 μg/L	<4 ng/mL	1	1

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_20,

TUMOR MARKERS (CONT'D)	SI units	US units	SI→US ratio	US→SI ratio
Serum protein electrophoresis				
Total protein	60–80 g/L	6–8 g/dL	0.1	10
Globulins	25–35 g/L	2.5–3.5 g/dL	0.1	10
Alpha1	2–4 g/L	0.2–0.4 g/dL	0.1	10
Alpha2	5–9 g/L	0.5–0.9 g/dL	0.1	10
Beta	6–11 g/L	0.6–1.1 g/dL	0.1	10
Gamma	7–17 g/L	0.7–1.7 g/dL	0.1	10

CHEMISTRY	SI units	US units	SI→US ratio	US→SI ratio
Albumin	35–50 g/L	3.5–5 g/dL	0.1	10
Calcium				
Regular	2.05–2.55 mmol/L	8.2–10.2 mg/dL	4	0.25
Ionized	1.1–1.4 mmol/L	4.5–5.6 mg/dL	4	0.25
Cardiac enzymes				
CK	40–150 U/L	40–150 U/L	1	1
Troponin				
Troponin I	0–0.4 μg/L	0.4 ng/mL	1	1
Troponin T	0–0.1 μg/L	0.1 ng/mL	1	1
CRP (high sens)	<8 mg/L	<8 mg/L	1	1
Electrolytes panel				
Na	136–142 mmol/L	136–142 mEq/L	1	1
K	3.5–5.0 mmol/L	3.5–5.0 mEq/L	1	1
Cl	96–106 mmol/L	96–106 mEq/L	1	1
HCO_3	22–30 mmol/L	22–30 mEq/L	1	1
Urea (BUN)	2.9–8.2 mmol/L	8–23 mg/dL	2.78	0.36
Creatinine	53–106 μmol/L	0.6–1.2 mg/dL	0.011	88.4
Cr clearance	1.24–2.08 mL/s	75–125 mL/min	59.9	0.017
Glucose				
Fasting	4.2–6.4 mmol/L	75–115 mg/dL	18.02	0.0555
Postprandial 2 h	<6.7 mmol/L	<120 mg/dL	18.02	0.0555
ESR				
Male	0–17 mm/h	0–17 mm/h	1	1
Female	1–25 mm/h	1–25 mm/h	1	1
Folate	7.0–39.7 nmol/L	3.1–17.5 ng/mL	0.44	2.27
Iron studies				
Ferritin				
Male	30–300 μg/L	30–300 ng/mL	1	1
Female	100–20 μg/L	100–200 ng/mL	1	1
Iron	5.4–28.7 μmol/L	30–160 μg/dL	5.56	0.18
TIBC	40.8–76.7 μmol/L	228–428 μg/dL	5.56	0.18
Transferrin	0–0.4 μg/L	0–0.4 ng/mL	1	1
Lipid profile				
LDL				
Optimal	<2.59 mmol/L	<100 mg/dL	38.5	0.026
Near normal	2.59–3.34 mmol/L	100–129 mg/dL	38.5	0.026
Borderline high	3.36–4.12 mmol/L	130–159 mg/dL	38.5	0.026
High	4.13–4.99 mmol/L	160–189 mg/dL	38.5	0.026
Very high	≥4.91 mmol/L	≥190 mg/dL	38.5	0.026
HDL			38.5	0.026
Low	<1.03 mmol/L	<40 mg/dL	38.5	0.026
High	≥1.55 mmol/L	≥60 mg/dL		
Total cholesterol				
Desirable	<5.17 mmol/L	<200 mg/dL	38.5	0.026
Borderline high	5.17–6.17 mmol/L	200–239 mg/dL	38.5	0.026
High	≥6.18 mmol/L	≥240 mg/dL	38.5	0.026
Triglycerides	<1.8 mmol/L	<160 mg/dL	90.9	0.011
Liver function tests				
AST	20–48 U/L	20–48 U/L	1	1
ALT	10–40 U/L	10–40 U/L	1	1
ALP	50–120 U/L	50–120 U/L	1	1
Bilirubin				
Total	5–21 μmol/L	0.3–1.2 mg/dL	0.058	17.1
Direct	<3.4 μmol/L	<0.2 mg/dL	0.058	17.1

