Approach to Internal Medicine
Approach to Internal Medicine
A Resource Book for Clinical Practice
Third Edition

by

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and

Raj Padwal, MD, M.Sc., FRCPC
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.

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Asthma Exacerbation

Differential Diagnosis of Wheezing

Extrathoracic Airway Obstruction
- **Oropharynx**: enlarged tonsils, retropharyngeal abscess, obesity, post nasal drip
- **Larynx**: laryngeal edema, laryngostenosis, laryngocoele, 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 (Cont’d)

**Physical**
- HR ↑, RR ↑, pulsus paradoxus, O₂ 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: CBC, 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 O₂** 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, MgSO₄

Mechanical Ventilation: BIPAP, intubation
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 4 weeks, 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

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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

<table>
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<th>PEF (L/min)</th>
<th>PaO2</th>
<th>Action</th>
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<tr>
<td>Very severe</td>
<td>&lt;1.6 (&lt;40%)</td>
<td>&lt;200 (&lt;40%)</td>
<td>&lt;90% with O2</td>
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<tr>
<td>Severe</td>
<td></td>
<td></td>
<td>&lt;90%</td>
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<tr>
<td>Moderate</td>
<td>1.6 2.1</td>
<td>200 300</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Mild</td>
<td>&gt;2.1 (&gt;60%)</td>
<td>&gt;300 (&gt;60%)</td>
<td>&gt;90%</td>
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DISCHARGE CRITERIA consider discharging patient if peak flow >70% of usual (or predicted) value for at least 1 h after bronchodilator

OXYGEN DELIVERY DEVICES

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<th>Flow rates</th>
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<td>Nasal cannula</td>
<td>1 L/min</td>
<td>21 24%</td>
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<td>2 L/min</td>
<td>25 28%</td>
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<td></td>
<td>3 L/min</td>
<td>29 32%</td>
</tr>
<tr>
<td></td>
<td>4 L/min</td>
<td>33 36%</td>
</tr>
<tr>
<td></td>
<td>5 L/min</td>
<td>37 40%</td>
</tr>
<tr>
<td></td>
<td>6 L/min</td>
<td>41 44%</td>
</tr>
<tr>
<td>Simple oxygen face mask</td>
<td>6 L/min</td>
<td>35 60%</td>
</tr>
<tr>
<td>Face mask with oxygen reservoir (non rebreather mask)</td>
<td>6 L/min</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>7 L/min</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>8 L/min</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>9 L/min</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>10 15 L/min</td>
<td>95+%</td>
</tr>
<tr>
<td>Venturi mask</td>
<td>4 8 L/min</td>
<td>24 40%</td>
</tr>
<tr>
<td></td>
<td>10 12 L/min</td>
<td>40 50%</td>
</tr>
</tbody>
</table>

**NOTE:** delivered O2 (FiO2) 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 E₂ → ↑ leukotriene synthesis → asthma symptoms. Manage ment include ASA/NSAIDs avoidance and leukotriene antagonists (montelukast)

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)
- **PATHOPHYSIOLOGY** associated with asthma and cystic fibrosis. Due to colonization of the airways by *Aspergillus fumigatus*, leading to an intense, immediate hypersensitivity type reaction in the airways
- **CLINICAL FEATURES** history of asthma, recurrent episodes of fever, dyspnea, and productive cough (brownish sputum). Peripheral eosinophilia. CXR findings of patchy infiltrates and central bronchiectasis
- **TREATMENTS** systemic glucocorticoids, itraconazole

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** 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** Sensitivity
- **Spc** Specificity
- **LR+** Positive Likelihood Ratio
- **LR-** Negative Likelihood Ratio

<table>
<thead>
<tr>
<th>History</th>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking &gt;70 pack year</td>
<td>40%</td>
<td>95%</td>
<td>8</td>
<td>0.63</td>
</tr>
<tr>
<td>Smoking ever</td>
<td>92%</td>
<td>49%</td>
<td>1.8</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**Sens** 20% **Spc** 95% **LR+** 4 **LR-** 0.84
**Sens** 30% **Spc** 90% **LR+** 3 **LR-** 0.78
**Sens** 51% **Spc** 84% **LR+** 3.8 **LR-** 0.66
**Sens** 27% **Spc** 88% **LR+** 2.2 **LR-** 0.83
**Sens** 51% **Spc** 71% **LR+** 1.8 **LR-** 0.69
**Sens** 82% **Spc** 33% **LR+** 1.2 **LR-** 0.55

**PHYSICAL**
- **Wheeze** 15% **Sens** 100% **Spc** 36 **LR+** 0.85
- **Barrel chest** 10% **Sens** 99% **Spc** 10 **LR+** 0.90
- **Decreased cardiac dullness** 13% **Sens** 99% **Spc** 10 **LR+** 0.88

**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**
ACUTE MANAGEMENT

ABC O₂ to keep sat >90%, or 88–92% if CO₂ 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 (levofloxacin 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 influenzavaccine 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, therapeutically level 10-20 μg/mL

SIXTH LINE fifth line plus home O₂

CLINICAL FEATURES (CONT’D)

STEREOTYPES (not useful clinically)

- BLUE BLOATER (more chronic bronchitis) cough and sputum, hypoxemia, CO₂ 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) |

INVESTIGATIONS

BASIC

- LABS CBCD, lytes, urea, Cr, troponin/CK, Ca, Mg, PO₄
- 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=4
- SCORING hazard ratio for death from any cause per one point increase in BODE score is 1.34

NEJM 2004 350:10

JAMA 2000 283:14

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SIXTH LINE fifth line plus home O₂
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 O₂

INDICATIONS FOR SUPPLEMENTAL HOME O₂
ABG done in room air. PaO₂ <55 mmHg alone or PaO₂ <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 bronchial obliterans (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, centric) 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

**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 *Bacteroides*, Peptostreptococcus, *Fusobacterium* species and other Gram positive bacilli

**CHEMICAL PNEUMONITIS**

**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 for mation, parapneumonic effusion/empyema, pleur itis ± hemorrhage
- **EXTRAPULMONARY** purulent pericarditis, hypoxaemia, sepsis

**CLINICAL FEATURES**

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>LR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>1.8</td>
</tr>
<tr>
<td>Cough</td>
<td>1.8</td>
</tr>
<tr>
<td>Spurtm</td>
<td>1.3</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1.4</td>
</tr>
<tr>
<td>Fever</td>
<td>1.7</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.10</td>
</tr>
<tr>
<td>Dementia</td>
<td>3.4</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>2.2</td>
</tr>
<tr>
<td>Physical</td>
<td></td>
</tr>
<tr>
<td>RR &gt;25</td>
<td>1.5</td>
</tr>
<tr>
<td>Dulness to percussion</td>
<td>2.2</td>
</tr>
<tr>
<td>Decreased breath sounds</td>
<td>2.3</td>
</tr>
</tbody>
</table>

**CLINICAL FEATURES (CONT’D)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crickles</td>
<td>1.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Bronchial breath sounds</td>
<td>3.5</td>
<td>0.90</td>
</tr>
<tr>
<td>Egophony</td>
<td>2.0</td>
<td>8.6</td>
</tr>
</tbody>
</table>

**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

**INVESTIGATIONS**

**BASIC**
- **LABS** CBC, 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

**Related Topics**
- Hypoxemia (p. 92)
- Parapneumonic Effusion and Empyema (p. 10)
- Ventilator Associated Pneumonia (p. 96)
INVESTIGATIONS (CONT’D)

SPECIAL
- BRONCHOSCOPY
- NASOPHARYNGEAL SWAB if suspect viral infection, check for influenza A/B, parainfluenza, human metapneumovirus, RSV, adenosvirus
- 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), PaO2 <60 mmHg or O2 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 (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).

CAUSES OF RECURRENT PNEUMONIA immunocompromised (WISDOM)WISDOM immunocompromised (WISDOM) immunocompromised (WISDOM) immunocompromised (WISDOM) immunocompromised (WISDOM), antiinflammatory agents, antibiotics, diabetics, immuno compromised host, antibiotics, pulmonary embolism, pericardial effusion, tamponade.

SPECIFIC ENTITIES (CONT’D)

CAUSES OF RECURRENT PNEUMONIA

- IMMUNOCOMPROMISED ★SADDIST★
- SUPPRESSANTS (steroids, chemotherapy, transplant medications, alcohol), AIDS, DIABETICS, DECREASED NUTRITION, Immunglobulin (hypogammaglobulinemia), Solid organ failure (renal, liver, splenectomy), Tumors
- PULMONARY bronchiectasis, COPD, cystic fibrosis, abnormal anatomy
- GI aspiration

LUNG ABSCCESS

- 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.

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 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
- HYPERCOAGULABILITY 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

Pulmonary Embolism

NEJM 2008 359:26
INVESTIGATIONS

BASIC
- LABS  CBCD, lytes, urea, Cr, PTT, INR, troponin/CK x 3, D dimer (if low probability for PE or outpatien), 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 S1Q3T3 (tall S wave in lead I, Q wave and inverted T wave in lead III)
- ABG  if respiratory distress

SPECIAL
- ECHOCARDIOGRAM  to check for right heart strain (dilated RV and elevated RVSP). Particularly important if hemodynamic changes
- PULMONARY ANGIOGRAM  gold standard
- THROMBOPHILIA WORKUP  factor V Leiden, pro thrombin G20210A, anticardiolipin antibody, lupus anticoagulant, protein C, protein S, antithrombin III, fibrinogen; consider homocysteine level and workup for paroxysmal nocturnal hemo globinuria 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, Westmark’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), immobilitation 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

MANAGEMENT

ACUTE  ABC, O2 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

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

NEJM 2003 349:13
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

**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, urinohydrothorax, 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)

**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

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymmetric chest expansion</td>
<td>74%</td>
<td>91%</td>
<td>8.1</td>
<td>0.29</td>
</tr>
<tr>
<td>Auscultatory percussion</td>
<td>77%</td>
<td>92%</td>
<td>7.7</td>
<td>0.27</td>
</tr>
<tr>
<td>Crackles</td>
<td>56%</td>
<td>62%</td>
<td>1.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Diminished breath sounds</td>
<td>42%</td>
<td>83%</td>
<td>4.3</td>
<td>0.15</td>
</tr>
<tr>
<td>Dullness to conventional percussion</td>
<td>73%</td>
<td>91%</td>
<td>8.7</td>
<td>0.31</td>
</tr>
<tr>
<td>Pleural friction rub</td>
<td>5.30%</td>
<td>99%</td>
<td>3.9</td>
<td>0.96</td>
</tr>
</tbody>
</table>

**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)
CLINICAL FEATURES (CONT’D)

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced tactile fremitus</td>
<td>82%</td>
<td>86%</td>
<td>5.7</td>
<td>0.21</td>
</tr>
<tr>
<td>Reduced vocal resonance</td>
<td>76%</td>
<td>88%</td>
<td>6.5</td>
<td>0.27</td>
</tr>
</tbody>
</table>

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, surgical biopsy (video assisted thoracic surgery)

DIAGNOSTIC ISSUES (CONT’D)

- FLUID EOSINOPHILIA (>10%) paragonimiasis, malignancy, Churg Strauss, asbestos, drug reaction, pulmonary embolism, hemotorax, 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 O₂, 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 location 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 uniloculated 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 hemotorax. 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, neoplasms, 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
• SINUS IMAGING
• METHACHOLINE CHALLENGE
• ESOPHAGEAL pH MONITORING

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
**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**
- CBC, 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**
- **Anemia 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, O₂, 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 × 1 dose or FFP); **Antibiotics;** radiation for tumors; **Diuresis** for HF; **Immunosuppression** for vasculitis

**Specific Entities**

**Goodpasture Disease**

**Pathophysiology** antibasement membrane antibodies → attack pulmonary and renal base ment membrane

**Clinical Features** hemoptysis and hematuria, with respiratory and renal failure if severe

**Diagnosis** lung/kidney biopsy

**Treatments** steroids, cyclophosphamide, plasma pheresis

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**Solitary Pulmonary Nodule**

**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**
- CBC, 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**
- **Age** >50
- **Border** irregular, nodular cavity with thick wall, or spiculation
- **Calcification** eccentric or uncalcified

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**Solitary Pulmonary Nodule**

**NEJM 2003 348:25**
DIAGNOSTIC ISSUES (CONT’D)
- Diameter >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/uncalculated 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 trans thoracic (CT/US guided) biopsy. If high probability, thoracotomy with resection or video assisted thoraicoscopy (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

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

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

GROUP II. PULMONARY VENOUS HYPERTENSION
- LEFT SIDED ATRIAL OR VENTRICULAR HEART DISEASE, LEFT SIDED VALVULAR HEART DISEASE

WHO CLASSIFICATION OF PULMONARY HYPERTENSION (CONT’D)
- 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

NEJM 2004 351:15; NEJM 2004 351:16
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 dis orders), 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

INVESTIGATIONS

BASIC

LABS CBC, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, INR, albumin, ANA, RF, anti CCP, anti SCL 70, anticitrionere 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 O₂, 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, sulfonlyurea, gold, penicillamine, phenytoin, amiodarone, nitrofurantoin

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

Inhalation Injury

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, sulfonlyurea, gold, penicillamine, phenytoin, amiodarone, nitrofurantoin

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, anticientromere antibody, anti Jo antibody
- IMAGING CXR, CT chest (high resolution), echo cardiogram (if suspect pulmonary hypertension)

ABG

PFT

SPECIAL
- BIOPSY bronchoscopy (transbronchial biopsy), open lung biopsy

DIAGNOSTIC ISSUES (CONT’D)

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 asbestosis

- 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 FIBROSI S (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, subpleural, 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

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**Obstructive Sleep Apnea**

**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)

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**Specific Entities** (cont’d)

- 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

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**Obstructive Sleep Apnea**

**NEJM 2007 356:17**

**DIFFERENTIAL DIAGNOSIS OF SLEEP DISORDERS**

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

**NARCOLEPSY**

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

**RESTLESS LEG SYNDROME**

Pathophysiology associated with iron deficiency, hypoparathyroidism, uremic neuropathy, diabetic neuropathy, rheumatoid arthritis, and fibromyalgia.

Clinical features: desire to move extremities, associated with paresthesias, dysesthesias, and motor restlessness (floor pacing, leg rubbing). Symptoms tend to be worse at rest, particularly in the evenings and at night. Relieved by activity.

Treatments: dopamine agonists (pergolide, pramipexole, or ropinirole), levodopa/carbidopa, gabapentin, clonazepam, and oxycodone if precipitated by pain. A trial of iron therapy is indicated in all patients even in the absence of overt iron deficiency.

NEJM 2003 348:21

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**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** PaCO₂ >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, O₂, 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** \( \text{PaCO}_2 < 40 \text{ mmHg} \) (or lower limit of normal), which is synonymous with hyperventilation

**Investigations**

**Basic/C15 Labs**
- CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, TSH, urinalysis, βhCG in women of reproductive age

**Imaging**
- CXR, CT chest

**ABG**

**Special**
- **Septic Workup** blood C&S, urine C&S
- **D Dimer** if suspect PE but low probability

**Management**

**Acute** ABC, O₂, 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 Interpretation**

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, O₂ 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>PA Film</th>
<th>Lateral Film</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular hypertrophy</td>
<td>Enlargement of left heart border inferiorly and laterally</td>
<td>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)</td>
</tr>
<tr>
<td>Left atrial enlargement</td>
<td>Prominence of left atrial appendage</td>
<td>Enlargement of posterior border of heart</td>
</tr>
<tr>
<td>Right atrial enlargement</td>
<td>Bulging right heart border</td>
<td>Enlargement of anterior and superior aspects of heart</td>
</tr>
<tr>
<td>Right ventricular hypertrophy</td>
<td>Enlargement of left heart border laterally</td>
<td>Enlargement of anterior and superior aspects of heart</td>
</tr>
</tbody>
</table>

## Approach to Chest X Ray Interpretation (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**: Nodular or reticulonodular 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 (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, pneumocystis, 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), non specific inflammation (sarcoidosis, silicosis, Berylliosis, connective tissue disease)
LUNG MASS ABUTTING THE HILUM

MEDIASTINAL MASSES

SUPERIOR MEDIASTINUM (above horizontal line drawn between sternum/manubrial joint and T4 vertebra) thyroid goiters, cystic hygromas, adenopathy, aneurysm
ANTERIOR MEDIASTINUM (in front of heart border)★5Ts★
- Thymoma
- Thyroid retrosternal
- Teratoma
- Terrible lymphoma
- Tumor 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, ganglioneurinoma]), 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 dia phragms, 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 sarcoïdosis, 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 extra thoracic obstruction, compared to intrathoracic obstruction, affecting the expiratory curve (i.e. positive portion of the flow volume loop).

**RESTRICTIVE DISEASE**

Expiratory portion of curve appears relatively tall (preserved flow rates), but narrow (↓ lung volumes)

**SPIROMETRY AND LUNG VOLUME PATTERNS**

**OBSTRUCTIVE DISEASE**

↓ FEV1/FVC ratio (↓ FEV1 out of proportion to ↓ FVC); definitions vary but GOLD criteria define ↓ FEV1/FVC as <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**

<table>
<thead>
<tr>
<th>Obstructive</th>
<th>TLC</th>
<th>FEV1/FVC</th>
<th>MIP</th>
<th>MEP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N/↑</td>
<td>↓</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Restrictive

- Parenchymal ↓ N/↑ N N
- Extraparenchymal (inspiratory) ↓ N N/↓ N
- Extraparenchymal (in+expiratory) ↓ ↓ N/↑ N/↓ N/↓
ANALYZING DLCO

<table>
<thead>
<tr>
<th>REFERENCE VALUES FOR DLCO</th>
<th>% predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt;140%</td>
</tr>
<tr>
<td>Normal</td>
<td>81 140%</td>
</tr>
<tr>
<td>Borderline low</td>
<td>76 80%</td>
</tr>
<tr>
<td>Mild decrease</td>
<td>61 75%</td>
</tr>
<tr>
<td>Severe decrease</td>
<td>&lt;40%</td>
</tr>
</tbody>
</table>

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

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

**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
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, pleuritis
- VASCULAR pulmonary embolism, pulmonary hypertension

Gastrointestinal (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 syncpe/hemiplegia/death
- ANTERIOR SPINAL paraplegia/quadruplegia, 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?

<table>
<thead>
<tr>
<th></th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Sudden chest pain</td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Tearing or ripping pain</td>
<td>1.2</td>
<td>10.8</td>
</tr>
<tr>
<td>Physical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse deficit</td>
<td>5.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Focal neurological deficit</td>
<td>6.6</td>
<td>33</td>
</tr>
<tr>
<td>Diastolic murmur</td>
<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>CXR/ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enlarged aorta or wide mediastinum</td>
<td>2.0</td>
<td>0.3</td>
</tr>
<tr>
<td>LVH on ECG</td>
<td>0.2</td>
<td>3.2</td>
</tr>
</tbody>
</table>

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

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
- AORTOGRAPHY

IMAGING

ECG

SPECIAL

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 O₂ 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

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 esophageitis, esophageal cancer, GERD, peptic ulcer disease, Boerhaave’s, cholecystitis, pancreatitis

OTHERS musculoskeletal (costochondritis), shin splints, anxiety

PATHOPHYSIOLOGY

Pre clinical
Angina
Pathologic changes
Atherosclerosis
Luminal narrowing
Plaque rupture or thrombus
Partial occlusion
Complete occlusion
Clinical presentation
Asymptomatic
Central chest discomfort; worsened by exertion, emotion, and eating; relieved by rest and nitroglycerine
Worsening pattern or rest pain
Non ST elevation MI
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

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>LR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation to right arm</td>
<td>2.9</td>
</tr>
<tr>
<td>Radiation to left arm</td>
<td>2.3</td>
</tr>
</tbody>
</table>

CLINICAL FEATURES (CONT’D)

<table>
<thead>
<tr>
<th>Feature</th>
<th>LR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation to both arms</td>
<td>7.1</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>1.9</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>2.0</td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>0.2</td>
</tr>
<tr>
<td>Sharp or stabbing chest</td>
<td>0.3</td>
</tr>
<tr>
<td>Positional chest pain</td>
<td>0.3</td>
</tr>
<tr>
<td>Chest pain reproducible</td>
<td>0.2</td>
</tr>
</tbody>
</table>

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 CBC, lytes, urea, Cr, glucose, troponin/CK × 3 q8h, AST, ALT, ALP, bilirubin, INR/PTT, Mg, Ca, PO4, 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
ACUTE MANAGEMENT

ABC  O₂ to keep sat >95%, IVs, inotropes, consider balloon pump if hemodynamic instability

PAIN CONTROL  nitroglycerin (nitro drip) 25 mg in 250 mL DSW, 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.

IN HOSPITAL OUTCOMES

<table>
<thead>
<tr>
<th></th>
<th>NSTEMI</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>0.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>2.8%</td>
<td>6.4%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.7%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>10%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>ACTION registry 2008/2009 data</td>
<td></td>
</tr>
</tbody>
</table>
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**

- **ANTIPATELET** 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. Tenecteplase 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 contra indicated. 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**

<table>
<thead>
<tr>
<th></th>
<th>Stable angina</th>
<th>Unstable angina or NSTEMI</th>
<th>STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Nitrates</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Morphine</td>
<td>±</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>β blockers</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>HMG CoA inhibitors</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Heparin or antithrombin</td>
<td>NO</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>NO</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>GPIIb/IIa inhibitors</td>
<td>NO</td>
<td>✓ (if TIMI ≥3)</td>
<td>NO</td>
</tr>
<tr>
<td>Fibrinolytics or PCIa</td>
<td>NO</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cardiology consult</td>
<td>Outpatientb</td>
<td>CCUc</td>
<td>CCUc</td>
</tr>
</tbody>
</table>

*afor 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
bOutpatient cardiology for stress test
CcCCU 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 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. Angio-plasty 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

#### 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. Contra indicated 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 anis streptolase (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
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, hematoma, 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. 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) cardiac 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)

### 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

### OUTCOMES FOR FIBRINOLYTTICS VS. PRIMARY PCI

<table>
<thead>
<tr>
<th></th>
<th>Fibrinolysis</th>
<th>Primary PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal reinfarction</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Stroke</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Death (4–6 weeks)</td>
<td>7% 9%</td>
<td>5% 7%</td>
</tr>
<tr>
<td>Combined endpoint of death/fatal reinfarction and stroke</td>
<td>14%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*NEJM 2007 356:1; NEJM 2007 356:10; NEJM 357:16*
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, post pericardiotomy

---

**CLINICAL FEATURES**

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

<table>
<thead>
<tr>
<th><strong>Sens</strong></th>
<th><strong>Spc</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>87 89%</td>
</tr>
<tr>
<td>Fever</td>
<td>25%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>20%</td>
</tr>
<tr>
<td>Cough</td>
<td>7  10%</td>
</tr>
</tbody>
</table>

**Physical**

- Tachycardia 77%
- Pulsus paradoxus >10 mmHg 82%
- Elevated JVP 76%
- ↓ heart sounds 28%
- Hypotension 26%
- Hypertension 33%
- Tachypnea 80%
- Peripheral edema 21 28%
- Pericardial rub 19 29%
- Hepatomegaly 28 55%
- Kussmaul sign 26%

**ECG**

- Low voltage 42%
- Atrial arrhythmia 6%
- Electrical alternans 16 21%
- ST elevation 18 30%
- PR depression 18%

*aPulsus paradoxus LR+ 3.3, LR 0.03

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

JAMA 2007 297:16

**DISTINGUISHING FEATURES OF ACUTE TAMPOANDE AND CHRONIC CONSTRUCTIVE PERICARDITIS**

<table>
<thead>
<tr>
<th><strong>Acute tamponade</strong></th>
<th><strong>Constrictive pericarditis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitals</td>
<td>Hypotension, Pulsus paradoxus (rare)</td>
</tr>
<tr>
<td></td>
<td>Elevated, Kussmaul (rare)</td>
</tr>
<tr>
<td>JVP</td>
<td>Prominent x’ descent but blunted y descent</td>
</tr>
<tr>
<td></td>
<td>(Friedrich’s sign)</td>
</tr>
<tr>
<td>Apex beat</td>
<td>Impalpable</td>
</tr>
<tr>
<td>Heart sounds</td>
<td>Distant</td>
</tr>
<tr>
<td>Other features</td>
<td>Impalpable</td>
</tr>
<tr>
<td></td>
<td>Distant, early S3/knock</td>
</tr>
<tr>
<td></td>
<td>Hepatosplomegaly, edema</td>
</tr>
</tbody>
</table>

(Ewart sign)
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

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

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

MANAGEMENT

ACUTE PERICARDITIS
- ASA (650 mg PO TID x 3-4 weeks), NSAIDs (indomethacin 25-50 mg PO TID x 2-4 weeks). Add colchicine 0.6 mg PO BID x 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 x 4-8 weeks) or NSAIDs (indomethacin 25-50 mg PO TID x 2-4 months). Add colchicine (0.6 mg PO BID x 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

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

CONSTRUCTIVE PERICARDITIS
- complete pericardectomy

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)

CONSTRUCTIVE 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

Differential Diagnosis of HF Exacerbation/Dyspnea

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

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

MANAGEMENT (CONT’D)

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

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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
• 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, rubella, varicella, 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, hyperthyroidism, acromegaly, pheochromocytoma), storage diseases (glycogen storage disease, Fabry’s disease, Gaucher’s disease, Nieman Pick disease), nutritional deficiencies (Beriberi, Kwashiorkor, pellagra), deposition (amyloidosis, hemochromatosis, sarcoidosis)

• Muscular dystrophies (mostly dilated) Duchenne, Becker’s, myotonic dystrophy

• Neuromuscular Friedreich’s ataxia (hyper trophic), Noonan’s syndrome, lentigines

• General systemic disease (mostly dilated) con nective 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), cardiac myopathy (restrictive, hypertrophic), and pericardial disease

• Mixed dysfunction in many cases, diastolic dysfunction is present with systolic heart failure

**PRESIDENTS OF HF ★FAILURE★**

- Forget to take medications (non adherence)
- Arrhythmia, anemia
- Infection, ischemia, infarction
- Lifestyle change
- Uregulators (thyroid, pregnancy)
- Rheumatic heart disease, acute valvular disease
- Embolism

**CLINICAL FEATURES**

**DISTINGUISHING FEATURES BETWEEN COPD AND HEART FAILURE**

<table>
<thead>
<tr>
<th>COPD</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Previous COPD</td>
</tr>
<tr>
<td>Inspect</td>
<td>Nicotine stain, barrel chest</td>
</tr>
<tr>
<td>Cardiac exam</td>
<td>Laryngeal height &lt;4 cm</td>
</tr>
</tbody>
</table>
CLINICAL FEATURES (CONT’D)

<table>
<thead>
<tr>
<th>COPD</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resp. exam</td>
<td>Hyperresonance</td>
</tr>
<tr>
<td></td>
<td>Prolonged expiratory time</td>
</tr>
<tr>
<td>Investigations</td>
<td>CXR shows hypeinflation</td>
</tr>
<tr>
<td></td>
<td>ABG shows hypercapnia and hypoxemia</td>
</tr>
<tr>
<td></td>
<td>CXR shows redistribution and cardiomegaly</td>
</tr>
<tr>
<td></td>
<td>ABG shows hypoxemia</td>
</tr>
<tr>
<td></td>
<td>Elevated BNP</td>
</tr>
</tbody>
</table>

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

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?

<table>
<thead>
<tr>
<th>History</th>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial clinical judgment</td>
<td>61%</td>
<td>80%</td>
<td>4.4</td>
<td>0.45</td>
</tr>
<tr>
<td>Hx heart failure</td>
<td>60%</td>
<td>90%</td>
<td>5.8</td>
<td>0.45</td>
</tr>
<tr>
<td>Myocardial infarction disease</td>
<td>40%</td>
<td>87%</td>
<td>3.1</td>
<td>0.69</td>
</tr>
<tr>
<td>Coronary artery</td>
<td>52%</td>
<td>70%</td>
<td>1.8</td>
<td>0.68</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>23%</td>
<td>87%</td>
<td>1.7</td>
<td>0.89</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28%</td>
<td>83%</td>
<td>1.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Hypertension</td>
<td>60%</td>
<td>56%</td>
<td>1.4</td>
<td>0.71</td>
</tr>
<tr>
<td>Smoker</td>
<td>62%</td>
<td>27%</td>
<td>0.84</td>
<td>1.4</td>
</tr>
<tr>
<td>COPD</td>
<td>34%</td>
<td>57%</td>
<td>0.81</td>
<td>1.1</td>
</tr>
<tr>
<td>PND</td>
<td>41%</td>
<td>83%</td>
<td>2.6</td>
<td>0.70</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>50%</td>
<td>77%</td>
<td>2.2</td>
<td>0.65</td>
</tr>
<tr>
<td>Edema</td>
<td>51%</td>
<td>76%</td>
<td>2.1</td>
<td>0.64</td>
</tr>
<tr>
<td>Dyspnea on exertion</td>
<td>84%</td>
<td>34%</td>
<td>1.3</td>
<td>0.48</td>
</tr>
<tr>
<td>Fatigue and weight gain</td>
<td>31%</td>
<td>70%</td>
<td>1.0</td>
<td>0.99</td>
</tr>
<tr>
<td>Cough</td>
<td>36%</td>
<td>61%</td>
<td>0.93</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>S3</td>
<td>13%</td>
<td>99%</td>
<td>11</td>
<td>0.88</td>
</tr>
<tr>
<td>AJR</td>
<td>24%</td>
<td>96%</td>
<td>6.4</td>
<td>0.79</td>
</tr>
<tr>
<td>JVD</td>
<td>39%</td>
<td>92%</td>
<td>5.1</td>
<td>0.66</td>
</tr>
<tr>
<td>Rales</td>
<td>60%</td>
<td>78%</td>
<td>2.8</td>
<td>0.51</td>
</tr>
<tr>
<td>Any murmur</td>
<td>27%</td>
<td>90%</td>
<td>2.6</td>
<td>0.81</td>
</tr>
<tr>
<td>Lower extremity edema</td>
<td>50%</td>
<td>78%</td>
<td>2.3</td>
<td>0.64</td>
</tr>
<tr>
<td>Valsalva maneuver</td>
<td>73%</td>
<td>65%</td>
<td>2.1</td>
<td>0.41</td>
</tr>
<tr>
<td>SBP &lt;100 mmHg</td>
<td>6%</td>
<td>97%</td>
<td>2.0</td>
<td>0.97</td>
</tr>
<tr>
<td>S4</td>
<td>5%</td>
<td>97%</td>
<td>1.6</td>
<td>0.98</td>
</tr>
<tr>
<td>SBP ≥150 mmHg</td>
<td>28%</td>
<td>73%</td>
<td>1.0</td>
<td>0.99</td>
</tr>
<tr>
<td>Wheezing</td>
<td>22%</td>
<td>58%</td>
<td>0.52</td>
<td>1.3</td>
</tr>
<tr>
<td>Ascites</td>
<td>1%</td>
<td>97%</td>
<td>0.33</td>
<td>1.0</td>
</tr>
<tr>
<td>CXR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary venous congestion</td>
<td>54%</td>
<td>96%</td>
<td>12</td>
<td>0.48</td>
</tr>
</tbody>
</table>
CLINICAL FEATURES (CONT’D)

<table>
<thead>
<tr>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial edema</td>
<td>34%</td>
<td>97%</td>
<td>12</td>
</tr>
<tr>
<td>Alveolar edema</td>
<td>6%</td>
<td>99%</td>
<td>6.0</td>
</tr>
<tr>
<td>Cardiomegaly</td>
<td>74%</td>
<td>78%</td>
<td>3.3</td>
</tr>
<tr>
<td>Pleural effusions</td>
<td>26%</td>
<td>92%</td>
<td>3.2</td>
</tr>
<tr>
<td>Any edema</td>
<td>70%</td>
<td>77%</td>
<td>3.1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4%</td>
<td>92%</td>
<td>0.50</td>
</tr>
<tr>
<td>Hyperinflation</td>
<td>3%</td>
<td>92%</td>
<td>0.38</td>
</tr>
</tbody>
</table>

ECG

<table>
<thead>
<tr>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>26%</td>
<td>93%</td>
<td>3.8</td>
</tr>
<tr>
<td>New Twave changes</td>
<td>24%</td>
<td>92%</td>
<td>3.0</td>
</tr>
<tr>
<td>Any abnormal finding</td>
<td>50%</td>
<td>78%</td>
<td>2.2</td>
</tr>
<tr>
<td>ST elevation</td>
<td>5%</td>
<td>97%</td>
<td>1.8</td>
</tr>
<tr>
<td>ST depression</td>
<td>11%</td>
<td>94%</td>
<td>1.7</td>
</tr>
</tbody>
</table>

BNP

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

APPROACH

“The features evaluated in more than one study with the highest LRs (>3.5) for diagnosing heart failure were the following: the overall clinical judgment, history of heart failure, S3, jugular venous distension, pulmonary venous congestion or interstitial edema on CXR, and atrial fibrillation on ECG. The features evaluated in more than one study with the lowest LRs (<0.60) for diagnosing 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 abdominoguargal reflux (AJR). To perform the AJR, the blood pressure cuff is pumped 6× and then pressed against the abdomen at 20–35 mmHg for 15–30 s. Normal = no change in JVP, or transient increase of >4 cm that returns to baseline before 10 s, or sustained increase <3 cm throughout. Positive AJR occurs when abdominal compression causes a sustained increase in JVP >4 cm (sens 24%, spc 96%, LR+ 6.4).

APPROACH

“once the JVP is identified, measure the vertical height. A distance ≥4 cm above the sternal angle is considered abnormal (i.e. CVP ≥9cmH2O). 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

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 abdominoguargal 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...
Heart Failure

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

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 nitroprusside 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 cardioverter 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

HYDRAHALINE/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. Contra indications include fluid overload and severe asthma. Start only when patient euvoletic

SPIRONOLACTONE (RALES 1999, EPHEUS 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 euvoletic → add spironolactone/epilrenone if NYHA III/IV → add digoxin ± ARB if still symptomatic. If ejection fraction is < 30% despite optimal medical therapy, consider revascularization, implant table 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)

DEN M 2004 350:13

Digoxin Intoxication

DIFFERENTIAL DIAGNOSIS

OVERDOSE intentional, accidental (digoxin, fox glove, 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

MANAGEMENT

ACUTE ABC, O2, 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
- TRANVENOUS PACING can precipitate arrhythmias and deterioration

HALF LIVES plasma t½ 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

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 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

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 (antiarrhythmics, antiarrhythmics), DVT/PE risk factors

PATHOPHYSIOLOGY (CONT’D)
• METABOLIC thyrotoxicosis, obesity
• DRUGS theophylline, adenosine, digitalis, ß agonists, alcohol
• IDIOPATHIC (10%)

CLINICAL FEATURES

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

<table>
<thead>
<tr>
<th></th>
<th>Any arrhythmia</th>
<th></th>
<th>Significant arrhythmia</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Any arrhythmia</td>
<td></td>
<td>Significant arrhythmia</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>2.03</td>
<td>0.71</td>
<td>0.42</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.63</td>
<td>0.76</td>
<td>1.20</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td>1.70</td>
<td>0.83</td>
<td>1.89</td>
</tr>
<tr>
<td>Smoking &gt;11/day</td>
<td>0.78</td>
<td>1.03</td>
<td>0.77</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>0.98</td>
<td>1.01</td>
<td>0.92</td>
</tr>
<tr>
<td>FH of palpitations</td>
<td>0.86</td>
<td>1.04</td>
<td>1.07</td>
</tr>
<tr>
<td>EtOH &gt;10 days/week</td>
<td>0.76</td>
<td>1.05</td>
<td>1.02</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>0.26</td>
<td>1.30</td>
<td></td>
</tr>
<tr>
<td>Any psychiatric disorders</td>
<td></td>
<td></td>
<td>0.67</td>
</tr>
</tbody>
</table>

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
Any arrhythmia  Significant arrhythmia

<table>
<thead>
<tr>
<th></th>
<th>LR+</th>
<th>LR</th>
<th>LR+</th>
<th>LR</th>
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</thead>
<tbody>
<tr>
<td>Continuous symp</td>
<td>1.06</td>
<td>0.93</td>
<td>1.20</td>
<td>0.86</td>
</tr>
<tr>
<td>HR &gt;100/min</td>
<td>0.91</td>
<td>1.08</td>
<td>0.86</td>
<td>0.86</td>
</tr>
</tbody>
</table>

**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 1.23 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

**APPRAOCH**

“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”

**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** O2 to keep sat >95%, IV

**SUSTAINED 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 15min. Alternatively, infusion 60 mg/h over 6 hours, then 30 µg/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
- **CALCULUS 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
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; ALTERNATELY 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 blockers (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 thrombus

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

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**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

**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

### BLOOD PRESSURE (CONT’D)

**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**

- **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

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 (CONT’D)

HEART SOUNDS

SUSTAINED LEFT PARASTERNAL MOVEMENT (“lift/heave”) tricuspid regurgitation, mitral regurgitation
- PALPABLE P2 pulmonary regurgitation in mitral stenosis, LR+ 3.6

EXTRA HEART SOUNDS

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

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 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 monary pressure (left ventricular failure, mitral stenosis, pulmonary hypertension), increased pulmonary flow (atrial septal defect)
- LOUD S2 AT AORTIC AREA hypertension, hyper dynamic 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, pul monary stenosis, pulmonary hypertension
- PARADOXICAL (REVERSED) SPLITTING (splitting only during expiration) left bundle branch block, severe aortic stenosis, RV pacing

PRECORDIAL EXAMINATION

INSPECTION apex, right ventricular heave
PALPATION apex, heaves, thrills, palpable heart sounds
- DISPLACED APICAL BEAT (lateral to mid clavicular line) left ventricular dilatation, LR+ 8.0
- ENLARGED APICAL BEAT ($>2.5$ cm) left ventricular dilatation, LR+ 4.7
- SUSTAINED APICAL BEAT (outward impulse extends to, or past, S2) left ventricular pressure overload (aortic stenosis), volume overload (aortic regurgitation, VSD), severe cardiomyopathy, or ventricular aneurysm
- RETRACTING APICAL BEAT (retraction during systole; inward motion begins at S1, outward impulse after S2) constrictive pericarditis (up to 90%), tricuspid regurgitation

EXTRA HEART SOUNDS

Sound Heard Pitch Others
S1 LUSB High Aortic stenosis
Early systolic click RUSB High MVP, louder standing
Mld systolic click Apex High Splitting
S2 LUSB High Mitral stenosis
Opening snap (early diastolic) Apex High Heart failure
S3 (early diastolic) Apex Low HTN, aortic stenosis
S4 (late diastolic) Apex Low
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 heard at apex with the bell while S1 is best heard at base.
2. S4 is usually more widely separated from S1 than splitting of S1.
3. S4 is loudest at the start of expiration, softest at mid inspiration.
4. S4 may be accentuated by lying down, exercise, or forced inspiration with closed glottis.
5. S4 has a lower pitch than S1.

DISTINGUISHING FEATURES BETWEEN S3 AND OPENING SNAP

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

DISTINGUISHING FEATURES BETWEEN S3 AND S4

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

MURMURS

TIMING

- **MID-SYSTOLIC** aortic stenosis, aortic sclerosis, pulmonic 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 monary shunts.
- **LATE SYSTOLIC** mitral valve prolapse, papillary muscle dysfunction.
- **EARLY DIASTOLIC** aortic regurgitation, pulmonic 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, cres cendo 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 Val salva 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. Squat ting (or usually passive leg raising, both ↑ venous return and ↑ systemic arterial resistance) produces opposite effect.
- **ISOMETRIC EXERCISE** (↑ systemic arterial resistance) murmurs caused by blood flow across normal or obstructed valves (e.g. mitral or pulmonic stenosis) become louder. Murmurs of mitral and aortic regurgitation and ventricular septal defect also increase with handgrip exercise.
- **TRANSIENT ARTERIAL OCCLUSION** (↑ systemic arterial resistance) transient external compression of both arms by bilateral cuff inflation to 20 mmHg greater than peak systolic pressure augments the murmurs of mitral regurgitation, aortic regurgitation, and ventricular septal defect, but not murmurs due to other causes.
DISTINGUISHING FEATURES AMONG COMMON SYSTOLIC AND DIASTOLIC MURMURS

**Tricuspid stenosis**
- Loud heart sounds are usually due to mild-moderate stenotic lesions, while light heart sounds are usually due to regurgitant or severe stenotic lesions
- For mitral valve prolapse, maneuvers that increase murmur intensity also move both the click and murmur closer to S1
- Regurgitant murmurs usually start early, while stenotic murmurs tend to start mid-way
- Not all findings listed for each condition may be present on examination

**Aortic stenosis**
- 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 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), deMusset's sign (head bob), Mueller's sign (pulsatile uvula), Mayne's sign (DBP<SBP by 15 mmHg), Ger-hard's sign (pulsatile spleen), Robertson's sign (pulsatile liver), Traube's sign (pistol shot pulse in femoral arteries), Dunson's sign (femoral artery bruit with compression), HFS sign (optical SBB-infrared SBB by 60 mmHg)

**Tricuspid stenosis**
- Increased V wave
- Prominent a wave (pul. HTN)

**Diastolic murmurs**
- Prominent a wave
- Absent a wave (AF)

**Palpation**
- Palpable P2 (pul. HTN), thrill, RV heave

**JVP**
- Increased V wave

**Associated murmurs/clinical features**
- Graham Steell murmur (pul. HTN)
- Acute, pulsatile liver, edema

**Murmurs (CONT'D)**

**MITRAL STELLATION**
- 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, brachialorary delay. The absence of any systolic murmur or murmur radiation to the right carotid artery reduces the likelihood of aortic stenosis

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

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

**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, except in the setting of acute MI. Cardiologists can accurately distinguish left sided regurgitant murmurs, such as mitral regurgitation and ventricular septal defect, using transient arterial occlusion

**RATIONAL CLINICAL EXAMINATION SERIES:**
**DOES THIS PATIENT HAVE AN ABNORMAL SYSTOLIC MURMUR?**

**MITRAL REGURGITATION**
- For mitral stenosis, the murmur is classically described as dia-stolic with pre-systolic accentuation

**Other signs**
-office of all 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), delMussel’s sign (head bob), Mueller’s sign (pulsatile uvula), Mayne’s sign (DBP<SBP by 15 mmHg), Gerhard’s sign (pulsatile spleen), Robertson’s sign (pulsatile liver), Traube’s sign (pistol shot pulse in femoral arteries), Dunson’s sign (femoral artery bruit with compression), HFS sign (optical SBB-infrared SBB by 60 mmHg)
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 like lihood 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”

MURAL 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 ≥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 ★★★
- Bleeding (angiodysplasia + aortic stenosis + acquired vWD type IIa = Hedye’s syndrome)
- Endocarditis
- Embolic events (cerebral, systemic)

CLINICAL FEATURES

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

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

DISTINGUISHING FEATURES BETWEEN AORTIC SCLEROSIS AND AORTIC STENOSIS MURMUR

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Aortic sclerosis</th>
<th>Aortic stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid pulse</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>S2</td>
<td>Normal</td>
<td>Soft single S2 (P2)</td>
</tr>
<tr>
<td>Murmur</td>
<td>Mid systolic murmur</td>
<td>Late peaking of systolic murmur</td>
</tr>
</tbody>
</table>

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### Distinguishing Features Between Aortic Stenosis, Mitral Regurgitation, and Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>Aortic Stenosis</th>
<th>Mitral Regurgitation</th>
<th>HOCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid upstroke</td>
<td>Slow, low amplitude</td>
<td>Normal or low amplitude</td>
<td>Brisk</td>
</tr>
<tr>
<td>S1</td>
<td>Normal</td>
<td>Soft</td>
<td>Normal</td>
</tr>
<tr>
<td>S2</td>
<td>Single if severe</td>
<td>Normal</td>
<td>Often reversed</td>
</tr>
<tr>
<td>S3</td>
<td>No</td>
<td>Loud</td>
<td>No</td>
</tr>
<tr>
<td>S4</td>
<td>If severe</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Loudest murmur</td>
<td>RUSB</td>
<td>Apex</td>
<td>LLSB and apex</td>
</tr>
</tbody>
</table>

#### 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 cm²
- Mild = 1.5 - 2 cm² or mean gradient <25 mmHg
- Moderate = 1.5 - 2 cm² or mean gradient 25 - 40 mmHg
- Severe = <1 cm² or mean gradient >40 mmHg
- Symptoms: usually do not appear until valve area <1 cm². The significance of valve area depends on patient size (larger patient = more severe for same valve area)
- Progression: valve area decreases by ~0.1 cm²/year and the mean gradient increases by 7 mmHg/year (particularly if cardiac risk factors)

#### Prognosis of Aortic Stenosis ★ASH★

- 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 (Cont’d)

#### 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 child bearing age
Aortic Regurgitation

DIFFERENTIAL DIAGNOSIS

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

AORTIC DILATATION  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 decom pensation leading to left ventricular dysfunction (heart failure)

CLINICAL FEATURES

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), Muel ler’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)

CARDIA  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

<table>
<thead>
<tr>
<th>Feature</th>
<th>Austin Flint</th>
<th>Mitral stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M &gt; F</td>
<td>F &gt; M</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Almost never</td>
<td>Likely mitral stenosis</td>
</tr>
<tr>
<td>Rhythm</td>
<td>Sinus</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>M1</td>
<td>Usually faint</td>
<td>Usually loud</td>
</tr>
<tr>
<td>P2</td>
<td>Normal or ↑</td>
<td>Usually loud</td>
</tr>
<tr>
<td>Ventricular gallop/S3</td>
<td>Always present</td>
<td>Absent</td>
</tr>
<tr>
<td>Diastolic murmur</td>
<td>Usually early or mid diastolic</td>
<td>Often presystolic accentuation (if in sinus rhythm)</td>
</tr>
<tr>
<td>Opening snap</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>CXR</td>
<td>Boot shaped</td>
<td>LAE</td>
</tr>
<tr>
<td>ECG</td>
<td>Sinus, LHV, Prolonged PR</td>
<td>Atrial fibrillation, P mitrale</td>
</tr>
</tbody>
</table>
**Mitral Stenosis**

**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

**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 hyper tension and eventually right heart failure

**VALVE AREA** normal 4 5 cm$^2$, mild symptoms 1.5 2 cm$^2$ (mean gradient <5 mmHg), moderate symp toms 1 1.5 cm$^2$ (mean gradient 5 10 mmHg), severe symptoms <1 cm$^2$ (mean gradient >10 mmHg)

**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

**SPECIAL**
- ECG P mitrale, RVH
- CARDIAC CATHETERIZATION

**CLINICAL FEATURES**

- symptoms related to pulmonary hyper tension (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
DIAGNOSTIC AND PROGNOSTIC ISSUES