CHEMISTRY (CONT'D)				
	SI units	**US units**	**SI→US ratio**	**US→SI ratio**
LDH	50–200 U/L	50–200 U/L	1	1
Magnesium	0.8–1.2 mmol/L	1.8–3.0 mg/dL	2.4	0.41
Phosphate	0.97–1.45 mmol/L	3–45 mg/dL	3.1	0.32
Uric acid	240–510 μmol/L	4.0–8.5 mg/dL	0.017	60
Vitamin B12				
Normal	>185 pmol/L	>250 pg/mL	1.35	0.74
Deficient	<92 pmol/L	<125 pg/mL	1.35	0.74
Amylase	25–100 U/L	25–100 U/L	1	1
Lipase	0–160 U/L	0–160 U/L	1	1

ENDOCRINE TESTING				
	SI units	**US units**	**SI→US ratio**	**US→SI ratio**
ACTH	<26 pmol/L	<120 pg/mL	4.54	0.22
Aldosterone				
Supine	55–250 pmol/L	2–9 ng/dL	0.036	27.7
Standing	2–5× supine value	2–5× supine value		
Calcitonin				
Male	0.8–7.6 pmol/L	3–26 pg/mL	3.42	0.292
Female	0.58–5.0 pmol/L	2–17 pg/mL	3.42	0.292
Cortisol				
8 am–noon	138–690 nmol/L	5–25 μg/dL	0.036	27.6
Noon–8 pm	138–414 nmol/L	5–15 μg/dL	0.036	27.6
8 pm–8am	0–276 nmol/L	0–10 μg/dL	0.036	27.6
EPO	5–36 U/L	5–36 U/L	1	1
Glucagon	20–100 ng/L	20–100 pg/mL	1	1
Insulin	14–140 pmol/L	2–20 μU/mL	0.14	6.95
Metanephrine				
Plasma	<0.5 nmol/L	<0.5 nmol/L	1	1
Urine, 24 h	<5 μmol	<1 mg	0.20	5.1
Norepinephrine	89–473 nmol	15–80 μg	0.17	5.9
Urine, 24 h				
Prolactin				
Male	0–20 μg/L	0–20 ng/mL	1	1
Female	0–15 μg/L	0–15 ng/mL	1	1
PTH	10–60 ng/L	10–60 pg/mL	1	1
Renin	0.7–1.0 pmol/L	30–40 pg/mL	42.2	0.024
Testosterone				
Men	9.4–37.1 nmol/L	270–1070 ng/dL	28.6	0.035
Women	0.21-2.98 nmol/L	6–86 ng/dL	28.6	0.035
Thyroglobulin	0–60 μg/L	0–60 ng/mL	1	1
TSH	0.5–5.0 mU/L	0.5–5.0 μU/mL	1	1
T3				
Free	3.5–6.5 pmol/L	230–420 pg/dL	65	0.015
Total	0.92–2.78 nmol/L	60–181 ng/dL	65	0.015
T4				
Free	10.3–35 pmol/L	0.8–2.7 ng/dL	0.078	13
Total	58–140 nmol/L	4.5–10.9 μg/dL	0.078	13
Vitamin D				
1,25–$(OH)_2$–vit D	60–108 pmol/L	25–45 pg/mL	0.42	2.4
25–(OH) vit D	35–150 nmol/L	14–60 ng/mL	0.4	2.5

DRUG LEVELS				
	SI units	**US units**	**SI→US ratio**	**US→SI ratio**
Acetaminophen				
Therapeutic range	66–199 μmol/L	10–30 μg/mL	0.15	6.6
Toxic range	>1324 μmol/L	>200 μg/mL	0.15	6.6
Amitriptyline				
Therapeutic range	433–903 nmol/L	120–250 ng/mL	0.28	3.6
Toxic range	>1805 nmol/L	>500 ng/mL	0.28	3.6
Carbamazepine				
Therapeutic range	26–51 μmol/L	6–12 μg/mL	0.24	4.2
Toxic range	>63 μmol/L	>15 μg/mL	0.24	4.2