MITRAL VALVE AREA AND SEVERITY

- **NORMAL** = 4.5 cm²
- **MILD** = 1.5 - 2.5 cm² or mean gradient <5 mmHg
- **MODERATE** = 1 - 1.5 cm² or mean gradient 5 - 10 mmHg
- **SEVERE** = <1 cm² or mean gradient >10 mmHg

SYMPTOMS usually do not appear until valve <2.0 cm². Symptoms at rest appear when valve <1.5 cm². Onset of symptoms usually precipitated by exercise, emotional stress, infection, pregnancy, or rapid atrial fibrillation

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

MANAGEMENT

LIFESTYLE CHANGES  salt restriction/diuretics

MEDICATIONS  negative chronotropic agents 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 cm²

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

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)
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, 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 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)
- CLINICAL FEATURES  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

TWO SUBTYPES OF MITRAL VALVE PROLAPSE

<table>
<thead>
<tr>
<th>Mild subtype</th>
<th>Severe subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Mainly women (age 20-50)</td>
</tr>
<tr>
<td>Pathology</td>
<td>Minimal MR</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Physical findings</td>
<td>Mid systolic click with or without a late systolic murmur</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Few patients have progressive MR</td>
</tr>
</tbody>
</table>

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★
  - Haemophilus
  - Actinobacillus
- SPECIAL MEDIA  Mycoplasma, Chlamydia, Legionella, Brucella, Bartonella, Coxiella burnetii (Q fever), Histoplasma, Tropheryma whippelli
- MARANTIC ENDOCARDITIS  non-bacterial thrombotic endocarditis secondary to malignancy (usually adenocarcinoma) or SLE (Libman Sacks endocarditis)

DIFFERENTIAL DIAGNOSIS (CONT’D)

- Cardiobacterium
- Eikenella
- Kingella
- SPECIAL MEDIA  Mycoplasma, Chlamydia, Legionella, Brucella, Bartonella, Coxiella burnetii (Q fever), Histoplasma, Tropheryma whippelli

Endocarditis  NEJM 2001 345:18
**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, ischaemic heart disease, previous CABG
- **NON-CARDIAC** IDU, poor dental hygiene, long term indwelling catheter, procedures (GU, GI, surgical wound infection), dia betes, 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 (non tender, erythematous, hemorrhagic punctate 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**
- **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&H, 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, con junctival hemorrhages, Janeway lesions), immuno logical 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, peri valvular 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
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 embolic 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 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 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
  - cephalosporin 1 g IV/IM
  - azithromycin 500 mg PO
  - clarithromycin 500 mg PO

Peripheral Vascular Disease

**DIFFERENTIAL DIAGNOSIS OF CLAUDICATION**

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

- **BURGER’S TEST** abnormal pallor with elevation of leg 90° for 2 min and deep rubor when lowered for 2 min

**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?

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

**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*
### Distinguishing Features of Common Causes of Leg Pain

<table>
<thead>
<tr>
<th>Common Cause</th>
<th>Claudication</th>
<th>Spinal Stenosis</th>
<th>Venous Congestion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong></td>
<td>Cramp, tiredness</td>
<td>Cramp, tiredness, tingling</td>
<td>Tightness, bursting</td>
</tr>
<tr>
<td><strong>Sites</strong></td>
<td>Buttock, hip, thigh, calf, foot</td>
<td>Buttock, hip, thigh</td>
<td>Groin, thigh</td>
</tr>
<tr>
<td><strong>Worse</strong></td>
<td>Walking</td>
<td>Walking, standing</td>
<td>Walking</td>
</tr>
<tr>
<td><strong>Better</strong></td>
<td>Rest</td>
<td>Sitting or change in position</td>
<td>Leg elevation</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Vascular dx, ↓ pulse</td>
<td>Lower back pain</td>
<td>History of DVT</td>
</tr>
</tbody>
</table>

### 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 angiography 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. Preventive 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**
Differential Diagnosis

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
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
5 Neurologic Cushing’s triad (hypertension, bradycardia and respiratory depression associated with increased intracranial pressure)
6 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

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

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 meta nephrine and creatinine, serum osmolality, urine osmolality, urine electrolytes, selective adrenal vein sampling
• RENAL ARTERY STENOSIS WORKUP renal dopplers, captopril renogram, CT/ MR angiogram, renal angiogram
• SLEEP OXIMETRY TEST yes = consider ambulatory BP monitoring (step 6) or proceed to step 5

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 140/90 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)

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ACUTE MANAGEMENT (CONT’D)

to usually target 3 /kg/min (rarely >4 /kg/min, maximum 10 /kg/min). Nicardipine 5 mg/hr IV initially, titrate to a maximum of 15 mg/hr. Fenoldopam 0.1 /kg/min IV initially, titrate dose q15min. Consider ICU admission. Workup and treatment of under lying 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

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 cardiopul monary 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/m², 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, terezosin 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), LHV
• CONTRAINDICATIONS pregnancy, ESRD, bilateral RAS
• ADVERSE EFFECTS cough (less with ARB), angio dema, 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)

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

OVERALL APPROACH TO CHOICE OF THERAPY

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN without other indications</td>
<td>A/B/C/D → AC/AD/BC/BD → ABC/ACD/BCD/ABD → ABCD</td>
</tr>
<tr>
<td></td>
<td>Avoid B as first line if age &gt; 60</td>
</tr>
<tr>
<td></td>
<td>ACEi may be less effective in blacks</td>
</tr>
<tr>
<td>Isolated systolic hypertension</td>
<td>ARB/C1/D → ARB plus either C1 or D → ARB plus C1 plus D</td>
</tr>
<tr>
<td></td>
<td>Avoid B</td>
</tr>
<tr>
<td>Angina</td>
<td>ACEi/B → ACEi plus B → add C1</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>AB → ABC</td>
</tr>
<tr>
<td>Heart failure</td>
<td>AB → ABD (including spironolactone) → ACEi/ARB/B/D. Avoid hydralazine and minoxidil if LVH</td>
</tr>
<tr>
<td>Prior cerebrovascular disease</td>
<td>AD → add other agents</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>A/B/C/D plus ASA.</td>
</tr>
<tr>
<td>Diabetes without nephropathy</td>
<td>A/C1/D → AC1/AD → add B or C2</td>
</tr>
<tr>
<td>Diabetes with nephropathy</td>
<td>A → AC/AB/AD</td>
</tr>
<tr>
<td>CKD ± proteinuria</td>
<td>A → AD → add other agents</td>
</tr>
<tr>
<td>Asthma</td>
<td>A/C/D. Avoid B</td>
</tr>
<tr>
<td>BPH</td>
<td>B blockers</td>
</tr>
<tr>
<td>Perioperative</td>
<td>B (if moderate to high risk)</td>
</tr>
<tr>
<td>Migraine</td>
<td>B</td>
</tr>
<tr>
<td>Thyrotoxicosis</td>
<td>B</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>B</td>
</tr>
<tr>
<td>Postural hypotension</td>
<td>Avoid vasodilators and diuretics</td>
</tr>
<tr>
<td>Raynaud’s</td>
<td>C (dihydropyridine)</td>
</tr>
<tr>
<td>Gout</td>
<td>D</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>D</td>
</tr>
</tbody>
</table>

BLOOD PRESSURE TREATMENT TRIGGERS AND TARGETS

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

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### TREATMENT ISSUES (CONT’D)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalemia</td>
<td>A/B/C/D. Avoid aldosterone antagonists</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>A/B/C. Avoid D</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>B/methyldopa/vasodilators. Avoid ACE inhibitors and ARB</td>
</tr>
</tbody>
</table>

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

**DIFFERENTIAL DIAGNOSIS OF ABDOMINAL BRUiTS**

- **CARDIOVASCULAR** abdominal aortic aneurysm, aortocaval fistula
- **RENAL VASCULAR** renal artery stenosis
- **GI VASCULAR** celiac artery compression syn drome, mesenteric ischemia
- **HEPATIC VASCULAR** cirrhosis, hepatoma, AV malformation, arterioporal 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?**

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic and diastolic abdominal bruit</td>
<td>39%</td>
<td>99%</td>
<td>39</td>
<td>0.6</td>
</tr>
<tr>
<td>Any epigastric or flank bruit, including isolated systolic bruit</td>
<td>63%</td>
<td>90%</td>
<td>6.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Systolic bruit</td>
<td>78%</td>
<td>64%</td>
<td>2.1</td>
<td>3.5</td>
</tr>
</tbody>
</table>

**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)
DIFERENTIAL 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)

DIFERENTIAL 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)

DIFERENTIAL DIAGNOSIS OF LOW HDL

**PRIMARY**
obesity, smoking, inactivity

**SECONDARY**

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 g can (TGL).
- **Exercise**

RISK REDUCTION MEDICATIONS

- **RESINS**: Cholestyramine 2 24 g PO daily, colestipol 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**: 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 hepatoxicity, myalgia and myopathy

- **FIBRATES**: gemfibrozil 600 1200 mg daily, fenofibrate 67 200 mg daily. Main side effects include GI upset, gallstones, and myalgia

- **NIACIN**: 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 TARGETS BASED ON RISK CATEGORY (CCS 2009 Guideline)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL High</th>
<th>LDL Moderate</th>
<th>LDL Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>&lt;2 mmol/L (&lt;77 mg/dL) or ≥50% ↓ LDL</td>
<td>&lt;2 mmol/L (&lt;77 mg/dL) or ≥50% ↓ LDL</td>
<td>≥50% ↓ LDL</td>
</tr>
<tr>
<td>ApoB</td>
<td>&lt;0.80 g/L (&lt;80 mg/dL)</td>
<td>&lt;0.80 g/L (&lt;80 mg/dL)</td>
<td>&lt;0.80 g/L (&lt;80 mg/dL)</td>
</tr>
</tbody>
</table>

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 >2mg/L,

- **LOW**: <10% 10 year CAD risk. Consider initiating treatment if LDL ≥5.0mmol/L (≥193 mg/dL)
- **UTILITY**: 10 year risk calculation is based on Framingham study (gender, age, total chol, HDL, SBP, smoking)

TREATMENT ISSUES (CONT’D)

- men age >50, women age >60, or significant family history
- 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]

FAMILIAL DYSLIPIDEMIA

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

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 suddenly 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 with R’ taller than r. May also see QR’ complex in V1 (suggestive of old or new infarct). QRS polarity positive in V1. Causes include LAD involve/ment/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. Causes include hypotension, CAD, dilated cardio myopathy, rheumatic heart disease, infiltrative disease, 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 <0.50 of RR interval; normal QTc 390–460 ms (women), 390–450 ms (men)

CAUSES genetic, metabolic (hypokalemia, hypomagnesemia, hypocalcemia), antiarrhythmics (奎尼丁, 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), overt rive 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

LHV 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

<table>
<thead>
<tr>
<th>Territory</th>
<th>Leads</th>
<th>Artery</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inferior</td>
<td>II, III, aVF a</td>
<td>RCA, LAD b</td>
<td>RV, SA, AV nodes</td>
</tr>
<tr>
<td>Lateral</td>
<td>I, aVL, V5, V6</td>
<td>LCX, RCA</td>
<td></td>
</tr>
<tr>
<td>Posterior</td>
<td>V1i, V2i, V8, V9 c</td>
<td>RCA</td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>V1, V4 d</td>
<td>LAD</td>
<td>Massive LV</td>
</tr>
<tr>
<td>RV</td>
<td>R leads (V1), V4R</td>
<td>RCA</td>
<td>Preload</td>
</tr>
</tbody>
</table>

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- =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 down ward sloping/scooping of ST. ST depression in I, II, aVF, V2 V6
DIGITALIS TOXICITY  unifocal or multifocal PVCs, first degree heart block, ventricular bigeminy, parox ysmal atrial tachycardia, bidirectional VT
HYPERKALEMIA  tall, peaked T wave (especially pre cordial 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. Pharmacologi cal treatments include amiodarone and procainamide. AV nodal blocking drugs (adenosine, β blockers, verapamil/diltiazem, digoxin) are con traindicated 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
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, hyper tension, chronic kidney disease and renal artery ste nosis, 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 CBC, 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
CrCl=(140 ag e ×(weight in kg)/(Cr in μmol/L), multiply by 1.2 if male
CrCl=(140 ag e ×(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 (UNa/Pna)/(Ucr/Pcr) x100%, <1%
- URINALYSIS bland, high specific gravity

DISTINGUISHING FEATURES BETWEEN PRE RENAL FAILURE AND ATN

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pre renal</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea:Cr ratio</td>
<td>(Urea × 10) &gt;Cr</td>
<td>(Urea × 20) &lt;Cr</td>
</tr>
<tr>
<td>Urea:Cr ratio</td>
<td>Urea &gt;(Cr × 20)</td>
<td>Urea &lt;(Cr × 10)</td>
</tr>
<tr>
<td>Increase in Cr</td>
<td>Variable</td>
<td>&lt;44 μmol/L/day [&lt;0.5 mg/dL/day]</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>Normal</td>
<td>Heme granular casts</td>
</tr>
<tr>
<td>Urine Na</td>
<td>&lt;20 mmol/L</td>
<td>&gt;30 mmol/L</td>
</tr>
<tr>
<td>FEna</td>
<td>&lt;1%</td>
<td>&gt;2%</td>
</tr>
<tr>
<td>Urine osmo</td>
<td>&gt;500 mOsm/kg</td>
<td>&lt;350 mOsm/kg</td>
</tr>
</tbody>
</table>
### 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**

- **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, amphoteracin, 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, amphoteracin)

**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

**ETOLOGY WORKUP**
- **ANA**, anti dsDNA, **ENA**, p anca, c anca, anti GBM antibody, C3, C4, **CK**, uric acid, ASO titer, HBV/HCV serology, RF, cryoglobulinemia, 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
DISTINGUISHING FEATURES BETWEEN VARIOUS RENAL ETIOLOGIES

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>Other tests</th>
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<tbody>
<tr>
<td>Vascular</td>
<td>Periperal smear (TTP)</td>
</tr>
<tr>
<td>Bland</td>
<td>p anca (PAN)</td>
</tr>
<tr>
<td>Urinary eosinophils (cholesterol emboli)</td>
<td>ANA, ENA (lupus)</td>
</tr>
<tr>
<td>Tubular</td>
<td>CK (rhabdomyolysis)</td>
</tr>
<tr>
<td>Muddy brown casts (ATN)</td>
<td>Uric acid (gout)</td>
</tr>
<tr>
<td>Interstitial</td>
<td>Systemic eosinophilia</td>
</tr>
<tr>
<td>WBC casts, urinary eosinophils</td>
<td>c anca (Wegener’s)</td>
</tr>
<tr>
<td>Glomerular</td>
<td>p anca (PAN)</td>
</tr>
<tr>
<td>RBC casts</td>
<td>Eosinophilia (Churg Strauss)</td>
</tr>
<tr>
<td>Acanthocyte (dysmorphic RBC)</td>
<td>Anti GBM (Goodpasture’s syndrome)</td>
</tr>
<tr>
<td>Oval fat body</td>
<td>ANA, anti dsDNA (SLE)</td>
</tr>
<tr>
<td>Fatty cast</td>
<td>ASO titer (PSGN)</td>
</tr>
<tr>
<td></td>
<td>Blood C&amp;S, echo (infectious endocarditis)</td>
</tr>
<tr>
<td></td>
<td>HBV/HCV serology, SPE, UPE (multiple myeloma)</td>
</tr>
<tr>
<td></td>
<td>Cryoglobulins, rheumatoid factor</td>
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<td></td>
<td>(cryoglobulinemia)</td>
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</table>

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)

RENA L REPLACEMENT dialysis (peritoneal, hemodialysis)

SPECIFIC ENTITIES (CONT’D)

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

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 abso lutely required, use low (iohexol) or iso osmolar (iodixanol) non ionic agents. Hydration options include (1) IV 1/2 NS at 1 mL/kg/h starting 12 h before until 12 h after contrast exposure; (2) IV NS or NaHCO₃ 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

SPECIFIC ENTITIES (CONT’D)
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 (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  hydrenephrosis suggests post renal causes. However, retroperitoneal fibrosis and acute post renal obstruction may not show hydrenephrosis

MANAGEMENT
TREAT UNDERLYING CAUSE  Foley catheter. For BPH (tamsulosin 0.4 mg PO daily or TURP)
RENAL REPLACEMENT  dialysis (peritoneal, hemo dialysis)

Glomerulopathies

PATHOPHYSIOLOGY OF GLOMERULOPATHIES
AUTOIMMUNE PHENOMENON  antibodies binding to structural components of glomeruli (more glomerular basement membrane and podocytes involvement in nephrotic syndrome, more mesangium and endothelium involvement in nephritic syndrome), circulating antigen antibody complexes, and/or cell mediated immunity  →  further immune activation and damage to glomeruli

PATHOLOGY TERMS  focal  = <50% of glomeruli, 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
Clindistinguishing features between nephrotic and nephritic syndromes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nephrotic</th>
<th>Nephritic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Slower</td>
<td>Faster</td>
</tr>
<tr>
<td>Edema</td>
<td>++++</td>
<td>++</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>N/</td>
<td>↑</td>
</tr>
<tr>
<td>Volume/JVP</td>
<td>N/</td>
<td>↑</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>&gt;3 g/day</td>
<td>May be &lt;3 g/day</td>
</tr>
<tr>
<td>Hematuria</td>
<td>May occur</td>
<td>+++</td>
</tr>
<tr>
<td>Urine sediment</td>
<td>Hyaline casts, lipid droplets (oval fat body)</td>
<td>Dysmorphic RBC, WBC, RBC casts, granular casts</td>
</tr>
<tr>
<td>Albumin</td>
<td>↓↓↓</td>
<td>N/mild</td>
</tr>
<tr>
<td>Creatinine</td>
<td>N/</td>
<td>Usually ↑</td>
</tr>
<tr>
<td>Serum Na</td>
<td>May be ↓↓</td>
<td>N/mild</td>
</tr>
</tbody>
</table>

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 glomerulo sclerosis, 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 (≥GBM, 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, myco phenolate mofetil

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, autoimune thyroiditis, syphilis, HBV, HCV, chronic trans plant rejection)
- Clinical features pure nephrotic (minimal hematuria, no RBC casts)
- Pathology light microscopy (basement membrane thickening, spikes), immunofluorescence (immune complexes IgG, and complements in sub epithelial 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 α3 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 microscopic 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
**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 m², proteinuria)  observe, consider ACE inhibitor
- **STAGE II**  (GFR 60 90 mL/min/1.73 m²)  consider ACE inhibitor, nephrology referral
- **STAGE III**  (GFR 30 60 mL/min/1.73 m²)  nephrology referral
- **STAGE IV**  (GFR 15 30 mL/min/1.73 m²)  consider renal replacement therapy (dialysis or transplantation)
- **STAGE V**  (GFR <15 mL/min/1.73 m²)  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**

**INVESTIGATIONS**

**BASIC**
- **LABS**  CBC, electrolytes, urinalysis, Cr, glucose, Hba1C, Ca, PO₄, Mg, PTH, albumin, fasting lipid profile, 24 h urinary albumin collection, 24 h urinary protein collection

**SPECIAL**
- **MYELOMA WORKUP**  serum protein electrophoresis, urinary protein electrophoresis

**DISTINGUISHING FEATURES BETWEEN CHRONIC AND ACUTE RENAL FAILURE**
- Previous creatinine (>3 months of elevated creatinine suggests CKD),
- Acute Renal Failure (p. 68)
- Chronic Kidney Disease (p. 73)

**Related Topics**
- Acute Renal Failure
- Chronic Kidney Disease

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**Clinical Features (Cont’d)**

- **Calcium/Phosphate Balance**  ↓ ↓ 1,25(OH)₂ vitamin D₃ synthesis in kidney, ↓ PO₄ 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

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**Clinical Features (Cont’d)**

- **Diabetes**  proteinuria
- **Glomerulonephritis**
- **Polycystic Kidney Disease**
- **Multiple Myeloma**
- **Nephrotoxins**  NSAIDs
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

TREATMENT ISSUES (CONT’D)

TREATMENT ISSUES

CRITERIA FOR DIALYSIS IN CHRONIC KIDNEY DISEASE

DIACINOSIS

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 β2 microglobulin filter through but are reabsorbed at proximal tubules (affected in tubular proteinuria)
Hematuria

**DIFFERENTIAL DIAGNOSIS**

**PIGMENTS** beets, myoglobinuria, hemoglobinuria, porphyrin, rifampin, food coloring  
**TRANSIENT** menstruation, urinary tract infections, fever, exercise (march hematuria), trauma, endometriosis, renal vein thrombosis  
**GLOMERULAR**  
- **NEPHRITIC SYNDROME** MPGN 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 (CONT’D)**

**HISTORY** blood clots, other sources of bleeding (GI, hemoptysis, epistaxis), beets, fever, strenuous exercise, urinary tract infections (dysuria, frequency), 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** CBC, lytes, urea, Cr, HbA1C, fasting glucose, albumin  
- **URINALYSIS** inaccurate and dependent on urine volume, detects mainly negative charged proteins such as albumin and less so light chains  
- **SULFOSALICYLIC ACID TEST** detects all proteins  
- **SPOT PROTEIN/Cr RATIO** (SI Units) to estimate daily protein excretion in mg  
  \[ \text{ratio} \times 0.14 \ 0.16 \text{mg/kg/day} \times \text{weight in kg} \]  
  \[ \text{ratio} \times 0.18 \ 0.20 \text{mg/kg/day} \times \text{weight in kg} \]  
**INVESTIGATIONS (CONT’D)**  
- **24-H URINARY PROTEIN** most accurate but cumbersome method to quantify urinary protein  
- **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  
**SPECIAL**  
**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

**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  

**DIAGNOSTIC ISSUES**

- **LABS** CBC, lytes, urea, Cr, INR, PTT, urinalysis, urine C&S, urine cytology  
- **IMAGING** KUB, U/S abd, IVP, CT abd  
- **CYSTOSCOPY** if suspect extra glomerular bleed  
- **KIDNEY BIOPSY** if suspect glomerular pathology  
- **URINE TESTS** 24 h urine calcium, oxalate, and urate  

**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
Cystic Kidney Diseases

CAUSES

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

INVESTIGATIONS

BASIC
- LABS CBDC, 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, ≥4 cysts in each kidney)
- TREATMENTS blood pressure control, ACE inhibitors, dialysis if endstage renal disease

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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)**
- **Muddy Cats**
- Methanol
- Uremia
- DKA
- Paraldehyde
- INH and Iron
- Lactic Acidosis
- Ethylene Glycol
- Cyanide
- Arsenic
- Toluene
- Salicylates

**Non Anion Gap (Hyperchloremic)**
- **Kult**
- Ketones
- Uremia
- Lactic Acidosis
- Toxins

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.

3. Metabolic initiated by change in \( HCO_3^- \)
   - Respiratory initiated by change in \( PCO_2 \)

4. Calculate anion gap (\( \uparrow \) anion gap in \( \text{MaC} \), \( \downarrow \) anion gap may be due to hypoalbuminemia [10:2.5 ratio], paraproteinemia (e.g. myeloma), halide ingestion (e.g. lithium) or laboratory error).

   \[ \text{AG} = Na^+ - Cl^- - HCO_3^- \]

   Normal \( pCO_2 = 40 \text{ mmHg}, HCO_3^- = 24 \text{ mmol/L} \)

4a. If anion gap metabolic acidosis, calculate osmolar gap to differentiate between causes

   \[ \text{Osmolar Gap} = (\text{Glucose} + \text{Urea} + \text{Na}^+ \times 2) \]

   Observed osmolality \( \ast \text{Gun2} \ast \) (see p. 104 for more details)

4b. Calculate “delta ratio” (also known as “delta delta”) to check for any superimposed metabolic disorder.

   \[ \Delta \text{AG/} \Delta \text{HCO}_3^- = (\text{AG} \times 10)/(24 \text{ HCO}_3^-) \]

Note: be wary of over interpretation, use clinical judgment.

Investigations

**Basic**
- Labs CBC, lytes, urea, Cr, glucose, lactate, ketone, serum alcohol/methanol, serum osmolality, urinalysis, urine lytes
- ABG

**Special**
- Urine oxalate crystals if suspect ethylene glycol ingestion

Related Topics
- Osmolar Gap (p. 104)
- Overdose (p. 102)
- Respiratory Acidosis (p. 18)
- Respiratory Alkalosis (p. 18)
5. Any superimposed respiratory disorder? After adjusting pCO₂ to account for HCO₃ changes (see compensation table above), is there evidence of hypoventilation (↑pCO₂) or hyperventilation (↓pCO₂)?

MANAGEMENT

ACUTE ABC, O₂, IV, intubation, NaHCO₃ 1-2 amp IV bolus if pH < 7.0

TREAT UNDERLYING CAUSE

SPECIFIC ENTITIES

LYTES AND URINE LYTES
- ANION GAP METABOLIC ACIDOSIS serum chloride normal
- URINE NET CHARGE (UNC) urine Na + K - Cl. A negative UNC suggests unmeasured cation, implying that NH₄⁺ is present (i.e. type II RTA, not type I RTA). In the presence of acidosis, UNC should be negative (i.e. NH₄⁺ present). Therefore, look for GI losses (neGUTive)

RENAL TUBULAR ACIDOSIS TYPE I (distal)
- PATHOPHYSIOLOGY inability to make NH₄⁺. 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. HCO₃ and K supplement, or potassium citrate

RENAL TUBULAR ACIDOSIS TYPE II (proximal)
- PATHOPHYSIOLOGY inability to reabsorb HCO₃ at the proximal tubule. Causes include Fanconi’s syndrome (multiple myeloma, carbonic anhydride 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 HCO₃ challenge → check urine pH every 2 h → measure serum HCO₃ level when urine pH > 7 (expect relatively “low” serum HCO₃ in type II RTA). Urinary pH initially ↑ due to HCO₃ loss, but then ↓ as serum HCO₃ becomes low
- TREATMENTS usually self limiting in adults. HCO₃ supplement has limited utility due to HCO₃ wasting and may even lead to hypokalemia

RENAL TUBULAR ACIDOSIS TYPE IV
- PATHOPHYSIOLOGY causes include hyporeninemic 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. Flu drocortisone may be used with caution

DISTINGUISHING FEATURES FOR RENAL TUBULAR ACIDOSIS

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Type I</th>
<th>Type II</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum K</td>
<td>↑/↓</td>
<td>↓</td>
<td>↑ Ald deficiency</td>
</tr>
<tr>
<td>Serum HCO₃</td>
<td>Variable</td>
<td>10 20  &gt;17</td>
<td></td>
</tr>
<tr>
<td>Urine pH</td>
<td>&gt;5.3</td>
<td>Variable</td>
<td>&lt;5.3</td>
</tr>
<tr>
<td>UNC</td>
<td>Positive</td>
<td>Negative</td>
<td>Variable</td>
</tr>
</tbody>
</table>

Metabolic Alkalisos
**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
  - SERUM ALDOSTERONE AND RENIN

**DIAGNOSTIC ISSUES**

**LYTES AND URINE LYTES**

<table>
<thead>
<tr>
<th>Vomit HCl loss</th>
<th>Burn NaCl loss</th>
<th>Physiologic renal loss</th>
<th>Pathologic renal loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
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</table>

- **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 NH₄ excretion)

**MANAGEMENT**

- **ACUTE** — ABC, O₂, 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

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**Hyponatremia**

*NEJM 2000 342:21; NEJM 2007 356:20*

**DIFFERENTIAL DIAGNOSIS OF HYPOOSMOLAR HYponatremia (CON’T)**

- **HYPOVOLEMIC** (VOLUME DEPLETION)
  - Renal Loss — diuretics, hypoadrenalism, hypomagnesemia, Bartter’s
  - GIm 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

- **HYPERVOLEMIC** (edema)
  - Cardiac failure, cirrhosis, GI losing enteropathy, nephrotic syndrome, malnutrition
**PATHOPHYSIOLOGY**

**DEFINITION OF HYPONATREMIA**  
Na < 135 mmol/L. The serum osmolality should be less than 275 mmol/L for hyposmolar hyponatremia

**INVESTIGATIONS**

**BASIC**
- Labs: lytes, urea, Cr, glucose, TSH, cortisol, urine lytes, urine Cr, serum and urine osmolality (e.g., to rule out pseudohyponatremia)

**DIAGNOSTIC ISSUES**

**VOLUME STATUS**  
The patient’s volume status (hypovolemia, euvolemic, hypervolemic) helps to narrow the differential diagnosis and dictates the appropriate workup.

**SIADH CRITERIA**  
Diagnosis of SIADH requires the following: cause available, clinically euvolemic, hypotonic, 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 hypothryoidism, adrenal insufficiency, diuretic use, and psychogenic polydipsia. See NEJM 2007 356:20 for more details.

**CALCULATING CORRECTION RATE**

- **CHANGE IN SERUM Na**  
  \[ \frac{\text{Na}_{\text{infusate}} - \text{Na}_{\text{serum}}}{\text{(total body water + 1)}} \]
  where total body water ≈ 0.5 × body weight (kg) in women and 0.6 × body weight (kg) in men.

- **VOLUME OF INFUSATE NEEDED**  
  (in liters) = intended change in serum Na over a defined period of time (usually 8 mmol/L over 24 h)/change in serum Na

- In patients with chronic hyponatremia, the daily limit of increase in serum Na should be ≤ 8 mmol/L to minimize the risk of 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 ×3 days. Hypertonic saline or furosemide if severe (be extremely cautious)

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

**MANAGEMENT (CONT'D)**

**HYPEROVOLUMIC**  
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 K⁺, and burn victims.

- **DIAGNOSIS**  
  CT head, MRI head.

- **TREATMENTS**  
  Dismal prognosis with no effective therapy. Prevention is key.
### Hypokalemia

**DIFFERENTIAL DIAGNOSIS**

**HYPHOVOLEMIC**
- Rare

**SHIFT INTO CELL**
- Hyperinsulinemia, hypothermia

**OUTPUT**
- 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).

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### Hypernatremia

**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

**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

**MANAGEMENT**

**HYPOVOLEMIC**
- Hypertonic fluid infusion. Treat underlying cause

**EUVOLEMIC**
- ADH if central diabetes insipidus. Free water hydration. Treat underlying cause (see POLYURIA p. 347)
CLINICAL FEATURES

SYMPTOMS usually not present unless K < 2.5 mmol/L
- MUSCULAR weakness or paralysis (periodic hypo-kalemia 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
- 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 > 8 = normal renal response (appropriate aldosterone activity)
- TTKG < 7 = suggests hypoaldosteronism in hyperkalemic patient (kidneys not secreting K appropriately)
- TTKG < 5 = very suggestive of hypoaldosteronism in hyperkalemic patient (adrenal insufficiency)

MANAGEMENT

ACUTE (K < 3.0 mmol/L) KCI 10 mEq in 100 mL DSW IV bolus × 3. For continuous infusion, maximum KCI concentration is 40 mEq/L

K SUPPLEMENT KCI 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

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
**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, hypercalcaemia, tubular dysfunction (alcohol, aminoglycosides, amphotericin B, cisplatin, cyclosporine, acute tubular necrosis in diuretic phase, primary renal magnesium wasting)

**PATHOPHYSIOLOGY**
**DEFINITION OF HYPOMAGNESEMA** Mg <0.7 mmol/L [ <1.4 mEq/L]

**CLINICAL FEATURES**
- **SYMPTOMS**
  - **LYTES/CA/PO₄** ↓ K, ↓ Ca, PTH resistance, vitamin D deficiency

**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 HYPOPHOSPHATHEMIA** PO₄ <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
INVESTIGATIONS

BASE
- Labs  Ca, Mg, PO₄, PTH, CK, 24 hour urinary PO₄ collection (<100 mg), urine PO₄, urine Cr

DIAGNOSTIC ISSUES
FePO₄ = (U_PO₄/UCr)/(P PO₄/PCr), <5 suggests not due to output

MANAGEMENT
PO₄ Supplement potassium phosphate (22 mmol K⁺, 15 mmol PO₄ in 250 mL NS over 4 h, or sodium phosphate (20 mmol Na⁺, 15 mmol PO₄) in 250 mL NS over 4 h, or sodium phosphate 1 g PO TID (replaces ~100 mmol/day)

TREAT UNDERLYING CAUSE vitamin D deficiency (vitamin D 800 U PO daily)

Ureteral Calculi

CAUSES
CALCIUM (80%) calcium oxalate or calcium phosphate, radiodense
URIC ACID (10 15%) 20% of patients also have gout, radiolucent
STRUVITE (10 15%) urea splitting bacteria (Proteus, Klebsiella), infected stone. Staghorn calculi if filled entire renal pelvis, radiodense
CYSTINE (1%) autosomal recessive disorders of renal tubular absorption of dibasic amino acids, radiodense

PATHOPHYSIOLOGY
STONE FORMATION
- PROMOTERS low urine volumes, urine cystine, pH (distal RTA), uric acid, Ca/oxalate/PO₄, anatomic defects (medullary sponge kidney)
- INHIBITORS high urine volumes, urine citrate, Mg, Tamm Horsfall proteins, nephrrocalcin, uric acid, matrix (organic substances associated with urea producing bacteria), indinavir (radiolucent on X ray and CT)

INVESTIGATIONS

BASIC
- Labs CBCD, lytes, urea, Cr, Ca, PO₄, PTH, uric acid, urinalysis (artifact most times)
- Imaging unenhanced CT abd/pelvis (sens 96%, spc 100%), KUB (consider EWSL if see stone on film), U/S abd, IVP

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, uroscopy, 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, alkalinaization of urine with K citrate or NaHCO₃). Hypomagnesia (Mg gluconate 500 mg PO TID)

Hypertension

See HYPERTENSION (p. 57)
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 (AV graft, AV fistula), 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 splay 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]
- HCO₃⁻  
25 40 mmol/L (usually 35 mmol/L)
- CA²⁺  
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, CI 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/mm³. Treat with intraperitoneal ceftazidime and vancomycin empirically until cultures available.

- **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
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 H2 blockers (e.g. ranitidine 50 mg IV q8h or 150 mg PO/NG q12h) preferred unless high risk as use of proton pump inhibitors is associated with increased risk of ventilator associated pneumonia

VENOUS THROMBOEMBOLISM particularly in patients with trauma and prolonged bed rest. Prophylaxis includes heparin SC, LMWH, fondaparinux, or pneumatic compression stockings

SEDATION, ANALGESIA, PARALYSIS IN THE ICU

SEDMATION/ANOMESIA 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 inter mediate to prolonged sedation, longer duration than midazolam, most potent amnestic

ALGJESIA fentanyl 50 100 μg q5min IV load to effect, then 1 4 μg/kg/h by continuous IV infusion,

SEDATION, ANALGESIA, PARALYSIS IN THE ICU (CONT'D)
typical infusion range 50 300 μg/h, 100× more potent than morphine. Used in patients with hemo dynamic 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 BLOCKADE 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, dura tion 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, dura tion ~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 354:13)

• LANDMARK palpate radial artery immediately proximal to scaphoid. Insert 20 gauge (48 mm length) catheter at 30°
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%), hema toma (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 sur face 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 (CaO2)**
- \( C_aO_2 = O_2 \text{ carried by hemoglobin} + O_2 \text{ dissolved in blood} \)
- \( C_aO_2 = 1.36 \times Hb \times S_aO_2 + 0.003 \times P_aO_2 \)
- where \( S_aO_2 \) = arterial Hb saturation

**VENOUS OXYGEN CONTENT (CvO2)**
- \( C_vO_2 = O_2 \text{ carried by hemoglobin} + O_2 \text{ dissolved in blood} \)
- \( C_vO_2 = 1.36 \times Hb \times S_vO_2 + 0.003 \times P_vO_2 \)
- where \( S_vO_2 \) = mixed venous Hb saturation (\( C_vO_2 \) if using central venous saturation)

**OXYGEN FLUX (DO2)**
- \( DO_2 = \text{amount of oxygen delivered to tissues/min} \)
- \( DO_2 = CO \times C_aO_2, \text{where } C_aO_2 \sim 1.36 \times Hb \times S_aO_2 \)
- \( DO_2 \) since 0.003 \( \times \) \( P_aO_2 \) is negligible

**OXYGEN CONSUMPTION (VO2)**
- \( VO_2 = \text{the arteriovenous oxygen content difference multiplied by cardiac output} \)
- \( VO_2 = CO \times (C_aO_2 - C_vO_2) \approx \text{constant} \)
- (the body normally extracts ~25% of the delivered oxygen except in fever, sepsis, hyperthyroidism, i.e. \( VO_2/DO_2 = 0.25 \))

**INTERPRETATION**
- As \( CO \times (C_aO_2 - C_vO_2) \approx \text{constant} \)
- \( \downarrow C_aO_2 \) sug gests \( \downarrow CO \)
- \( S_vO_2 \) is about 75% saturated. A mixed venous saturation of <50% is alarming, <25% is usually unsustainable

**ACUTE PHYSIOLOGIC AND CHRONIC HEALTH EVALUATION (APACHE) II SHEET**

**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 PaO2
- **CBC** Hct, WBC
- **CHEMISTRY** Na, K, Cr

VENTILATION 95% of patients with acute respira tory failure can be weaned within 7 days of intuba tion. 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 prob ability 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
• SN  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 (decere brate), 3=flexion to pain (decorticate), 4=with draws, 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 Cold water, nystagmus fast phase moves toward Opposite side;

BRAIN DEATH (CONT’D)

with Warm water, nystagmus fast phase moves toward Same side)

ANOXIC BRAIN INJURY SPECTRUM

1. Good recovery (mild disability)
2. Moderate disability (independent with ADLs)
3. Severe disability (dependent for ADLs)
4. Persistent vegetative state (unawareness but awake at times)
5. Persistent coma (unawareness at all times but potentially reversible)
6. Brain death (unawareness at all times and irreversible)

DEFINITION OF BRAIN DEATH

• HISTORY  documentation of cause and irreversibility, absence of drug intoxication or poisoning, absence of hypothermia, 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, caloric), 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°C [<82.4°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 SaO2, or arrhythmia
4. Apnea present if respiratory movements are absent, PaCO2 ≥60 mmHg (and increased ≥20 mmHg above baseline) and pH ≤7.28
RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT DEAD, VEGETATIVE, OR SEVERELY NEUROLOGICALLY IMPAIRED (ASSESSING OUTCOME FOR COMATOSE SURVIVORS OF CARDIAC ARREST)?

<table>
<thead>
<tr>
<th>Clinical signs that predict death or poor neurological outcome</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent corneal reflexes at 24 h</td>
<td>12.9</td>
<td>0.60</td>
</tr>
<tr>
<td>Absent pupillary response at 24 h</td>
<td>10.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Absent withdrawal response to pain at 24 h</td>
<td>4.7</td>
<td>0.2</td>
</tr>
<tr>
<td>No motor response at 24 h</td>
<td>4.9</td>
<td>0.6</td>
</tr>
<tr>
<td>No motor response at 72 h</td>
<td>9.2</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**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*

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**Hypoxemia**

**DIFFERENTIAL DIAGNOSIS**

- **R TO L SHUNT** (unresponsive to supplemental O₂, 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 O₂ PARTIAL PRESSURE** (A a normal) high altitude

**PATHOPHYSIOLOGY**

- **DEFINITION OF HYPOXEMIA** P₅O₂ <60 mmHg. Note that hypoxia refers specifically to decreased oxygen supply to tissues and organs

**INVESTIGATIONS**

- **BASIC** CBCD, lyses, 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 oxime try required for accurate results (run ABG). Continuous oximetry is better than spot measurements
  - **CORRELATION** S₉O₂ 50% = P₅O₂ 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 P₅O₂
2. Exclude diffusion defects and low partial pressure of O₂
3. Check PaCO₂. If normal or low, then hypventilation is excluded. This leaves either shunt or V/Q mismatch, which can be distinguished with response to O₂ (absence of response suggests shunt. V/Q mismatch should respond to O₂.)
4. If high PaCO₂, then hypventilation 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 O₂ to distinguish between these two possibilities)
DIAGNOSTIC ISSUES (CONT’D)

ALVEOLAR ARTERIAL (A-a) O₂ GRADIENT

- NORMAL: A-a gradient < age/4 + 0.4 × age. Usually < 15 mmHg in young, up to ~30 mmHg in elderly
- CALCULATION: A-a gradient = \( P_{aO2} - PaO2 = [(Pb - 47) \times 0.21 - PaCO2/0.8] \) where \( Pb \) barometric pressure ≈ 760 mmHg if at sea level
- INTERPRETATION: calculation used when FiO₂ is 21% (room air). Normal range changes with supplemen tal oxygen. If A-a gradient normal, consider hypoventilation or low inspired O₂ as causes of hypoxemia. If A-a gradient high, consider V/Q mismatch, R to L shunt, and/or diffusion defects

\( P_{aO2}/PaO2 \) RATIO when FiO₂ > 21% (i.e. on supplemen tal O₂ therapy), \( P_{aO2}/PaO2 \) ratio should be used instead of A-a gradient

- NORMAL: \( P_{aO2}/PaO2 \geq 0.99 \) (0.003 × age), usually > 0.82
- INTERPRETATION: unlike A-a gradient, \( P_{aO2}/PaO2 \) ratio decreases in the presence of V/Q mismatch, R to L shunt, and/or diffusion defects

STUDIES

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)

Acute Respiratory Distress Syndrome

PATHOPHYSIOLOGY (CONT’D)

DEFINITION OF ARDS

- ACUTE ONSET
- BILATERAL ALVEOLAR INFILTRATES usually asym metric/patchy, peripheral > central
- HYPOXEMIA: \( P_{aO2}/FiO2 \leq 200 \)
- ABSENCE OF LEFT ATRIAL HYPERTENSION: historically defined as pulmonary arterial wedge pressure ≤ 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 mem brane permeability and protein rich fluid exudation into the alveolar space, impairing oxygenation. Ongoing inflammation may lead to extensive fibrosis

MANAGEMENT

ACUTE: ABC, O₂, IV, mechanical ventilation if severe respiratory failure (invasive or non invasive)

TREAT UNDERLYING CAUSE

TREATMENT ISSUES

AVOID OVER CORRECTING O₂ SATURATION IN HYPOVENTILATION: O₂ displaces CO₂ from Hb, causing elevated CO₂ in blood. In addition, O₂ may change V/Q relationship and may decrease hypoxic drive. For patients with chronic hypover tilation (↑ HCO₃⁻), O₂ to keep saturation between 88 and 92% only

SPECIFIC ENTITIES

HYPOXEMIC RESPIRATORY FAILURE: \( P_{aO2} < 50 \) mmHg even with \( FiO₂ > 50 \) failure to oxygene, see DIFFERENTIAL DIAGNOSIS OF HYPOXEMIA

HYPERCARBIC RESPIRATORY FAILURE: \( P_{aCO2} \) greater than baseline with concomitant acidosis failure to ventilate, see hypoventilation under DIFFERENTIAL DIAGNOSIS OF HYPOXEMIA

INVESTIGATIONS

BASIC

- LABS: CBCD, lysates, urea, Cr, troponin/CK, urina lysis, lactate
- MICROBIOLOGY: blood C&S, sputum Gram stain/ C&S/AFB, urine C&S
- IMAGING: CXR, CT chest, echocardiogram
- ABG
- ECG
- SWAN–GANZ CATHETERIZATION

 PATOPHYSIOLOGY

PHASES OF ARDS: <10 days = exudative phase, 10–14 days = fibroproliferative/fibrotic phase

HYPOXEMIA IN ARDS: caused mainly by right to left shunt, thus the \( P_{aO2}/FiO2 \) ratio is low. V/Q mismatch and hypoventilation may also contribute

CAUSES: over 80% of ARDS are caused by infec tions, aspiration, and trauma

- PULMONARY: pneumonia (bacterial, viral, fungal, PJP), aspiration, drowning, inhalation injury (O₂, smoke, NO₂), reperfusion injury (post lung transplant or cardiopulmonary bypass)
- GI: acute pancreatitis
- CNS: neurogenic (intracerebral hemorrhage)
- SYSTEMIC: sepsis, transfusion reaction, major trauma, drugs (heroine, cocaine, aspirin, chemotherapy)

Acute Respiratory Distress Syndrome

93
DIAGNOSTIC AND PROGNOSTIC ISSUES

ACUTE LUNG INJURY  milder form of ARDS with \( P_{a}O_{2}/F_{i}O_{2} \leq 300 \)

PROGNOSIS OF ARDS  overall mortality rate \( \sim 45\% \). 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 \( \sim 8 \text{ mL/kg} \), based on ideal body weight, maintain plateau pressure \( \leq 30 \text{ cmH}_2\text{O} \)

- PEEP should be employed to keep FiO\_2 in pre assumed 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\_2\text{O} 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 prophyaxis. 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 \( P_{a}O_{2}/F_{i}O_{2} \))

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 ≤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\_2\text{O}

- 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)** maintains the positive pressure throughout exhalation. PEEP improves Pao2 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 cmH2O. > 15 cmH2O may cause barotrauma.

- **PEAK AIRWAY PRESSURE (Ppeak)** maximal inspiratory pressure to distend alveoli and to overcome airway resistance. Ppeak is dependent on inflation volume, airways resistance, and lung/chest wall compliance. Happens about halfway through inspiration phase.

- **PLATEAU PRESSURE (Pplat)** pressure to prevent lungs from deflating at end inspiration. Related to lung/chest wall compliance. Normal is 33 ± 9 cmH2O.

- **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 ≤35°
- **THYROMENTAL DISTANCE** <6 cm [<2.4 in.] (3 finger breadths)
- **MOUTH OPENING** <4 cm (<1.6 in.) (2 3 finger breadths)
- **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 (CONT’D)

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.

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 O2 (via upper airway), suction of upper and lower airways, deflate cuff completely, remove inner cannula if present, insert plug and lock it in place, assess patient for airway patency, increased work of breathing and stridor.

- **DECANNULATION CRITERIA** breathing spontaneously without ventilator assistance, consistent cough and ability to expectorate secretions, awake enough to protect airway, on minimal FiO2 (<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 cmH2O (almost no support) to 30 cmH2O (max). Normal = 14 16 cmH2O. In pressure limited modes only.

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.

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VENTILATORY SETTINGS (CONT’D)

INSPIRATORY TIME determines duration over which the pressure is delivered. In pressure limited modes only
\[ F_{O_2} \] 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\(_2\)O, max 15–20 cmH\(_2\)O (usually in ARDS)

VENTILATORY MODES
- **ASSIST CONTROL** (AC) mandatory ventilator controlled breaths at set rate. Patient may breathe spontaneously (i.e., trigger the ventilator, “assist” breaths) 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 (\( P_{\text{high}} \) and \( P_{\text{low}} \)). This mode attempts to maximize mean airway pressure and thus alveolar recruitment at \( P_{\text{high}} \) while dropping briefly to \( P_{\text{low}} \) 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\(_2\)O, up to 20 cmH\(_2\)O) and expiratory positive airway pressure phase (EPAP, start at 6 cmH\(_2\)O, up to 10 cmH\(_2\)O). 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, no metabolic acidosis, clear CXR, adequate hemoglobin, adequate nutrition
- **\( F_{O_2} \) SETTING** effective oxygenation at \( F_{O_2} \) 0.5 or less
- **PEEP SETTING** effective gas exchange at PEEP 7.5 cmH\(_2\)O 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\(_2\)O, 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. Deescalate 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?