DRUG LEVELS (CONT'D)	SI units	US units	SI→US ratio	US→SI ratio
Clonazepam				
Therapeutic range	48–190 nmol/L	15–60 ng/mL	0.31	3.2
Toxic range	>254 nmol/L	>80 ng/mL	0.31	3.2
Clozapine				
Therapeutic range	0.6–1.0 μmol/L	200–350 ng/mL	333	0.003
Cocaine				
Toxic dose	>3300 nmol/L	>1000 ng/mL	0.30	3.3
Diazepam				
Therapeutic range	0.35–3.51 μmol/L	100–1000 ng/mL	285	0.0035
Toxic range	>17.55 μmol/L	>5000 ng/mL	285	0.0035
Digoxin				
Therapeutic range	1.0–2.6 nmol/L	0.8–2.0 ng/mL	0.78	1.28
Toxic range	>3.2 nmol/L	>2.5 ng/mL	0.78	1.28
Ethanol				
Toxic dose	>65 mmol/L	>300 mg/dL	4.6	0.22
Gentamicin				
Peak	16.7–20.9 μmol/L	8–10 μg/mL	0.48	2.1
Trough	<4.2–8.4 μmol/L	<2–4 μg/mL	0.48	2.1
Imipramine				
Therapeutic range	446–893 nmol/L	125–250 ng/mL	0.28	3.57
Toxic range	>1784 nmol/L	>500 ng/mL	0.28	3.57
Lidocaine				
Therapeutic	6.4–26 μmol/L	1.5–6.0 μg/mL	0.23	4.3
Lithium				
Therapeutic	0.6–1.2 nmol/L	0.6–1.2 mEq/L	1	1
Toxic range	>2 mmol/L	>2 mEq/L	1	1
Methadone				
Therapeutic range	0.32–1.29 μmol/L	100–400 ng/mL	313	0.0032
Toxic range	>6.46 μmol/L	>2000 ng/mL	313	0.0032
Morphine				
Therapeutic range	35–280 nmol/L	10–80 ng/mL	0.29	3.5
Toxic range	>700 nmol/L	>200 ng/mL	0.29	3.5
Nortriptyline				
Therapeutic range	0.19–0.65 nmol/L	50–170 ng/mL	263	0.0038
Toxic range	>1.9 μmol/L	>500 ng/mL	263	0.0038
Phenytoin				
Therapeutic range	40–79 μmol/L	10–20 μg/mL	0.25	3.95
Toxic range	>79 μmol/L	>20 μg/mL	0.25	3.95
Salicylates				
Therapeutic range	1086–2172 μmol/L	150–300 μg/mL	0.14	7.24
Toxic range	>2172 μmol/L	>300 μg/mL	0.14	7.24
Theophylline				
Therapeutic range	44–111 μmol/L	8–20 μg/mL	0.18	5.5
Toxic range	>110 μmol/L	>20 μg/mL	0.18	5.5
Tobramycin				
Peak	17–21 μmol/L	8–10 μg/mL	0.44	2.25
Trough	<9 μmol/L	<4 μg/mL	0.44	2.25
Valproic acid				
Therapeutic range	347–1040 μmol/L	50–150 μg/mL	0.14	6.9
Toxic range	>1040 μmol/L	>150 μg/mL	0.14	6.9
Vancomycin				
Peak	12–18 μmol/L	18–26 μg/mL	1.67	0.6
Trough	3–7 μmol/L	5–10 μg/mL	1.67	0.6
Amikacin				
Peak	43–60 μmol/L	25–35 μg/mL	0.59	1.7
Trough	6.8–13.7 μmol/L	4–8 μg/mL	0.59	1.7

Appendix D
HISTORY TEMPLATE

BASIC SCHEME

CHIEF COMPLAINT:

HISTORY OF PRESENT ILLNESS:
Onset
Position/posture
Previous history
Progression
Quality
Radiating
Severity
Temporal factors
Treatment
Understanding

Aggravating
Alleviating
Associated symptoms

Etiologies
Risk factors
Complications

How has illness affected your life
Support systems
Worries, fears
Expectations

PAST MEDICAL HISTORY:
Hospitalization (time, tx, recovery)
Medical illnesses (time, tx, recovery)
Injuries (time, tx, recovery)

MEDICATIONS:
drug name, dose, route, frequency

ALLERGIES:

IMMUNIZATIONS:

SOCIAL HISTORY:
☐ **Living arrangement, marital**
☐ **Support system** ☐ Hobbies

☐ **ADLs** ☐ **IADLs**
☐ Education ☐ **Occupation**

☐ **Smoking** ☐ **Alcohol**
☐ **Illicit drugs** ☐ Diet

FAMILY HISTORY:
Father **Mother**
Siblings Children
☐ **Cancer** ☐ **Heart disease**
☐ Diabetes ☐ Genetic disease