<table>
<thead>
<tr>
<th>Physical and investigations</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>1.2</td>
<td>0.86</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>1.3</td>
<td>0.74</td>
</tr>
<tr>
<td>Purulent sputum</td>
<td>1.3</td>
<td>0.63</td>
</tr>
</tbody>
</table>

**VENTILATOR ASSOCIATED PNEUMONIA (CONT’D)**

<table>
<thead>
<tr>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥2 of fever/↑ WBC/purulent sputum</td>
<td>2.8</td>
</tr>
<tr>
<td>Crepitation on auscultation</td>
<td>1.2</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>1.1</td>
</tr>
</tbody>
</table>

**Radiographic features**

- New infiltrate on radiograph
- Air bronchogram
- Silhouette sign
- Alveolar infiltrate
- Fissure abutment
- Atelectasis

**Pulmonary secretion analysis**

- >50% neutrophils
- Intracellular (PMN) bacteria

**Positive Gram stain**

- Blind bronchial aspirate
- Mini BAL fluid
- BAL fluid

**Culture**

- Blind bronchial asp. (>10^5 CFU/mL)
- BAL fluid (>10^4 CFU/mL)

**Clinical pulmonary infection score**

- Score >6

**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*

**DIFFERENTIAL DIAGNOSIS**

- **SHOCK**
  - **SEPTIC** pneumonia, bacteremia, UTI, intraabdominal 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, idioopathic, familial, autoimmune

- **DISEASES**
  - **KIDNEY** acute/chronic renal failure, glomerulonephritis
  - **LIVER** hepatic failure
  - **HORMONAL** adrenal insufficiency, myxedema
  - **MUSCULOSKELETAL** arthritis, myositis, osteitis
  - **SPINAL** cord compression

**PATHOPHYSIOLOGY**

- **DEFINITION** hypotension leading to cellular hypoperfusion, hypoxia, lactic acidosis, and subsequent
organ failure (oliguria, hepatic and GI dysfunction, altered mental status)

**IT'S SIMPLE MATH**

\[ \text{BP} = \text{CO} \times \text{SVR} = (\text{SV} \times \text{HR}) \times \text{SVR}, \]

where

\[ \text{CO} = \text{cardiac output and HR = heart rate} \]

**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 pulmonary 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, S3

**URINE** urine output

**EXTREMITIES** peripheral pulses, skin temperature, capillary refill

**FEET EXAMINATION**

**WARM FEET** vasodilation → distributive shock → give fluids and consider vasopressors

**COLD FEET** vasoconstriction → cardiogenic vs. hypovolemic/obstructive vs. late septic shock → give fluids and consider inotropes especially if suspect cardiogenic cause. Also check troponin and consider echocardiogram

**INVESTIGATIONS**

**BASIC**

**LABS** CBCD, lyes, urea, Cr, INR, PTT, AST, ALT, ALP, bilirubin, Ca, Mg, PO4, TSH, D dimer, lactate, CK, troponin, urinalysis

**MICROBILOGY** 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**

**DISTINGUISHING FEATURES BETWEEN SHOCK STATES**

<table>
<thead>
<tr>
<th>CO CVP PCWP SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distributive</td>
</tr>
<tr>
<td>Hypovolemic</td>
</tr>
<tr>
<td>Cardiogenic</td>
</tr>
<tr>
<td>Isolated RHF</td>
</tr>
<tr>
<td>Isolated LHF</td>
</tr>
<tr>
<td>Tamponadea</td>
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</tbody>
</table>

*aIn tamponade or tension pneumothorax, observe equalization of pressures, i.e. CVP=RA=RV EDP=PCWP; cardiogenic shock gives heart failure picture on CXR, whereas tamponade usually has clear CXR with cardiomegaly only*
**MANAGEMENT**

**ACUTE**  ABC, O₂, cardiac and oximetry monitoring, IV fluid resuscitation (1 5 L), ICU consult, consider intubation/mechanical ventilation, inotropes/vasopressors  
*Nor*epinephrine 1 30 μg/min IV. *Vasopressin* 0.01 0.04 U/min IV. *Epinephrine* 1 20 μg/min IV. *Phenylephrine* 20 200 μg/min IV.  
*Ephedrine* 5 25 mg IV q5 10 min until blood pressure stable.  
*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  
  - α₁ → ↑ PVR, ↑ CO  
  - β₁ = inotropic and chronotropic effect  
  - β₁ → ↑ 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, ↑ renal perfusion/GFR (controversial)  
Dopamine 1 2 μg/kg/min | DA → dilates renal, mesenteric, cerebral arteries and airways | HF/sepsis; AE: tachycardia  
Dopamine 5 10 μg/kg/min | DA, β₁ → ↑ CO | Sepsis/HF; AE: tachycardia  
Dopamine >10 μg/kg/min | α₁ → ↑ PVR | Sepsis; oral  
Midodrine | α₁ → ↑ PVR |  

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

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**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 PₐCO₂ <32 mmHg, WBC >12 x 10⁹/L or <4 x 10⁹/L or >10% bands  
- **SEPSIS** SIRS plus documented or suspected infection 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, fibrinolitics → 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 x 10^9/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**
- **ScvO2 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 (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%

**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 vaso pressor dependent shock.

**Blood Products** in septic shock patients with low ScvO2 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.

**NEJM 2001 345:19**

**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 (↓ O₂ 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, O₂ to keep sat >94%, IV, HCO₃ 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 hypercalcemia in 20% of patients when rhabdomyolysis resolves

**COMPLICATIONS** acute kidney injury, DIC

**INVESTIGATIONS**

**BASIC**
- **LABS** lytes, urea, Cr, CK, AST, ALT, Ca, PO₄, Mg, uric acid, troponin, urine myoglobin

**DIAGNOSTIC ISSUES**

**MONITORING IN RHABDOMYOLYSIS** CK, urine output, Cr, Ca, PO₄ should be checked regularly (q4 24h) until CK normalized

**MANAGEMENT**

**ACUTE** ABC, O₂ 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
kidney injury. However, if acute kidney injury already established be careful not to cause fluid overload. 

Alkaline diuresis (add 3 amps NaHCO₃ 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 levo dopa 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.

- TREATMENTS discontinue all antidopaminergic medications. Supportive measures. Specific treatments include dantrolene, bromocriptine, and amantadine

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, O₂, IV, monitor, vitals (HR, RR, BP, temp, O₂ sat, blood sugar, GCS)

INVESTIGATIONS

- BLOOD TESTS CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, Ca, Mg, PO₄, 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, HCO₃ if cardiac arrhythmia, sedation with benzodia zepines PRN

SYMPATHOMIMETIC SYNDROMES

CAUSES cocaine, amphetamines, LSD, PCP, metham phetamine, 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 acetylcycteine, the antitode, 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 acetylcycteine 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 acetylcycteine

KING’S COLLEGE CRITERIA FOR LIVER TRANSPLANTATION IN TYLENOL OVERDOSE ★The rule of 3’s★ either pH <7.3 or grade III/IV encephalopathy plus Cr >300 μmol/L (>[3.3 mg/dL] plus INR >6.5 (~5% survival with medical therapy alone)

NEJM 2008 359:3

ACETAMINOPHEN OVERDOSE (CONT’D)

of 3’s★ either pH <7.3 or grade III/IV encephalopathy plus Cr >300 μmol/L (>3.3 mg/dL) plus INR >6.5 (~5% survival with medical therapy alone)

SALICYLATE OVERDOSE

CAUSES ★The rule of 3’s★ a single dose of 10 30 g (30 tablets of 325 mg) can be fatal. Symptoms may occur with salicylate >3.0 mmol/L (>[40 mg/mL])

CLINICAL FEATURES common (tinnitus, vertigo, N&V, diarrhea, tachypnea, metabolic acidosis, respiratory alkalosis), serious (hyperthermia, pulmonary edema, delirium, seize, 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 (NaHCO3 1 3 amps IV push, then 3 amps of NaHCO3 in 1 L D5W at 250 mL/h). Consider hemodialysis if altered mentation, cerebral edema, fluid overload, pulmonary edema, severe renal failure, salicylate >7.2 mmol/L (>100 mg/mL) in acute ingestion or >5 mmol/L (>70 mg/mL) in chronic toxicity, rising levels or clinical deterioration

MORTALITY RATE acute ~1 2% (usually suicidal attempt in young patient), chronic ~25% (often elderly patient, delayed diagnosis due to low index of suspicion)

OPiates, 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 alkalization (if barbiturates)

β BLOCKER OVERDOSE

CLINICAL FEATURES common (hypotension, bradycardia, bronchospasm, hypoglycemia), serious (shock, asystole, seizure, coma)

TREATMENTS supportive measures, fluid resuscitation, glucagon (initial dose 0.05 0.15 mg/kg up to
a max dose of 10 mg over 2 min, then infusion 0.07 mg/kg). IV calcium, phosphodiesterase inhibitor (mirtroline 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, amldipine, 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 acute toxicities include CNS acute ingestion or 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 dia betes insipidus, leukocytosis, and goiter

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

DIAGNOSTIC ISSUES FOR OVERDOSE

OSMOLAR GAP measured osmolality calculated osmolality, where \( \text{Osmo}_{\text{calc}} \) ★GUN2★

- \( \text{Osmo}_{\text{calc}} = (\text{Glucose in mmol/L}) + (\text{Urea in mmol/L}) + 2 \times (\text{Na mmol/L}) \)
- or in US units: \( \text{Osmo}_{\text{calc}} = (\text{Glucose in mg/dL})/18 + (\text{Urea in mg/dL})/2.8 + 2 \times (\text{Na mEq/L}) \)
- NORMAL OSMOLAR GAP typically 2 to +6 mOsm/kg
- INCREASED OSMOLAR GAP and ANION GAP ethylene glycol, methanol, diabet ic or alcoholic ketoacidosis, lactic acidos is, 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.A G

- Abnormal 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 actu ally 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, hydro gen 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, thia mine 50 100 mg IV). Supportive care for airway protection (intubation if GCS ≤8, severe hypo xemia/hypercapnia and/or hemodynamic instabil ity), 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 inges tion (should be tried even after 60 min if delayed gastric emptying, e.g. TCA overdose) and if
MANAGEMENT OF OVERDOSES (CONT’D)

carbon 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 NaHCO3 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, alcohol (ethanol, isopropanol, acetone, methanol, ethylene glycol), lithium, procainamide, theophylline, salicylates, heavy metals, trichloroethanol, atenolol, or sotalol

4. SPECIFIC ANTIDOTES acetaminophen CHRONIC ALCOHOLISM/ACUTE WITHDRAWAL/ACUTE INTOXICATION AT RISK FOR ALCOHOLISM = 150 mL (5 oz) of wine = 45 mL (1.5 oz) of distilled 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)

4. SPECIFIC ANTIDOTES acetaminophen (N-acetyl cysteine 150 mg/kg (~60 mL) in 200 mL D5W IV over 1 h, then 50 mg/kg (~20 mL) in 500 mL D5W IV over 4 h, then 100 mg/kg (~40 mL) in 1 L D5W IV over 16 h. Alternatively, N-acetylcysteine 140 mg/kg PO/NG, followed by 70 mg/kg q4h for 17 doses). 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 glycol level <3.2 mmol/L (<20 mg/dL). Digitalis (Digibind 10 20 vials IV if life threatening arrhythmia). Calcium channel blockers (CaCl2 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 (pyrithioxine given gram to gram of INH ingested). Tri cyclic antidepressant (NaHCO3 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 30min 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, homocide, 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 Cut down, Annoyed by criticisms, Guilty about drinking, Eye 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
DELIRIUM TREMENS (DT)
WITHDRAWAL SEIZURES
ALCOHOLIC HALLUCINATIONS
RISK FACTORS
SYMPTOMS
TIMING

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, nau sea 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 medical 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 conscious ness/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 drink ing, history of previous delirium tremens, concurrent illness, greater number of days since the last drink

INVESTIGATIONS (CONT’D)

BASIC
• LABS CBCD (macrocytosis, cytopenias), lyes, urea, Cr, glucose, TSH, AST, ALT (AST/ALT >2), ALP, bilirubin, GGT, Ca, Mg, PO₄, 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, O₂ to keep sat >94%, IV (NS 1 L bolus, then 100 mL/h). Consider causes of patient’s symp toms 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) chloralhydrate 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?”
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 ≤8/67 points, moderate withdrawal 9 15 points, severe withdrawal >15 points (higher risk of delirium tremens and seizures). Use of benzodiazepines recommended when score >9. Symptom triggered regimens require intense monitoring, but have been shown to result in less medication use and shorter duration of treatment

SPECIFIC ENTITIES

THIAMINE DEFICIENCY SYNDROMES
- WERNICKE'S ENCEPHALOPATHY encephalopathy (profound disorientation, indifference, inattentive ness, 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 meta bolites 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). \( \text{Na}_2\text{CO}_3 \) 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 (tomepizole 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 ≈ 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 → \text{CO}_2 + \text{H}_2\text{O}); thiamine 100 mg IV q6h and pyridoxine 50 mg IV q6h until ethylene glycol no longer measurable (accelerates glyoxylate → glycine + α hydroxy β keto adipate. This reaction requires magnesium supple mentation). Hemodilysis for confirmed intox ication (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, adre nal insufficiency, hypoglycemia

CAUSES (CONT’D)
- METABOLIC anorexia nervosa, malnutrition
- 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 $<35\degree C$ ($<95\degree F$) (by rectal, tympanic, or esophageal thermometer). Hypothermia may be mild ($34-35\degree C$ [$93-95\degree F$]), moderate ($30-34\degree C$ [$86-93\degree F$]), or severe ($<30\degree C$ [$<86\degree F$])

**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 CBC, lymphocytes, urea, Cr, glucose, CK, troponin, AST, ALT, ALP, bilirubin, TSH, urinalysis
- Microbiology blood cultures
- ECG Osborn wave (elevated J point), prolonged RR, PR, ORS, and QT intervals

**MANAGEMENT**

**MANAGEMENT (CONT’D)**

**REWARMING** environment (remove cold clothing. Warming blanket). **Active rewarming** (warm IV fluids $\sim 40-42\degree C$ [$104-108\degree F$]). If severe hypothermia, consider colonic/bladder irrigation, peritoneal or pleural lavage, extracorporeal blood rewarming. Goal of rewarming is $0.5\degree C/h$ [$1.8\degree F/h$] 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 CBC, lymphocytes, 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 CBC, lymphocytes, 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 PaO₂, PaCO₂, and CO Hb levels
- LARYNGOSCOPY/BRONCHOSCOPY if significant burns

MANAGEMENT

ACUTE ABC, high flow O₂ 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 O₂
- CLINICAL FEATURES nausea, malaise, headache, dyspnea, angina, confusion, coma
- TREATMENTS 100% O₂ (decreases t½ 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)
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
- INFECTIOUS 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 cricopharyngeal contraction followed by relaxation seconds before vomiting

INVESTIGATIONS

BASIC
- LABS CBC, lytes, urea, Cr, glucose, Ca, Mg, PO4, AM cortisol, urinalysis
- MICROBIOLOGY urine C&S
- IMAGING CXR, AXR
- SPECIAL GASTROSCOPY
- CT HEAD

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 q4h, 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, dolastron 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)
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, cerebrovascular accidents, 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), video fluoroscopy (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 narrow ing), 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**
- Acid hypersecretion Zollinger Ellison disease
- Alcohol abuse
- Connective tissue disease scleroderma
- Infections of esophagus CMV, HSV, candidiasis
- Diabetic gastroparesis
- Drug therapy
- Smoking

**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 postprandial 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 DYSPESIA?

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>OR</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organic dyspepsia</strong></td>
<td></td>
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<tr>
<td>Diagnosis reached by the clinician or computer model</td>
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<tr>
<td><strong>Peptic ulcer disease</strong></td>
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<td>0.45</td>
</tr>
<tr>
<td>Diagnosis reached by the clinician or computer model</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL FEATURES (CONT’D)

**Esophagitis**
Diagnosis reached by the clinician 2.4 0.5
or computer model

**APPROACH** “functional dyspepsia is defined as pain or discomfort centered in the epigas trium with a normal endoscopy. Neither clinical impression nor computer models that incorpo rated 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, musculos keletal, medications, and dietary indiscretion) and investigate those causes if likely. Otherwise proceed to step 2
2. If age >50 or alarm symptoms Very BAD (Vomiting, Bleed/anemia, Abdominal mass/ weight loss, Dysphagia), 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/H2 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


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. Anti secretory 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): clari thromycin 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). Antisecre tory treatment (proton pump inhibitors more effec tive 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 pres sure, decreased esophageal peristalsis, gastric acid hypersecretion, delayed gastric emptying, and overeating
- PATHOPHYSIOLOGY reflux of stomach contents, lead ing to a multitude of symptoms including heartburn, regurgitation, dysphagia, chest pain, complicated by esophagitis, esophageal stricture, Barrett’s esopha gus, and esophageal adenocarcinoma
- CLINICAL FEATURES esophageal (heartburn, regur gitation), extra esophageal (wheeze, cough, pneu monia, waterbrash, hoarseness, sore throat, glo bus, dental erosions)
- DIAGNOSIS clinical based on symptoms (≥2/week). Endoscopy to look for complications and rule out other potential diagnoses

**NSAIDS INDUCED GASTROPATHY**
- PATHOPHYSIOLOGY NSAIDs inhibit COX 1 (nor mally 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

H. 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

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 epigastic or periumbilical region; anorexia, nausea, or unsustained vomiting; migration of the initial pain to the RLQ; low grade fever

NEJM 2007 356:8
### RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE APPENDICITIS?

<table>
<thead>
<tr>
<th>History</th>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
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</thead>
<tbody>
<tr>
<td>Migration of pain to RLQ</td>
<td>64%</td>
<td>82%</td>
<td>3.18</td>
<td>0.5</td>
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<tr>
<td>RLQ pain</td>
<td>81%</td>
<td>53%</td>
<td>8.0</td>
<td>0.15</td>
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<tr>
<td>Pain before vomiting</td>
<td>100%</td>
<td>64%</td>
<td>2.76</td>
<td></td>
</tr>
<tr>
<td>No similar pain previously</td>
<td>81%</td>
<td>41%</td>
<td>1.5</td>
<td>0.32</td>
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</table>

#### Physical
- Rigidity: 27% (LR+ 3.76, LR 0.82)
- Fever: 67% (LR+ 1.94, LR 0.58)
- Rebound tenderness: 63% (LR+ 3.7, LR 0.4)
- Psoas sign: 16% (LR+ 2.38, LR 0.90)

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

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### 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).

---

### EXAMINATION OF ABDOMINAL MASSES

- **Right Upper Quadrant Mass**
  - Liver (downward with inspiration, left lobe, right lobe, gallbladder), kidney (downward with inspiration, ballottable, 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).

- **Left Upper Quadrant Mass**
  - Spleen (downward with medially with inspiration, notch, bruit), left kidney (downward with inspiration, ballottable, palpable upper border), colon (splenic flexure), 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 abdom/pelvic.

#### Special
- **Imaging**
  - IVP, barium contrast, CT abdom/pelvic.
- **ECG**
  - If suspect cardiac involvement.
- **Endoscopy**
ACUTE CHOLECYSTITIS

- 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 co son 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, O2, IV hydration. NPO, NG if severe N&V/obstruction. Morphin 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 (cefa zolin 1 g IV q8h, gentamicin 6 mg/kg IV q24h, metro nidazole 500 mg IV q12h)

SPECIFIC ENTITIES (CONT’D)

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

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

MURPHY SIGN

Murphy sign Sens 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 labora tory 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 prob ability 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”

ACUTE MESENTERIC ISCHEMIA

- PATHOPHYSIOLOGY embolism in the celiac or superior mesenteric artery from valvular heart dis ease 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

ACUTE ABDOMINAL X RAYS

APPROACH TO ABDOMINAL X RAYS

- FREE AIR pneumoperitoneum suggests perforation. May be secondary to choledocholithiasis. See p. 139
- OTHER STRUCTURES liver, spleen, bones
- FREE AIR may be seen with bowel infarction:
  - FREE AIR 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)
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ACUTE MESENTERIC ISCHEMIA

- PATHOPHYSIOLOGY embolism in the celiac or superior mesenteric artery from valvular heart dis ease 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

ACUTE ABDOMINAL X RAYS

APPROACH TO ABDOMINAL X RAYS

- FREE AIR pneumoperitoneum suggests perforation. May be secondary to choledocholithiasis. See p. 139
- OTHER STRUCTURES liver, spleen, bones
- FREE AIR may be seen with bowel infarction:
  - FREE AIR 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, O2, IV hydration. NPO, NG if severe N&V/obstruction. Morphin 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 (cefa zolin 1 g IV q8h, gentamicin 6 mg/kg IV q24h, metro nidazole 500 mg IV q12h)

SPECIFIC ENTITIES (CONT’D)

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

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

MURPHY SIGN

Murphy sign Sens 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 labora tory 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 prob ability 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”

ACUTE MESENTERIC ISCHEMIA

- PATHOPHYSIOLOGY embolism in the celiac or superior mesenteric artery from valvular heart dis ease 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.

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.

DIFFERENTIAL GI BLEED

PEPTIC ULCER DISEASE (PUD): gastric, duodenal.
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, hemoptyisis.

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.

RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT HYPOVOLEMIC? HYPOVOLEMIA DUE TO ACUTE BLOOD LOSS

For moderate blood loss:
- Postural pulse increment ≥30/min or severe postural dizziness: 22% Sens, 94% Spc.
- Postural hypotension ≥20 mmHg: 9% Sens, 94% Spc.
- SBP drop: 0% Sens, 96% Spc.
- Supine tachycardia: 13% Sens, 97% Spc.

For large blood loss:
- Postural pulse increment ≥30/min or severe postural dizziness: 97% Sens, 98% Spc.
- Supine tachycardia: 12% Sens, 96% Spc.
- Supine hypotension: 33% Sens, 97% Spc.

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).

HYPOVOLEMIA DUE TO VOMITING, DIARRHEA, DECREASED INTAKE, DIURETICS

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

Related Topic

Shock (p. 97)
### CLINICAL FEATURES (CONT’D)

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

**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 (CONT’D)

**MANAGEMENT**

**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 apy → balloon tamponade → TIPPS → portacaval/distal splenoportal 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 **nadolol** 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
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

(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%)

INFECTION: 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 (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 (BRPR), 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 ABDOMINAL PAIN (O2, IV hydration (two large bore IVs). Transfusion (especially if hematocrit <30%, platelets <50×10^9/L). NPO. Hold antihypertensive and diuretic therapy. If prolonged PT/PTT, vitamin K 10 mg IV (small risk of anaphylaxis) [see above comment for UGIB] and/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

- **C15** ulcerative colitis (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**

<table>
<thead>
<tr>
<th>Degree of involvement</th>
<th>Crohn’s disease</th>
<th>Ulcerative colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmental</td>
<td>Rectal sparing</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Abd pain</th>
<th>Bloody diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>Tenesmus</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>Fever</td>
<td></td>
</tr>
<tr>
<td>Perianal disease</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Serology</th>
<th>Saccharomyces cerevisiae IgG antibody (sens 77%, spec 92%, PPV 82%)</th>
<th>P ANCA (sens 70%, spec 88%, PPV 75%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Transmural granuloma</th>
<th>Mucosal inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No granuloma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complications</th>
<th>Obstruction</th>
<th>Toxic megacolon (1-2%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Strictures</td>
<td>Colorectal cancer (1%/year after 10 years)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Fistulas</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fissures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abscesses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer</td>
<td></td>
</tr>
</tbody>
</table>

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 steroids. Consider oral 5ASA if patient cannot tolerate suppositories. Maintenance therapy may be required.

DISTAL COLITIS / PROCTOSIGMOIDITIS 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°C [100.4°F], tachycardia >120/min, leukocytosis >10.5 x 10⁹/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.

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, chemo therapy

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, previous treatments, 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, Campylobacter*).

- **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.

- **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 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.

**NEJM 2002 346:5; NEJM 2008 359:18**
Chronic Diarrhea

DIFFERENTIAL DIAGNOSIS

★MISΟ★

**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**

- Pancreatic insufficiency, celiac disease, lactose intolerance, short bowel syndrome, enteric fistula

**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**

\[ 2 \times (\text{stool Na}^+ + \text{K}^+) \]

**MANAGEMENT**

**SYMPTOM CONTROL** hydration and nutritional support. Empiric treatment with antidiarrheal agents if not inflammatory (bismuth subsalicylate 2 tab PO q1h PRN or loperamide 4 mg × 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 Barley, Rye, Oat, Wheat ★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, osteopenosis 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

**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, anti transglutaminase 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
Malabsorption Syndromes

DIFFERENTIAL DIAGNOSIS

SALIVARY (lipase, amylase; rare cause) radiation, sicca

STOMACH (intrinsic factor, R factor; rare cause) pernicious anemia, gastrectomy, vagotomy

HEPATOBILIARY (bile acids; 10% of extra colonic cases) hepatic failure, cholestasis, biliary obstruction, terminal ileal resection

PANCREAS (lipase, amylase, HCO3; 90% of extra colonic causes) cancer, chronic pancreatitis, cystic fibrosis

SMALL INTESTINE (brush border/enterocytes) celiac disease, lymphoma, infectious colitis, inflammatory colitis, ischemic colitis, radiation colitis

OTHERS β lipoprotein (abetalipoproteinemia), lymphatics (lymphoma)

PATHOPHYSIOLOGY

COMPLICATIONS OF MALNOURISHMENT infections (sepsis, abscess, pneumonia), poor wound healing, respiratory failure, death

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)

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, PO4, albumin, pre albumin, carotene, Fe, ferritin, antitranstglutaminase 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 H2, 14CO2, or 13CO2
• ANTIINTRINSIC FACTOR ANTIBODY for vitamin B12 deficiency (has replaced historical Schilling test)

Related Topics
Cachexia (p. 397)
Celiac Disease (p. 124)
Vitamin B12 Deficiency (p. 405)
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 with out 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

WATER SOLUBLE VITAMIN DEFICIENCY  
- VITAMIN B1 (THIAMINE) DEFICIENCY  Wernicke syndrome, Korsakoff syndrome, Leigh’s syndrome (subacute necrotizing encephalomyopathy)
- VITAMIN B3 (NIACIN, NICOTINIC ACID) DEFICIENCY  Dermatitis (photosensitive, pigmented, pellagra), Diarrhea, Dementia, Death
- VITAMIN B6 (PYRIDOXINE) DEFICIENCY  cheilosis, painless glossitis, acrodermatitis, angular stomatitis
- VITAMIN C DEFICIENCY  scurvy with impaired collagen synthesis leading to ecchymoses, gum bleeding, petechiae, hyperkeratosis, impaired wound healing, arthralgia, weakness, neuropathy, and depression

DIFFERENTIAL DIAGNOSIS

★DUODENUM★  
DIET  low fiber, dehydration
PSYCHIATRY  depression, somatization, obsessive compulsive disorder
OBSTRUCTION  cancer, strictures, adhesions
DRUGS  opioids, TCAs, neuroleptics, antihistamines, calcium channel blockers, iron, antacids
ENDOCRINE  diabetes, hypothyroidism, hypercalcemia, hypokalemia, hypomagnesemia, uremia
NEUROLOGIC  spinal cord compression/injury, Parkinson’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 constipating medications if possible

SPECIFIC ENTITIES

IRRITABLE BOWEL SYNDROME (IBS)  
- PATHOPHYSIOLOGY  heightened response to noxious visceral stimuli, such as balloon distention 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
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 >10×10^9/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

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower abd pain</td>
<td>90%</td>
<td>32%</td>
<td>1.3</td>
<td>0.29</td>
</tr>
<tr>
<td>Passage of mucus</td>
<td>45%</td>
<td>65%</td>
<td>1.2</td>
<td>0.88</td>
</tr>
<tr>
<td>Feeling of incomplete evacuation</td>
<td>74%</td>
<td>45%</td>
<td>1.3</td>
<td>0.62</td>
</tr>
<tr>
<td>Looser stools at onset of pain</td>
<td>59%</td>
<td>73%</td>
<td>2.1</td>
<td>0.59</td>
</tr>
<tr>
<td>More frequent stools at onset of pain</td>
<td>53%</td>
<td>72%</td>
<td>1.9</td>
<td>0.67</td>
</tr>
<tr>
<td>Pain relieved by defecation</td>
<td>60%</td>
<td>66%</td>
<td>1.8</td>
<td>0.62</td>
</tr>
<tr>
<td>Patient reported visible abdominal distension</td>
<td>39%</td>
<td>77%</td>
<td>1.7</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Diagnostic criteria

- Manning criteria: 78% Sens, 72% Spc, LR+ 2.9, LR 0.29
- Rome I criteria: 71% Sens, 85% Spc, LR+ 4.8, LR 0.34
- Kruis system: 77% Sens, 89% Spc, LR+ 8.6, LR 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

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, 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 (SHT3 antagonist) for diarrhea, and antispasmodics (hyoscymine), 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, V2V, 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 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, chlorproazine, diltiazem, estrogen, fluphenazine, gold, imipramine), TPN, primary biliary cirrhosis
- BILIARY DUCTAL OBSTRUCTION choledocholithiasis, pancreatic cancer, cholangiocarcinoma, pancreatitis, primary sclerosing cholangitis

INFLITRATIVE 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), ALT (specific for Liver), ALP (liver, gut, bone, placenta), GGT, 5’NT, LDH (bone, muscle, liver, lungs)

COMPLICATIONS OF HEPATIC FAILURE
★ SCREAM ★
- Sepsis
- Coagulopathy
- Renal failure
- Encephalopathy
- Ascites
- Metabolic changes (hypoglycemia, electrolyte abnormalities, acidosis)

INVESTIGATIONS

BASIC
- LABS CBCD, peripheral smear, NAD, 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, antithrombin type antibody (ASMA), antithromboplastin antibody (AMA), quantitative immunoglobulin, ferritin, Fe,
INVESTIGATIONS (CONT'D)

- TIBC, % sat, ceruloplasmin, α1 antitrypsin, AFP, antitransthyretinase antibody, lipase, amylase, LDH, haptoglobin, acaminophen, 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 |
| ALP/BILI | ask about pain, symptoms of infiltrative disease, or IBD. To confirm liver involvement, perform bilirubin fractionation, GGTT, S'NT, abdominal US, AMA, and quantitative Ig. Consider MRI/ERCP and liver biopsy |
| 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, O2, 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 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 NaHCO3 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

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 × 28 days 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 ACUTE HEPATIC FAILURE (rule of 3’s)’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-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 hepatoma cellular 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, micro nodular cirrhosis
- DIAGNOSIS AST:ALT = 2:1 (low ALT activity due to Portal hypertension), AST/ALT > 2 or 3 of following: age < 40 or > 60, 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]
- TREATMENTS abstinence, nutrition, prednisolone 40 mg PO × 28 days, pentoxifylline 400 mg PO TID × 4 weeks, S adenosylmethionine 1200 mg PO daily × 2 years
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)

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**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. Life time risk of hepatocellular carcinoma/death in patients with chronic hepatitis is 40% for χ and 15% for ϕ

**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

**SPECIFIC ENTITIES (CONT'D)**

- **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**
  - CBC, 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

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)
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

<table>
<thead>
<tr>
<th>Acute infection</th>
<th>HBsAg</th>
<th>HBclgM</th>
<th>HBsAb</th>
<th>HBclgG</th>
<th>HBeAg</th>
<th>HBeAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Window</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Late</td>
<td>+/+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunity</td>
<td>Vaccinated</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cured</td>
<td>+/+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Chronic infection</td>
<td>Infectious/active</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre core mutant</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low replicative</td>
<td>+</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

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

TREATMENT ISSUES

**TREATMENT DECISION FOR CHRONIC HEPATITIS B INFECTIONS**

- **HBeAg positive patients** no spontaneous seroconversion after 6 months with recurrent flares,

- **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

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 decompen-
sation, 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

**Hepatitis C**

**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: CBC, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, anti HCV IgM and total (sens 92-97%), HCV RNA PCR (qualitative, quantitative), genotyping, hCG (before treatment), HAV serology, HBV serology, HDV serology, iron, TIBC, HIV serology

IMAGING: U/S abd

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 PREDICTIVE 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 contra indications 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: decompenated 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 anti-trypsin deficiency, glycogen storage disease
BILIARY CIRRHOSIS: primary biliary cirrhosis, primary sclerosing cholangitis, secondary biliary cirrhosis (stones, strictures)

PATHOPHYSIOLOGY OF CHRONIC LIVER DISEASE

CHRONIC LIVER DISEASE: CIRRHOSIS

CHILD PUGH CLASSIFICATION OF LIVER CIRRHOSIS

<table>
<thead>
<tr>
<th>Stage</th>
<th>Encephalopathy</th>
<th>Ascites</th>
<th>Albumin</th>
<th>Total Bili</th>
<th>INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>None</td>
<td>&gt;35 g/L</td>
<td>&lt;34 µM</td>
<td>&lt;1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[&gt;3.5 g/dL]</td>
<td>[&lt;2 mg/dL]</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Slight</td>
<td>28 35 g/L</td>
<td>34 52 µM</td>
<td>1.7 2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[2.8 3.5 g/dL]</td>
<td>[2 3 mg/dL]</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>Mod</td>
<td>&lt;28 g/L</td>
<td>&gt;52 µM</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[&lt;2.8 g/dL]</td>
<td>[&gt;3 mg/dL]</td>
<td></td>
</tr>
</tbody>
</table>
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 \text{ in mg/dL}) + 3.78 \times \log_e(\text{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 \times MELD \times (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, spleno megaly, 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

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 mid clavicular 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, >1 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, hemo chromatosis, 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 (o penicillamine or trientine), and zinc. For severe liver failure, consider orthotopic liver transplantation

AUTOIMMUNE HEPATITIS
- SUBTYPES I (classic, female predominance, extra hepatic 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 anti body, 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. Intrapleteral injection of 99mTc labeled serum albumin may be helpful to confirm diagnosis
- TREATMENTS O2, 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 ↓ pro duction of vasoconstricting substance → pulmonary capillary dilatation → diffusion perfusion imbalance → hypoxemia, dyspnea on exertion and/or at rest, orthodeoxia and platypnea, cyanosis, 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 O2, liver transplant

PORTOPULMONARY HYPERTENSION
- PATHOPHYSIOLOGY portal hypertension → unknown substance reaches pulmonary vasculature causing vasoconstriction → findings similar to primary pul monary hypertension
- DIAGNOSIS echocardiogram, right heart catheterization
- TREATMENTS O2, 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 oliguric or anuric. Type II includes patients not meeting criteria for type I and is characterized by asctes 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 replace ment 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, heroin, ecstasy
- **OTHERS** salicylates

**INFECTIOUS** pneumonia, UTI, meningitis, encephalitis, abscess, spontaneous bacterial peritonitis

**METABOLIC**
- **ORGAN FAILURE** hepatic, azotemia, hypothyroid ism, hypoxemia, CO₂ narcosis
- **ELECTROLYTES** ketoacidosis, hyponatremia, hyper magnesemia, hypercalcemia, glucose (hypo, hyper)

**STRUCTURAL**
- **HEMORRHAGE** subarachnoid, epidural, subdural, intracerebral
- **STROKE** basilar
- **TUMOR**
- **EPILEPSY**

**NEUROPSYCHIATRIC**

**PATHOPHYSIOLOGY (CONT’D)**

- ↑ Diffusion across blood–brain barrier
- ↓ Metabolism dehydration, hypotension, hypox emia, 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** CBC, lytes, urea, Cr, glucose, TSH, AST, ALT, ALP, bilirubin, INR, PTT, NH₄, Ca, Mg, PO₄, osmolality, CK, troponin (as part of delirium workup), urinalysis
- **MICROBIOLOGY** blood C&S, urine C&S, sputum Gram stain/C&S
- **IMAGING** 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

**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**
- ↑ NH₄ production ↑ protein intake, constipation, GI bleed, transfusion, infection (spontaneous bacterial peritonitis), azotemia, hypokalemia
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

TREAT UNDERLYING CAUSE liver transplant

DIFFERENTIAL DIAGNOSIS
\[ \text{HYDROSTATIC PRESSURE} \]
- CARDIAC right heart failure, tricuspid regurgitation, constrictive pericarditis
- HEPATIC pre sinusoidal (portal vein thrombosis, schistosomiasis), sinusoidal (cirrhosis), post sinusoidal (Budd-Chiari, veno-occlusive)

\[ \text{ONCOTIC PRESSURE} \]
malnutrition, liver disease, nephrotic, protein losing enteropathy

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ASCITES?

<table>
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<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
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<td>77%</td>
<td>4.16</td>
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<td>67%</td>
<td>79%</td>
<td>3.2</td>
<td>0.42</td>
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<tr>
<td>93%</td>
<td>68%</td>
<td>2.8</td>
<td>0.10</td>
</tr>
<tr>
<td>67%</td>
<td>79%</td>
<td>3.2</td>
<td>0.42</td>
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<tr>
<td>47%</td>
<td>73%</td>
<td>2.04</td>
<td>0.73</td>
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<td>60%</td>
<td>58%</td>
<td>1.44</td>
<td>0.69</td>
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<tr>
<td>13%</td>
<td>85%</td>
<td>0.91</td>
<td>1.01</td>
</tr>
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</table>

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
- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bili, 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
- LAPAROSCOPY WITH PERITONEAL BIOPSY

DIFFERENTIAL DIAGNOSIS (CONT’D)
- CAPILLARY PERMEABILITY/LYMPHATIC OBSTRUCTION
- INFECTIONS spontaneous bacterial peritonitis
- MALIGNANCY ovarian, peritoneal metastasis
- PANCREATITIS
- OTHERS hypothyroidism
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

<table>
<thead>
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<th>Ascitic fluid WBC/PMN</th>
<th>LR+</th>
<th>LR</th>
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</thead>
<tbody>
<tr>
<td>Ascitic fluid WBC &gt;1000 cells/µL</td>
<td>9.1</td>
<td>0.25</td>
</tr>
<tr>
<td>Ascitic fluid WBC &gt;500 cells/µL</td>
<td>5.9</td>
<td>0.21</td>
</tr>
<tr>
<td>Ascitic fluid WBC &gt;250 cells/µL</td>
<td>0.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Ascitic fluid PMN &gt;500 cells/µL</td>
<td>10.6</td>
<td>0.16</td>
</tr>
<tr>
<td>Ascitic fluid PMN &gt;250 cells/µL</td>
<td>6.4</td>
<td>0.20</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ascitic fluid pH and blood ascitic pH gradient</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascitic fluid pH &lt;7.31</td>
<td>4.1</td>
<td>0.47</td>
</tr>
<tr>
<td>Ascitic fluid pH &lt;7.32</td>
<td>4.8</td>
<td>0.65</td>
</tr>
<tr>
<td>Ascitic fluid pH ≤7.31</td>
<td>5.8</td>
<td>0.43</td>
</tr>
<tr>
<td>Ascitic fluid pH &lt;7.35</td>
<td>9.0</td>
<td>0.31</td>
</tr>
<tr>
<td>Ascitic fluid pH &lt;7.40</td>
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</tr>
<tr>
<td>Blood ascitic fluid pH gradient</td>
<td>4.6</td>
<td>0.47</td>
</tr>
<tr>
<td>&gt;0.11</td>
<td>7.1</td>
<td>0.30</td>
</tr>
<tr>
<td>Blood ascitic fluid pH gradient</td>
<td>11.3</td>
<td>0.12</td>
</tr>
<tr>
<td>&gt;0.10</td>
<td>0.12</td>
<td></td>
</tr>
</tbody>
</table>

FEATURES SUGGESTIVE OF PORTAL HYPERTENSION

<table>
<thead>
<tr>
<th>Serum ascites albumin gradient (SAAG)</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ascites albumin gradient ≥11 g/L</td>
<td>4.6</td>
<td>0.06</td>
</tr>
</tbody>
</table>

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 HYERTENSION OR CONGESTIVE HEART FAILURE (serum albumin ascites albumin) ≥11 g/L [≥1.1 g/dL]. To distinguish between portal hyper tension 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 album 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
Jaundice

DIFERENTIAL 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
- INEFFECIVE ERYTHROPOIESIS  megaloblastic anemia

HEPATIC
- UPTAKE  Gilbert’s, drugs (rifampin, contrast)
- CONJUGATION  Gilbert’s, Crigler Najar I/II, hepatocellular diseases, drugs (chloramphenicol)
- EXCRETION  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)

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, haptoglobin, a1 antitrypsin, AFP, LDH, 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, xanthomas, 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)

Jaundice

and incidence of hepato renal syndrome. Secondary prophylaxis include ciprofloxacin 750 mg PO weekly or trimethoprim sulfamethoxazole D5 1 tab PO daily
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 (K, A, D, E) 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)

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

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, Ascarisasis
Idiopathic
Inherited familial
Trauma blunt
Surgery ERCP, sphincter of Oddi dysfunction

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, O2, IV hydration. NPO, NG if severe N/V or obstruction. Morphine 2.5 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)

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)

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Acute Pancreatitis

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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

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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)
Polycythemia

**DIFFERENTIAL DIAGNOSIS**

**SPURIOUS** stress (Geisbock’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 ♀

**INVESTIGATIONS**

**BASIC**

- **LABS** CBC, lytes, urea, Cr, LAP, vitamin B12, RBC mass (total blood volume × Hct, to rule out spurious causes), carboxyhemoglobin level, cortisol level, peripheral blood smear

**SPECIAL**

- **JAK2 MUTATION** JAK2 is a cytoplasmic tyrosine kinase activated by EPO binding to its receptor; the V617F mutation activates JAK2 and thereby drives EPO independent erythropoiesis

- **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

**DIAGONOSTIC ISSUES**

**CRITERIA FOR POLYCYTHEMIA RUBRA VERA (PRV)**

- **ABSOLUTE** ↑ RBC mass, no secondary cause (nor mal PaO₂, EPO not elevated)

- **MAJOR** splenomegaly, JAKV617F

- **MINOR** WBC >12 × 10⁹/μL, platelet >400 × 10⁹/μL, 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)

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, hepatosplenomegaly, excoriations, stigmata of a prior arterial or venous thrombotic event, gouty arthritis, and tophi
**Microcytic Anemia**

**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 → ↑ INF, TNF, 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 chloasma, 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 (transferin), % sat, Hb electrophoresis, fecal occult blood (if suspect GI bleed)

**SPECIAL**

- **ENDOSCOPY** gastroscopy and/or colonoscopy targeting symptoms in any man or post menopausal woman with iron deficiency or in anyone with suspected GI bleeding

- **SOLUBLE TRANSFERRIN RECEPTOR (sTfR)** helps to distinguish between iron deficiency and anemia of chronic disease

**INVESTIGATIONS (CONT’D)**

- **LIVER BIOPSY**

- **BONE MARROW ASPIRATE AND BIOPSY WITH IRON STAIN**

**DIAGNOSTIC ISSUES**

**IRON INDICES**

<table>
<thead>
<tr>
<th>Ferritin</th>
<th>Iron</th>
<th>TIBC</th>
<th>% sat</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓/N</td>
<td>↑</td>
<td>N/↓</td>
<td>N/↓</td>
</tr>
</tbody>
</table>

**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 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

**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 mg/ml iron deficiency anemia (PPV 92 98%)

- ↑30 100 mg/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

**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, anti biotics, antiepileptics), family history (thalassemia)

**PHYSICAL** vitals, jaundice, conjunctival pallor, car diac examination, liver examination. Check for macro glossia, 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 reticu loyte count to evaluate if bone marrow response to anemia is appropriate or hypoproliferative
- **RPI** = [retic count × (hematocrit in %/45)]/ maturation factor

**MATURATION FACTOR**

<table>
<thead>
<tr>
<th>Maturation factor</th>
<th>Hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0%</td>
<td>45%</td>
</tr>
<tr>
<td>1.5%</td>
<td>35%</td>
</tr>
<tr>
<td>2.0%</td>
<td>25%</td>
</tr>
<tr>
<td>2.5%</td>
<td>20%</td>
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</table>

**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, darbepoietin 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

- **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).

#### AUTOIMMUNE HEMOLYTIC ANEMIA: COLD AGGLUTININS

- **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

### CLINICAL FEATURES (CONT’D)

- alcohol, hypothyroidism, myelodysplasia), medications (chemotherapy, antibiotics, antiepileptics)

#### 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
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.

**Sickle Cell Disease**

**PATHOPHYSIOLOGY**

- **β CHAIN MUTATION** leads to formation of hemoglobin S (α2βS2 → 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, ten derness, 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
- **HEPATOMESPLenic** 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

**INVESTIGATIONS**

- **BASIC**
  - **LABS** CBC, 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, O2, 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, Nisseria meningitidis, hepatitis B virus, and influenza), exchange transfusion (goal HbS < 30%), hydroxyurea (increase levels of fetal Hb, decrease incidence of vasoocclusive pain), folic acid 1 mg PO daily

**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).
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**: sepsis
- **POST INFECTIONOUS**: sepsis
- **AUTOIMMUNE**: drug induced, SLE
- **NEOPLASTIC**: lymphoproliferative disorders, myelodyplasia, leukemias, myelophthisis
- **INFECTIONS**: sepsis, HIV
- **INSUFFICIENCY**: folate, vitamin B12
- **IATROGENIC**: chemotherapy, chloramphenicol, trimethoprim sulfamethoxazole, synthetic penicillins, phenytoin, carbamazepine, NSAIDs, gold, antithyroid medications, phenothiazines, clozapine

**INVESTIGATIONS (CONT’D)**

- **SPECIAL**: 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**

- **FEVER 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 $\times 10^3$/µL and still be considered normal.