REVIEW OF SYSTEMS

CONSTITUTIONAL:
☐ **Weight Δ** ☐ **Energy**
☐ **Fever, chills** ☐ **Night sweats**
☐ Appetite Δ ☐ Sleep
☐ Mood Δ

HEAD AND NECK:
☐ **Vision Δ** ☐ **Diplopia Δ**
☐ Smell ☐ Rhinorrhea
☐ Sinusitis ☐ Epistaxis
☐ **Hearing Δ** ☐ Discharge
☐ Tinnitus ☐ Vertigo
☐ Sore throat ☐ Teeth
☐ Tongue ☐ Oral lesions
☐ **Neck pain** ☐ Neck mass

CARDIAC:
☐ **Chest pain** ☐ **Dyspnea**
☐ **Syncope** ☐ **Palpitations**
☐ **Orthopnea** ☐ **PND**
☐ **Claudication** ☐ **Leg edema**
☐ Murmurs ☐ Hypertension
☐ Rheumatic fever

RESPIRATORY:
☐ **Dyspnea** ☐ **Cough**
☐ **Sputum** ☐ **Hemoptysis**
☐ **Pleuritic chest pain**

GASTROINTESTINAL:
☐ **Dysphagia** ☐ Odynophagia
☐ **Heartburn** ☐ Reflux
☐ **N&V** ☐ **Hematemesis**
☐ **Melena** ☐ **Abd pain**
☐ **Diarrhea** ☐ **Constipation**
☐ **Bowel habits** ☐ **Hematochezia**
☐ Bloating ☐ Flatus
☐ Pale stool ☐ Jaundice
☐ Hemorrhoid

GENITOURINARY:
☐ **Dysuria** ☐ **Frequency**
☐ **Urgency** ☐ Hesitancy
☐ **Incontinence** ☐ Slow stream
☐ **Hematuria** ☐ Nocturia
☐ Discharge
☐ Libido ☐ **Impotence**

RHEUMATOLOGIC:
☐ **Joint pain, swelling, redness**
☐ **AM stiffness** ☐ **Back pain**
☐ Myalgia ☐ Arthralgia
☐ Skin rash ☐ Raynaud's
☐ Dry eyes ☐ Dry mouth
☐ Oral ulcers ☐ Hair loss
☐ Photosensitivity
☐ Psoriasis ☐ IBD

OBS/GYN:
☐ **Menarche age** ☐ LMP
☐ Cycle regular ☐ Period length
☐ Periods freq. ☐ Period volume
☐ **Menopause age** ☐ HRT
☐ **Abnormal bleeding**
☐ **No. of preg.** ☐ Difficult preg.
☐ **Contraception** ☐ STDs
☐ Vaginal dryness or discharge
☐ Dyspareunia

BREASTS:
☐ **Masses** ☐ Swelling
☐ **Nipple discharge**
☐ Pain
☐ Self breast exam

ENDOCRINE:
☐ **Polydipsia** ☐ Polyphagia
☐ **Polyuria** ☐ Galactorrhea
☐ **Heat or cold tolerance**

NEUROPSYCHIATRIC:
☐ **Unconscious** ☐ **Syncope**
☐ **Vertigo** ☐ Dizziness
☐ Memory loss ☐ Dysphasia
☐ Head trauma ☐ Strokes
☐ **Headaches** ☐ **Seizures**
☐ **Weakness** ☐ **Paresis**
☐ Clumsiness ☐ Balance/gait

☐ **Depression** ☐ Suicidal
☐ **Anxiety** ☐ Previous ψ hx

SKIN:
☐ **Rashes** ☐ **Lumps**
☐ Pruritus ☐ Pigment Δ

REMARKS:

D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9_21,

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D. Hui, *Approach to Internal Medicine*, DOI 10.1007/978-1-4419-6505-9,

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Selected Internal Medicine Topics

Integrated Symptom-Based and Issue-Based Approach

from *Approach to Internal Medicine*, 3rd Edition

David Hui, MD, M.Sc., FRCPC

Signs and Symptoms

Approach to Physical Examination

JAMA Rational Clinical Examination Series

Approach to Investigations

Therapeutics Tables

Laboratory Abnormalities

Commonly Used Formulas

Medical Emergencies