**Eosinophilia**

**DIFFERENTIAL DIAGNOSIS**

- **PAIN**: interstitial lung disease, AIDS related pneumonia, idiopathic eosinophilic pneumonia
- **GASTROINTESTINAL**: eosinophilic gastroenteritis, eosinophilic esophagitis, primary biliary cirrhosis, primary sclerosing cholangitis
**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 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, naso pharynx), 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. Further more, 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], coccidioides), medications (NSAIDs, nitrofurantoin, ampicillin, minocycline, phenytoin, ranitidine), idiopathic (acute eosinophilic pneumonia, chronic eosinophilic pneumonia), others (Churg Strauss, allergic bronchopulmonary aspergillosis)
**Thrombocytosis**

**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**

<table>
<thead>
<tr>
<th></th>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying disease</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Digital ischemia/CVA</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>Y (40%)</td>
<td>N</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>Giant platelets</td>
<td>Normal platelets</td>
</tr>
<tr>
<td>Platelet function</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>BM megakaryocytes</td>
<td>↑, giant</td>
<td>↑, normal</td>
</tr>
</tbody>
</table>

**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

HYPERSENSITIVITY congestion, 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, anti phospholipid antibody syndrome
• INFECTIONS HIV, EBV, CMV
• MEDICATIONS heparin, GPIIb/IIIa inhibitors, quinine, ASA, NSAI Ds

PATHOPHYSIOLOGY

DEFINITION platelets < 150 × 10^3/μL. 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 (<10^5/μL)  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, NSAI Ds)

PHYSICAL vitals. Look for intracranial bleed (fun docscopy), petechiae, and purpura. Check for lymphadenopathy and hepatosplenomegaly

INVESTIGATIONS

BASIC LABS CBCD, lytes, urea, Cr, peripheral smear, and 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 × 10^3/μL and severe bleeding, platelets < 10×10^3/μL in febrile non bleeding patient, < 20×10^3/μL 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
HEMOLYTIC UREMIC SYNDROME (HUS) and THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

**Diagnosis**

**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). Anticogulation 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 dys function, fever (90 100%), neurologic abnormalities (90%) with delirium, focal neurologic deficit, sei zure, coma. Schistocytes on peripheral smear

- **Treatments** full volume plasma exchange (plas mapheresis + FFP infusions), steroids, and splenectomy if not resolving. Avoid platelet transfu sion, ASA and antimitotility agents

**NEJM 2006 354:18**

**Hemolytic Uremic Syndrome (HUS)**

- **Pathophysiology** exposure to Shiga toxin or defect in plasma factor H → arteriolar thrombosis → predominantly renal involvement

- **Causes** E. coli O157:H7

- **Clinical Features** microangiopathic hemolytic anemia (100%), thrombocytopenia (90%), renal dys function (90%). Schistocytes on peripheral smear

- **Treatments** supportive care only. Does not respond to plasma exchange

**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 II (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 >150×10⁹/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), infec tions (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 <20×10⁹/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 pro vide 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

**Related Topics**

- Anticoagulation Therapy (p. 160)
- Antiphospholipid Antibody Syndrome (p. 156)
- Thrombocytopenia in Pregnancy (p. 414)
SPECIFIC ENTITIES (CONT’D)

- **THIRD LINE** for patients with chronic refractory ITP (platelets $< 50 \times 10^3/\mu L$ after 3 months) who failed or refused splenectomy, consider observation if no bleeding and platelets $>20 \times 10^3/\mu L$. Otherwise, treat with romiplostim or eltrombopag.
- **OTHER OPTIONS** rituximab, chemotherapy (CVP), danazol. HAART for HIV associated ITP.

**NEJM 2002 346:13**

**PANCYTOPEANIA**

**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 (CONT’D)**

- **expression of the complement regulatory proteins CD55 and CD59, which are deficient on all blood cells among persons with PNH**

**DIAGNOSTIC ISSUES**

- PRE MDS 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) $\to$ T cell subsets produce local concentrations of INF-$\gamma$ $\to$ Fas on CD34+ cells (maturing stem cells) $\to$ apoptosis $\to$ severe pancytopenia and hypocellular marrow. Complications include paroxysmal nocturnal hemoglobinuria, acute leukemia, and MDS
  - TREATMENTS antithymocyte globulin, cycloporine, 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 platelets, vessels, coagulopathy
- EXTRINSIC PATHWAY (isolated PT $\uparrow$)
  - FACTOR DEFICIENCY OR INHIBITOR Vllr

**DIFFERENTIAL DIAGNOSIS (CONT’D)**

- VITAMIN K DEFICIENCY malnutrition, pancreatic insufficiency, recent antibiotic use, warfarin use (early stage)

**EVANS SYNDROME** ITP and autoimmune hemolytic anemia

**NEJM 2007 357:6**
**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 x 10^9/μL, 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

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**PATHOPHYSIOLOGY**

**HEMOSTASIS**
- **PRIMARY HEMOSTASIS** endothelium, platelets
- **SECONDARY HEMOSTASIS** clotting factors, clotting cascade

**PLATELET ACTIVATION PATHWAY**
1. Collagen binds to GPⅡa/Ⅲa on platelet membrane, also binds to GPIb/Ⅸa 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 GPIb/Ⅲa complex
6. Platelet fibrin clot formation: fibrin fibrin cross linked by factor XIII and platelet fibrin via GPIb/Ⅲa complex

**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

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**COAGULATION FACTOR PEARLS**
- **SYNTHESIZED IN LIVER** factors I, II, V, VII, 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**

- **Intrinsic pathway (PTT)**
  - XII → Tissue damage
  - XI → Endothelial damage with tissue factor release
  - IX → VII

- **Extrinsic pathway (INR)**
  - aVIII → X
  - aV → II (Prothrombin)
  - bFibrin → Cross linked fibrin

aNon enzymatic cofactors; bFactor 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

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**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: joint/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


- Antiphospholipid antibody syndrome workup: lupus anticoagulant, antiphospholipid 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

- Malignancy workup: serum protein electrophoresis

MANAGEMENT

ACUTE

ABC, O2, IV, transfusion 2 U PRBC IV over 2 h, transfusion platelets 6 U, FFP 15 mL/kg, cryoprecipitate 10 15 U q48h for fibrinogen deficiency

TREAT UNDERLYING CAUSE

Avoid 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)

VON WILLERBRAND 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

SPECIFIC ENTITIES

- 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

SPECIFIC ENTITIES (CONT’D)

- Specific entities
  - vWF: RCo
  - vWF multimer
  - RIPA
    - Level I
      - vWFantigen: Normal
      - vWF: RCo: Normal
      - vWF multimer: Normal
      - RIPA: Normal
    - Level II
      - vWFantigen: ↓
      - vWF: RCo: ↓ or N
      - vWF multimer: ↓ or N
      - RIPA: ↓ or N
    - Level III
      - vWFantigen: ↓
      - vWF: RCo: ↓ or N
      - vWF multimer: ↓ or N
      - RIPA: undetectable

SPECIFIC ENTITIES (CONT’D)

- Specific entities
  - 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)

- Specific entities
  - 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, cholesteryl 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

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, O2 to keep sat >94%, IV, consider thrombolysis

ANTICOAGULATION heparin (unfractionated heparin 5000U IV bolus, then 1000U/h and adjust to 1.5-2.5 x 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

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 >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/m², 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 phar macologic 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-j2GP1 (B2 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

SPECIFIC ENTITIES (CONT’D)

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%, spec 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 micro infarctions. 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), mar row 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

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

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

COMPRESSSION 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

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

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 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

Related Topics
Anticoagulation Therapy (p. 160)
Hypercoagulable States (p. 156)
Pulmonary Embolism (p. 8)
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 x 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 x 10^3/μL
- RELATIVE mild moderate bleeding diathesis or thrombocytopenia (20 - 100 x 10^3/μL), brain metastases from melanoma, renal cell carcinoma, choriovitcna, 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 saphenofemoral junction is involved.
### Approach to Anticoagulation Therapies

<table>
<thead>
<tr>
<th>Class/Drugs</th>
<th>Mechanism</th>
<th>Indications</th>
<th>Usual dose</th>
<th>Complications/monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Warfarin</strong></td>
<td>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)</td>
<td>DVT/PE, Atrial fibrillation, Prosthetic valves</td>
<td>Warfarin 5 mg PO daily ×3 days, then adjust based on INR</td>
<td>Complications—bleeding (may be reversed with vitamin K), coumadin induced skin necrosis. Monitor—INR</td>
</tr>
<tr>
<td><strong>Unfractionated heparin</strong></td>
<td><strong>Indirect thrombin and factor Xa inhibitor (non-selective).</strong> Binds to antithrombin (AT) and converts it from a slow form to a fast acting form, which binds and inactivates thrombin and factors Xa, IXa, Xla, Xlla. Heparin resistance is usually due to AT deficiency and could be treated with AT concentrates</td>
<td>Acute DVT/PE, Arterial embolism, Prosthetic valves, ACS, DVT prophylaxis</td>
<td>For acute clot, unfractionated heparin 5000 U 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</td>
<td>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</td>
</tr>
<tr>
<td><strong>Low molecular weight heparin:</strong></td>
<td><strong>Indirect factor Xa inhibitor (relatively selective).</strong> Binds to AT and converts it from a slow form to a 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.</td>
<td>Acute DVT/PE, Maintenance DVT/PE in cancer patients, Arterial embolism, Prosthetic valves, ACS, DVT prophylaxis</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td><strong>Heparinoids:</strong></td>
<td><strong>Direct factor Xa inhibitors (selective).</strong> 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.</td>
<td>HITT, Acute DVT</td>
<td>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</td>
<td>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.</td>
</tr>
</tbody>
</table>
## Approach to Anticoagulation Therapies (cont’d)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Fonaparinux</td>
<td><strong>Indirect factor Xa inhibitor (highly selective).</strong> 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.</td>
<td>DVT prophylaxis, Acute DVT/PE, Acute coronary syndrome, HIT (no cross reactivity with heparin dependent anti platelet antibodies)</td>
<td>For DVT prophylaxis, fonaparinux 2.5 mg SC daily (start 6–8 h after surgical hemostasis). For acute clots, fonaparinux 5 mg SC daily for weight &lt; 50 kg, 7.5 mg SC daily for weight 50–100 kg, 10 mg SC daily for weight &gt;100 kg. For UA/NSTEMI, fonaparinux 2.5 mg SC daily × 8 days or until discharge. For STEMI, fonaparinux 2.5 mg IV × 1 then 2.5 mg SC daily × 8 days or until discharge.</td>
<td><strong>Complications</strong>—bleeding; avoid in spinal surgery. <strong>Monitor</strong>—antifactor Xa activity.</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td><strong>Direct factor Xa inhibitors (highly selective).</strong> Similar to fondaparinux, but specifically inhibits factor Xa by binding to its active site without interacting with AT</td>
<td>DVT prophylaxis (phase II)</td>
<td>For HIT, lepirudin 0.1–0.4 mg/kg IV bolus, then 0.1–0.15 mg/kg/h; argatroban 2 μg/kg/min infusion</td>
<td><strong>Complications</strong>—bleeding. <strong>Monitor</strong>—antifactor Xa activity.</td>
</tr>
<tr>
<td>Direct thrombin inhibitors:</td>
<td><strong>Direct thrombin inhibitors (highly selective).</strong> AT independent. In contrast to heparin, LMWH, and heparinoid, direct thrombin inhibitors can inhibit clot bound thrombin because their sites for binding (active site ± exosite I) are not masked by fibrin. Does not depend on AT for action and thus unaffected by AT deficiency.</td>
<td>HIT (lepirudin, argatroban), ACS (hirudin, argatroban), DVT prophylaxis (hirudin, dabigatran)</td>
<td>For HIT, lepirudin 0.1–0.4 mg/kg IV bolus, then 0.1–0.15 mg/kg/h; argatroban 2 μg/kg/min infusion</td>
<td><strong>Complications</strong>—bleeding. <strong>Monitor</strong>—aPTT.</td>
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<td>Dabigatran</td>
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<td>Desirudin</td>
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<td>Lepirudin</td>
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<td>Argatroban</td>
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<tr>
<td>Ximelagatran</td>
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## Contraindications to Warfarin Therapy

### Absolute
- Neurosurgery, ocular surgery or intra cranial bleeding within the past 10 days, active bleeding, severe bleeding diathesis, or platelet <20×10^3/μL

### Relative
- Mild to moderate bleeding diathesis or thrombocytopenia (20 100×10^3/μL), brain metastases, recent major trauma, major abdominal surgery <2 days, GI or GU bleeding <2 weeks, endocarditis, severe hypertension (>200/120 mmHg)

## 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

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**Related Topics**
- DVT (p. 158)
- Hypercoagulable States (p. 156)
- Pulmonary Embolism (p. 8)
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 prothrombin 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 prothrombin complex concentrate in selected cases.

Transfusion Reactions

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Pathophysiology</th>
<th>Onset and Symptoms</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO incompatibility</td>
<td>Recipient Ab against donor RBC major antigen, 1/40,000</td>
<td>Immediate. Fever, ↓ BP, CP, lumbar pain, hemoglobinuria, and bleed</td>
<td>Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis</td>
</tr>
<tr>
<td>Acute hemolytic reaction</td>
<td>Recipient Ab against donor RBC minor antigen, 1/600,000</td>
<td>Acute/delay. Milder form of above</td>
<td>Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis</td>
</tr>
<tr>
<td>Febrile reaction</td>
<td>Recipient Ab against donor WBC PRBC, 1/300; or platelets (5U), 1/10</td>
<td>End of transfusion. Fever, chills</td>
<td>Antihistamine (diphenhydramine 50 mg IV ×1 dose), acetaminophen</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>Recipient Ab against donor IgA, 1/40,000</td>
<td>Immediate. ↓ BP, bronchospasm, no fever</td>
<td>Stop transfusion, epinephrine, corticosteroids</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Recipient IgE against donor antigens, 1/100 plasma containing products</td>
<td>Acute. Pruritic rash</td>
<td>Antihistamine (diphenhydramine 50 mg IV ×1 dose)</td>
</tr>
<tr>
<td>Post transfusion purpura (PTP)</td>
<td>Recipient Ab against donor platelet</td>
<td>7 10 days after. Consumptive thrombocytopenia and purpura</td>
<td>Steroids, plasmapheresis</td>
</tr>
<tr>
<td>Transfusion associated circulatory overload (TACO)</td>
<td>Hypervolemia 1/700</td>
<td>Acute/delay. Pulmonary edema</td>
<td>Epinephrine, corticosteroids</td>
</tr>
<tr>
<td>Septic transfusion</td>
<td>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</td>
<td>Acute. Fever, ↓ BP</td>
<td>Stop transfusion, empiric antibiotics</td>
</tr>
<tr>
<td>Air embolism</td>
<td>Donor Ab against recipient WBC, 1/5000 plasma containing products</td>
<td>Acute. SOB, ↓ BP</td>
<td>Supportive measures</td>
</tr>
<tr>
<td>TRALI</td>
<td>Donor Ab against recipient WBC, 1/5000 plasma containing products</td>
<td>Acute. Hypoxemic, pulmonary edema</td>
<td>Supportive measures</td>
</tr>
<tr>
<td>GVHD</td>
<td>Donor lymphocytes against recipient tissue</td>
<td>Delay. Rash, hepatitis, diarrhea</td>
<td></td>
</tr>
<tr>
<td>Infection risk</td>
<td>HIV 1/10 million, HCV 1/3 million, HBV 1/72,000, HTLV1 1/2 million, West Nile virus &lt; 1/1 million</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
ANISOCROMIA  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 hypoplasmenia, 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
### 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 cm³, 12 cm by 7 cm (4.7 in. by 2.8 in.). anatomically, the spleen lies below the left diaphragm. It follows the curvature of left 10th rib and points anteriorly toward the left colic flexure

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspection</td>
<td>Bulging mass over left costal margin</td>
<td>Low</td>
</tr>
<tr>
<td>Percussion</td>
<td>Castell's method (percuss lowest intercostal space in the left anterior axillary line during both expiration and full inspiration; dullness suggests splenomegaly)</td>
<td>82% 83%</td>
</tr>
<tr>
<td></td>
<td>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; &gt;8 cm suggests splenomegaly)</td>
<td>59% 94%</td>
</tr>
<tr>
<td></td>
<td>Traube's space (percuss space 6th rib superiorly, mid axillary line laterally and costal margin inferiorly; dullness suggests splenomegaly)</td>
<td>62% 72%</td>
</tr>
<tr>
<td>Palpation</td>
<td>Two handed palpation with patient in right lateral decubitus position</td>
<td>71% 90%</td>
</tr>
<tr>
<td></td>
<td>One handed palpation with patient supine</td>
<td></td>
</tr>
</tbody>
</table>

### 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"
INVESTIGATIONS

BASIC
- LABS: CBCD, peripheral smear, AST, ALT, ALP, bilirubin
- MICROBIOLOGY: blood C&S
- IMAGING: U/S abd

SPECIAL
- CT ABD: weight = 0.43 × Length × Width × Thickness
- SCINTIGRAPHY: 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

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 associated 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 × 10^9/L
- BLAST CRISIS (3–6 months): ≥30% blasts or extra medullary 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 × 10^9/L for at least 6 months), anemia, thrombocytopenia, and 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): elevated in PRV, MF, ET, and leukemoid reactions; can be decreased in CML and CMML
- VITAMIN B12: decreased in PRV
- EPO: decreased 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 dasatinib, nilotinib, and stem cell transplantation

ESSENTIAL THROMBOCYTOSIS aspirin, anagrelide (platelet via stabilizing membrane), hydroxyurea, alkylating agents.

MYELOFIBROSIS splenectomy, interferon α, thalidomide

TREATMENT ISSUES

RESPONSE CRITERIA FOR CML

- HEMATOLOGICAL RESPONSE
  - COMPLETE RESPONSE WBC <10×10^9/L with no immature granulocytes and <5% basophils, platelet <450×10^9/L, and non palpable spleen

TREATMENT ISSUES (CONT’D)

- PARTIAL RESPONSE persistence of immature cells in peripheral blood, platelets >450×10^9/L but <50% of pre treatment levels, or persistent spleenomegaly 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

<table>
<thead>
<tr>
<th>Months</th>
<th>Suboptimal</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>&lt; CHR</td>
<td>No HR</td>
</tr>
<tr>
<td>6</td>
<td>&lt; PCGR</td>
<td>&lt; CHR, no CGR</td>
</tr>
<tr>
<td>12</td>
<td>&lt; CCGR</td>
<td>&lt; PCGR</td>
</tr>
<tr>
<td>18</td>
<td>&lt; MMR</td>
<td>&lt; CCGR</td>
</tr>
<tr>
<td>Anytime</td>
<td>ACA, loss of MMR</td>
<td>Loss of CHR or CCGR</td>
</tr>
</tbody>
</table>

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, over expression or amplification of bcr abl

Acute Myelogenous Leukemia

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, SL/LCL) in origin. Myeloid leukemia seldom presents in lymph nodes

ACUTE LEUKEMIA involves immature blast cells. More aggressive course

Acute Myelogenous Leukemia

HEMATOLOGIC MALIGNANCIES OVERVIEW

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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, SL/LCL) 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.

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), aplastic anemia.

**DISTINGUISHING FEATURES BETWEEN TREATMENT INDUCED AMLs**

<table>
<thead>
<tr>
<th>Latency</th>
<th>Alkylating agents</th>
<th>Topoisomerase II inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS pre AML</td>
<td>5 7 years</td>
<td>Yes</td>
</tr>
<tr>
<td>AML types</td>
<td>All, M1 2</td>
<td>No</td>
</tr>
<tr>
<td>Karyotype</td>
<td>5, 7</td>
<td>11q23, 21q22, inv16</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Worse</td>
<td>Poor except for inv16 karyotype</td>
</tr>
</tbody>
</table>

**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), lyses, urea, Cr, Ca, P04, 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, radium, 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 SHT has resulted in cure rates of 50–60% for recipients in 1st remission

**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**

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>% blasts in BM</td>
<td>&lt;5</td>
<td>5</td>
<td>10</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Karyotype</td>
<td>Good</td>
<td>Med.</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenia</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For karyotype, good = y, del(5q), del(20q); medium = neither good nor poor; poor = chromosome 7 or complex abnormalities

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Score</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>5.7 years</td>
</tr>
<tr>
<td>Intermediate 1</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Intermediate 2</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>High</td>
<td>≥2.5</td>
<td>0.4 year</td>
</tr>
</tbody>
</table>

- **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, epi sodic 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

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): 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

<table>
<thead>
<tr>
<th></th>
<th>AML</th>
<th>Precursor ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blasts</td>
<td>Larger</td>
<td>Small</td>
</tr>
<tr>
<td>Auer rods</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TdT</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MPO</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

INVESTIGATIONS

BASIC
- LABS: CBCD, smear, lytes, urea, Cr, Ca, PO₄, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibronogen, flow cytometry of peripheral blood (immunophenotyping)
- BONE MARROW BIOPSY: >25% blast, flow cytometry for immunophenotyping, cytogenetic analysis (detection of BCRABL 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: BCRABL 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), TELAML1 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 >30×10°/μL in B ALL or >100×10°/μL 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 ± 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

**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)

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**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** CBC, smear (smudge cells), lysates, urea, Cr, Ca, PO4, Mg, uric acid, LDH, β2 microglobulin, albumin, quantitative immunoglobulin, serum protein electrophoresis, urinary protein electrophoresis

**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 $>5 \times 10^9/\mu L$, with $\geq 1$ 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, Slg+

- **NOTE** for patients with lymphocyte count $5 \times 10^3/\mu L$, lymphocyte phenotyping is required

**RAI STAGING**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lymphocytosis in blood or bone marrow.</td>
<td>$&gt;150$ months</td>
</tr>
<tr>
<td>I</td>
<td>Lymphocytosis + lymphadenopathy.</td>
<td>Median survival 101 months</td>
</tr>
<tr>
<td>II</td>
<td>Lymphocytosis + organomegaly.</td>
<td>Median survival 71 months</td>
</tr>
<tr>
<td>III</td>
<td>Lymphocytosis + anemia ($&lt;110$ g/L [$&lt;11$ g/dL]).</td>
<td>Median survival 19 months</td>
</tr>
<tr>
<td>IV</td>
<td>Lymphocytosis + thrombocytopenia ($&lt;100 \times 10^9/mL$).</td>
<td>Median survival 19 months</td>
</tr>
</tbody>
</table>
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 x 10^9/μL). 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+, unmuted IgVH 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]), lymphocytopenia (platelets <100 x 10^9/μL), 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

MANAGEMENT (CONT’D)
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 x 10^9/μL, neutrophils ≥1.5 x 10^9/μL, platelets >100 x 10^9/μL, 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 x 10^9/μL, platelets >100 x 10^9/μL, 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
- 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, heptosplenomegaly, 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

<table>
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<tr>
<th>Feature</th>
<th>Malignancy</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>Larger, grows</td>
<td>Smaller</td>
</tr>
<tr>
<td>Consistency</td>
<td>Rubberly, firm</td>
<td>Soft</td>
</tr>
<tr>
<td>Mobility</td>
<td>Immobile</td>
<td>Mobile</td>
</tr>
<tr>
<td>Matted</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Tenderness</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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
t2)
- III Involvement on both sides of diaphragm. III1 indicates involvement of the spleen or splenic hilar, celiac, or portal nodes. Stage III2 indicates involvement of the paraaortic, iliac, inguinal, or mesenteric nodes
- IV Diffuse or disseminated foci of involvement of one or more extralymphatic sites (e.g. bone marrow, extranodal sites that cannot be included in one radiation field)

DESIGNATIONS
- E extralymphatic site (i.e. involvement outside of lymph nodes, spleen, thymus, and Waldeyer’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.) max imum 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 <4×10⁹/μL, platelets <125×10⁹/μL
- 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
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 sarcoïdosis, 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 Waldenström’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 CUTANEOS 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, hepatosplenomegaly, 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

<table>
<thead>
<tr>
<th>174</th>
<th>Non-Hodgkin’s Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>PATHOPHYSIOLOGY (CONT’D)</td>
<td>CLASSIC TRANSLOCATIONS IN LYMPHOMA</td>
</tr>
<tr>
<td><strong>HAIRY CELL LEUKEMIA</strong> (HCL)</td>
<td><strong>MANTLE CELL LYMPHOMA</strong> t(11;14) in 95%, cyclin D1 (bc11)</td>
</tr>
<tr>
<td><strong>LYMPHOPLASMACYTIC LYMPHOMA</strong> (LPL, 2-3%) previously Waldenström’s macroglobulinemia</td>
<td><strong>FOLLICULAR LYMPHOMA</strong> t(14;18) in 85%, anti-apoptotic protein (bcl2)</td>
</tr>
<tr>
<td><strong>PLASMA CELL MYELOMA/PLASMACYTOMA</strong> (MM)</td>
<td><strong>DIFFUSE LARGE B-CELL LYMPHOMA</strong> t(3;14) in 40%, zinc finger transcription factor (bcl6)</td>
</tr>
<tr>
<td><strong>AGGRESSIVE B-CELL LYMPHOMAS</strong></td>
<td><strong>MALT</strong> t(1;14) in &lt; 5%, bcl10</td>
</tr>
<tr>
<td><strong>FOLLICULAR LYMPHOMA</strong> (FL) grade IIIB (sheets of centroblasts)</td>
<td><strong>BURKITT’S LYMPHOMA</strong> t(8;14), t(2;8), or t(8;22) in 100%, c-myc</td>
</tr>
<tr>
<td><strong>DIFFUSE LARGE B-CELL LYMPHOMA</strong> (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</td>
<td>INFECTIONS AND LYMPHOMA</td>
</tr>
<tr>
<td><strong>DOUBLE-HIT DLBCL</strong> (both c-myc and bcl2 translocations)</td>
<td><strong>EBV</strong> Hodgkin’s lymphoma, Burkitt lymphoma, post transplant lymphoproliferative disorders, primary CNS lymphoma</td>
</tr>
<tr>
<td><strong>LEUKEMIC B-CELL LYMPHOMAS</strong></td>
<td><strong>HCV</strong> splenic marginal zone lymphoma</td>
</tr>
<tr>
<td><strong>BURKITT’S LYMPHOMA</strong> (BL)</td>
<td><strong>HHV8</strong> Castleman disease, primary effusion lymphoma</td>
</tr>
<tr>
<td><strong>PRECURSOR B LYMPHOBLASTIC LYMPHOMA</strong> (ALL)</td>
<td><strong>HIV</strong> primary CNS lymphoma</td>
</tr>
<tr>
<td><strong>INDOLENT T-CELL LYMPHOMAS</strong></td>
<td><strong>HTLV</strong> adult T cell leukemia/lymphoma</td>
</tr>
<tr>
<td><strong>MYCOSIS FUNGOIDES</strong> (mf)</td>
<td><strong>BORRELIA BURGDORFERI</strong> cutaneous marginal zone lymphoma</td>
</tr>
<tr>
<td><strong>PRIMARY CUTANEOS ANAPLASTIC LARGE CELL</strong> (PCALC)</td>
<td><strong>CAMPYLOBACTER JEJUNI</strong> small bowel marginal zone lymphoma</td>
</tr>
<tr>
<td><strong>LYMPHOPROLIFERATIVE DISEASE OF LARGE GRANULAR LYMPHOCYTES</strong> (LGL)</td>
<td><strong>CHLAMYDIA PSITACCI</strong> eye marginal zone lymphoma</td>
</tr>
<tr>
<td><strong>INDOLENT NATURAL KILLER CELL LYMPHOMAS</strong></td>
<td><strong>H. PYLORI</strong> gastric MALT</td>
</tr>
<tr>
<td><strong>NATURAL KILLER CELL LARGE GRANULAR LYMPHOCYTE LEUKEMIA</strong> (NK LGL)</td>
<td>TRANSFORMATION OF INDOLENT LYMPHOMA</td>
</tr>
<tr>
<td><strong>AGGRESSIVE T-CELL LYMPHOMAS</strong></td>
<td>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</td>
</tr>
<tr>
<td><strong>PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED</strong> (PTCL NOS)</td>
<td><strong>MASS EFFECT</strong> lymphadenopathy (occipital, posterior auricular, preauricular, mandibular, submental, cervical, supra and infraclavicular, Waldeyer’s ring (tonsils, base of tongue, nasopharynx), epistaxis, axillary, inguinal, popliteal), hepatosplenomegaly, mediastinal/abdominal/pelvic/testicular/CNS masses may cause local destruction, obstruction, and compression</td>
</tr>
<tr>
<td><strong>PERIPHERAL T-CELL LYMPHOMA, SPECIFIED</strong> angioimmunoblastic (AILD++ type), nasal T/NK cell type, subcutaneous panniculitic, intestinal enteropathy associated, hepatosplenomegaly, anaplastic large cell including null cell</td>
<td><strong>HEMATOLOGIC</strong> anemia, thrombocytopenia, lymphocytosis</td>
</tr>
<tr>
<td><strong>LEUKEMIC T-CELL LYMPHOMAS</strong></td>
<td><strong>CONSTITUTIONAL</strong> B symptoms. Other constitutional symptoms include fatigue, anorexia, pruritus</td>
</tr>
<tr>
<td><strong>ADULT T-CELL LYMPHOMA/LEUKEMIA</strong> (HTLV)</td>
<td><strong>PARANEOPlastic SYNDROMES</strong></td>
</tr>
<tr>
<td><strong>PRECURSOR T LYMPHOBLASTIC</strong></td>
<td>NOTE: Lymphoma can mimic many diseases. Always have a high index of suspicion for lymphoma, particularly if B symptoms or multisystem involvement</td>
</tr>
<tr>
<td><strong>LEUKEMIA/LYMPHOMA</strong></td>
<td><strong>CLINICAL FEATURES</strong></td>
</tr>
</tbody>
</table>

**SYMPTOMS**

- **MASS EFFECT** lymphadenopathy (occipital, posterior auricular, preauricular, mandibular, submental, cervical, supra and infraclavicular, Waldeyer’s ring (tonsils, base of tongue, nasopharynx), epistaxis, 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 >38.8°C, drenching night sweats

INVESTIGATIONS
BASIC
- **LABS** CBCD, peripheral smear, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, PO4, Mg, uric acid, LDH, albumin, quantitative immunoglobulin, serum protein electrophoresis, HBV, HCV, and HIV serology
- **IMAGING** CXR, CT chest/abdomen/pelvis, PET scan
- **LYMPH NODE BIOPSY**
- **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 (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, and 3, 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 \( \times 8 \) 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) \( \times 3 \) 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 \( \times 6 \). 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, non bulky <5 cm, no bone marrow/blood/CNS
MANAGEMENT (CONT’D)

Disease and normal LDH), give CODOX MR (cyclophosphamide, doxorubicin, vincristine, methotrexate, rituximab) $\times 1$ then restage. If CR/PR, give IVAC R (ifosfamide, etoposide, cytarabine) $\times 1$ then CODOX MR $\times 1$; otherwise, give IVAC R $\times 1$ then proceed to stem cell transplant. For high risk disease, give CODOX MR $\times 1$, IVAC R $\times 1$ then restage. If CR/PR and no marrow infiltration at diagnosis, then autologous stem cell transplant; otherwise, individualized higher intensity treatment. Allogeneic transplant may be considered (balance between time to find allogeneic donor and use of contaminated stem cells). A total of 8 doses of intrathecal chemotherapy should be given during treatment course. All patients should receive tumor lysis syndrome prophylaxis (hydration, allopurinol). Cure rate $\sim 60\%$

• 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 (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 $\geq 50\%$ of previously involved sites from nadir

• Nodal masses: appearance of a new lesion(s) $>1.5$ cm in any axis, $\geq 50\%$ increase in SPD of more than one node, or $\geq 50\%$ 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

JCO 2007 25:5

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, periosseous 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
ACUTE LYMPHOBLASTIC LYMPHOMA
LOCALIZED PARANASAL SINUS LYMPHOMA
MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT)

Clinical Features

Pathophysiology

Treatments

Diagnosis

Associations

Non-Hodgkin’s Lymphoma

Specific Entities (Cont’d)

Macrophage Activation Syndrome

Burkitt’s Lymphoma

Pathophysiology

Clinical Features

Pathophysiology

Treatments

Diagnosis

Risk Factors

Testicular Lymphoma

Pathophysiology

Clinical Features

Pathophysiology

Risk Factors

Post Transplant Lymphoproliferative Disorders (PTLD)

Pathophysiology

Clinical Features

Pathophysiology

Treatments

Diagnosis

Risk Factors

Mycosis Fungoides

Pathophysiology

Clinical Features

Pathophysiology

Clinical Features

Mucosa Associated Lymphoid Tissue (MALT)

Pathophysiology

Clinical Features

Pathophysiology

Clinical Features

Acute Lymphoblastic Lymphoma

Pathophysiology

Clinical Features

Pathophysiology

Clinical Features

Specific Entities (Cont’d)
SPECIFIC ENTITIES (CONT’D)
cutaneous disease (erythroderma), nodal spread, and extracutaneous involvement (liver, spleen, lung, Gl 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
- 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 k or λ light chain
  - AL (PRIMARY) AMYLOIDOSIS λ or k light chain
- PATHOPHYSIOLOGY
  - EPIDEMIOLOGY
    - INCIDENCE 1%
    - MORTALITY 1%
- RISK FACTORS
  - PERSONAL old age, black race
  - DISEASES chronic polyclonal hypergamma globulinaemia
  - TREATMENT radiation
- CLINICAL FEATURES
  - SYMPTOMS pancytopenia weakness, fatigue, infections, gingival bleed, ecchymosis, epistaxis, menorrhagia

CLINICAL FEATURES (CONT’D)
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

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)

INVESTIGATIONS
- BASIC
  - LABS CBCD, peripheral smear, lytes, urea, Cr, Ca, β2 microglobulin, serum viscosity, quantitive immunoglobulin, albumin, serum protein electrophoresis (reciprocal depression), urinary
MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

SMOLDERING MULTIPLE MYELMA

NOTE: light chain myeloma (20%) may have normal serum protein electrophoresis. Urinary Bence Jones protein (urine protein electrophoresis) is required to detect paraproteinemia; non secretory myeloma (3%) requires bone marrow biopsy for diagnosis.

INVESTIGATIONS (CONT’D)

- Protein electrophoresis, 24 h urinary collection for Bence Jones protein
- Imaging: skeletal survey
- Bone marrow biopsy

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 calcium (>2.75 mmol/L [>11 mg/dL]), renal insufficiency (Cr >173 μmol/L [>1.9 mg/dL]), anemia (Hb <100 g/L [<10 g/dL] or drop by 20 g/L [2 g/dL]), bone 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 [≤3 g/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, Waldenström’s macroglobulinemia, primary amyloidosis, B cell lymphoma, or chronic lymphocytic leukemia) is about 1% per year

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 × 10^12/m^3) all of Hb >100 g/L (>10 g/dL), Ca²⁺ ≤2.6 mmol/L [≤10.4 mg/dL], bone 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 × 10^12/m^3) between stages I and III. Median survival ~30 months
- Stage III (high tumor burden, >1.2 × 10^12/m^3) any of Hb ≤85 g/L [≤8.5 g/dL], Ca²⁺ >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

NEJM 2006 355:26

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 transplantation. 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 (mel phalan + prednisone) ± thalidomide. Addition of interferon to MP provides small benefit. If bony disease, add bisphosphonate (alendronate, zolendronate). 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 IVG as last resort if recurrent infections despite prophylactic antibiotics), skeletal lesions (pamidronate 90 mg IV over 2 h q 3 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).

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 Polyneuropathy, Organomegaly, Endocrine (dia betes, hypothyroidism, parathyroid hypogonadism, HPA), Monoclonal protein, Skin changes (hyperpigmentation, Raynaud’s phenomenon, cryoglobulin, Raynaud’s phenomenon, or Purpura 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)

- **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, leuka pheresis (up to 3 times for autologous stem cell trans plant), faster engraftment, and improved overall survi val (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 mis matches in allogeneic transplant)

**COMMON INDICATIONS**

**DECIDING BETWEEN ALLOGENEIC AND AUTOLOGOUS STEM CELL SOURCE** dependent on age, underlying disease, donor availability, institutional pre ference. In general, allogeneic transplant is more suita ble 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 leu kemia (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 exo genous peptides to T cells. Mismatch between host and donor HLA type could result in graft vs. host disease, graft failure, or death. Note that trans plant 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 regi mens include cyclophosphamide plus total body ira diation (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 regi men more tolerable for older patients (e.g. fludarabine plus cyclophosphamide, melphalan). Monitor toxicities closely during this time

- **HEMATOLOGIC** pancytopenia, febrile neutropenia
- **EARLY NON–HEMATOLOGIC** alopecia, N&V, oropharyngeal mucositis, diarrhea, sinusoidal obstruction syndrome (previously known as hepatic venocclusive disease with tender hepatomegaly, jaun dice, ascites), seizures, parotitis, pericarditis, cardiomyopathy, interstitial pneumonitis, hemor rhagic 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 lymphoprolifera tive 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 >103/\(\mu\)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, flucona zole for fungal agents) until engraftment occurs. Fail ure 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. Immuno suppressive treatment can usually be stopped within 1 3 years post allogeneic transplant. Graft vs. host disease (GVHD) is a donor T cell mediated pro cess. Overall transplant related mortality is approxi mately 20–25%

**GRAFT VS. HOST DISEASE**

- **ACUTE GVHD** (<100 days) occurs in 40% of matched sibling and 80% of unrelated donor trans plant. Symptoms include rash, hepatic dysfunction, diarrhea, vomiting. Mortality up to 80% in grade III and IV acute GVHD. Prophylaxis consisting of meth otrexate 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 pre transplant 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)
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 septa, and has a propensity for aerogenous and lymphatic spread. May present as diffuse infiltration on chest X-ray
  - **SQUAMOUS** (25%) smokers, central, cavitory 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**

PARANEoplastIC SYNDROMES

<table>
<thead>
<tr>
<th>SIADH</th>
<th>SCLC</th>
<th>Squamous</th>
<th>Adenocarcinoma</th>
<th>Large cell</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ectopic Cushing’s</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological syndromes</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clubbing or hypertrophic osteoarthropathy</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hypercoagulable state</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

aNeurological syndromes associated with SCLC include dementia, cerebellar degeneration, limbic encephalopathy, optic neuritis and retinopathy, paraneoplastic sensory neuropathy (anti Hu antibodies), and Eaton Lambert syndrome
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
  - **T3a** ≤ 4 cm
  - **T3b** > 4 ≤ 7 cm
  - **T3c** > 7 cm
- **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**
- **M1a** malignant pleural effusion, pericardial effusion, separate tumor nodule(s) in contralateral lobe
- **M1b** distant metastasis

**STAGE GROUPINGS FOR NON SMALL CELL LUNG CANCER**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Median survival (months)</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1aN0M0, T1bN0M0</td>
<td>60</td>
<td>50%</td>
</tr>
<tr>
<td>IB</td>
<td>T2aN0M0</td>
<td>43</td>
<td>43%</td>
</tr>
<tr>
<td>IIA</td>
<td>T1N1M0, T2aN1M0, T2bN0M0</td>
<td>34</td>
<td>36%</td>
</tr>
<tr>
<td>IIB</td>
<td>T2bN1M0, T3N0M0</td>
<td>18</td>
<td>25%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3N1M0, T1 3N2M0, T4N0 1M0</td>
<td>14</td>
<td>19%</td>
</tr>
<tr>
<td>IIB</td>
<td>T@N3M0, T4N2M0</td>
<td>10</td>
<td>7%</td>
</tr>
<tr>
<td>IV</td>
<td>T@N@M1</td>
<td>6</td>
<td>2%</td>
</tr>
</tbody>
</table>

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
- **BIOPLAY** bronchoscopy with lavage/wash/brushings/biopsy, endoscopic U/S with biopsy, thoracentry (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

<table>
<thead>
<tr>
<th>PS</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>Normal, no complaints, no evidence of disease</td>
</tr>
<tr>
<td>90%</td>
<td>Able to carry on normal activity: minor symptoms of disease</td>
</tr>
<tr>
<td>80%</td>
<td>Normal activity with effort: some symptoms of disease</td>
</tr>
<tr>
<td>70%</td>
<td>Cares for self: unable to carry on normal activity or active work</td>
</tr>
<tr>
<td>60%</td>
<td>Requires occasional assistance but is able to care for needs</td>
</tr>
<tr>
<td>50%</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40%</td>
<td>Disabled: requires special care and assistance</td>
</tr>
<tr>
<td>30%</td>
<td>Severely disabled: hospitalization is indicated, death not imminent</td>
</tr>
<tr>
<td>20%</td>
<td>Very sick, hospitalization necessary: active treatment necessary</td>
</tr>
<tr>
<td>10%</td>
<td>Moribund, fatal processes progressing rapidly</td>
</tr>
<tr>
<td>0%</td>
<td>Dead</td>
</tr>
</tbody>
</table>
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 PaO2, 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 (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

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 IIIB (unresectable) AND IIIB no surgery. Concurrent chemoradiation (cisplatin etoposide ×4) with potential chance of cure. Can consider sequential chemotherapy 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)

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 IIIIB 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

TREATMENT ISSUES

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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)
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

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

INVESTIGATIONS

BASIC
- **LABS** CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin
- **IMAGING** CXR, CT chest/abd, or MRI chest

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, ≥3 adverse prognostic factors= <6 months median survival, stage II IV=10 months median survival

MANAGEMENT

STAGE I, II (resectable disease) **surgery** (extra pleural pneumonectomy, debulking) is controversial and of questionable benefit. It should be considered for highly selected patients (age <55, performance status ≤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 vita min 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

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 (reseactable 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

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)

Breast Cancer

NEJM 2004 350:14
### 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

**RISK FACTORS**
- **Personal** female, increased age, early age of menarche, late age of first parity, lack of breast feeding, late age of menopause, oral contraceptive (1 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 (CONT’D)

**locoregional** breast lump with or without pain, nipple discharge, 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, urea, Cr, AST, 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 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 or 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>5 Year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1N0M0</td>
<td>100%</td>
</tr>
<tr>
<td>IIA</td>
<td>T0 1N1M0, T2N0M0</td>
<td>90%</td>
</tr>
<tr>
<td>IIB</td>
<td>T2N1M0, T3N0M0</td>
<td>80%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T0 2N2M0, T3N1 2M0</td>
<td>70%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4N0 2M0</td>
<td>50%</td>
</tr>
<tr>
<td>IIIC</td>
<td>T@N3M0</td>
<td>40%</td>
</tr>
<tr>
<td>IV</td>
<td>T@N@M</td>
<td>20%</td>
</tr>
</tbody>
</table>

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 to 60, 3 < 40 years old
- INTERPRETATION add up the four factors

<table>
<thead>
<tr>
<th>VNPI score</th>
<th>Risk of relapse</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6</td>
<td>Low</td>
<td>Lumpectomy only</td>
</tr>
<tr>
<td>7 9</td>
<td>Mod</td>
<td>Lumpectomy plus radiation</td>
</tr>
<tr>
<td>≥ 10</td>
<td>High</td>
<td>Consider mastectomy</td>
</tr>
</tbody>
</table>

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 lymphocascular 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)

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 to 40 mm, 3 > 40 mm
- MARGIN WIDTH 1 > 10 mm, 2 = 10 to 1 mm, 3 < 1 mm
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 1-2h 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 (CONT’D)

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/arthritis, 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 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 ≥35, tumor ≤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)

ADJUVANT REGIMENS

- **FIRST GENERATION** CMF PO, AC×4, FEC50×6
- **SECOND GENERATION**CAF×6, FAC×6, CEF×6, FEC100×6, AC×4+D×4, DC×4
- **THIRD GENERATION** DAC×6, FEC100×3+D×3, AC×4+T×4 (dose dense), FEC×4+T×8
- **NOTE** A=doxorubicin, C=cyclophosphamide, D=docetaxel, E=epirubicin, F=5 fluorouracil, M=methotrexate, T=paclitaxel

ESTIMATED BENEFITS OF ADJUVANT CHEMO THERAPY

**RELATIVE RISK REDUCTION FOR MORTALITY**

<table>
<thead>
<tr>
<th></th>
<th>Postmenopausal</th>
<th>Premenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st gen.</td>
<td>8% ER+, 15% ER</td>
<td>30%</td>
</tr>
<tr>
<td>2nd gen.</td>
<td>26% ER+, 32% ER</td>
<td>44%</td>
</tr>
<tr>
<td>3rd gen.</td>
<td>40% ER+, 45% ER</td>
<td>55%</td>
</tr>
</tbody>
</table>

HORMONAL THERAPY 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 ≥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 ≥3 cm or node positive. Consider chemotherapy if 1 2.9 cm

ADJUVANT REGIMENS

- **FIRST GENERATION** CMF PO, AC×4, FEC50×6
- **SECOND GENERATION** CAF×6, FAC×6, CEF×6, FEC100×6, AC×4+D×4, DC×4
- **THIRD GENERATION** DAC×6, FEC100×3+D×3, AC×4+T×4 (dose dense), FEC×4+T×8
- **NOTE** A=doxorubicin, C=cyclophosphamide, D=docetaxel, E=epirubicin, F=5 fluorouracil, M=methotrexate, T=paclitaxel

ADVERSE EFFECTS OF ADJUVANT CHEMOTHERAPY

- **ALOPECIA** anthracycline or taxane regimes (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, ~1% with anthracycline doses used in adjuvant regimens), secondary cancers (AML, MDS with alkylating agents, ~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 + trastuzumab for Her2 positive breast cancer, dose dense anthracycline and docetaxel (e.g. ddACT) for ER negative patients, CMF or DC if anthracycline contra indicated or preexisting heart disease, and FAC or CAF for post menopausal women

WHICH REGIMEN SHOULD BE USED?

<table>
<thead>
<tr>
<th>FOR NODE NEGATIVE WOMEN</th>
<th>Premenopausal</th>
<th>Postmenopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>ddACT</td>
<td>ddACT</td>
</tr>
<tr>
<td>ER+</td>
<td>FEC, CEF</td>
<td>If G3 or large T, FAC, FEC, AC, DC</td>
</tr>
<tr>
<td>Lower risk</td>
<td>AC, DC, or no chemo</td>
<td>AC, DC or no chemo</td>
</tr>
</tbody>
</table>

ADVANTAGES AND DISADVANTAGES OF NEOADJUVANT AND ADJUVANT THERAPY

Neoadjuvant
Clinical staging is less accurate
Pathological confirmation of chemotherapy efficacy
Definitive treatment delayed
Reduced tumor improves local control
Surgery refusal in patients with complete response
Timely application of chemotherapy

Adjuvant
Accurate pathological staging
No confirmation
Definitive treatment early on
No reduction of tumor before surgery
All patients undergo surgery
Delayed or no chemotherapy in patients with post op complications
Impaired performance status post op

Better performance status allowing aggressive therapy
Intact blood/lymph vessels allowing optimal drug concentrations

PALLIATIVE CHEMOTHERAPY OVERVIEW

PALLIATIVE REGIMENS doublet regimens include doxorubicin plus paclitaxel, capcitabine plus docetaxel, docetaxel plus gemcitabine, paclitaxel plus gemcitabine, and weekly paclitaxel plus bevacizumab. Single agents include capcitabine, 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 chemotherapy to non cross resistance drugs. Use single agent only as no evidence for enhanced overall survival with doublets beyond first line

PALLIATIVE CHEMOTHERAPY OVERVIEW (CONT’D)

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

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)
### DISTINGUISHING FEATURES BETWEEN CARDIOTOXICITY DUE TO ANTHRACYCLINE AND TRASTUZUMAB

<table>
<thead>
<tr>
<th>Anthracycline</th>
<th>Trastuzumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Lipid peroxidation and vacuolation → myocyte fibrosis</td>
</tr>
<tr>
<td>Structural damage</td>
<td>Present</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Dilated</td>
</tr>
<tr>
<td>Dose dependent</td>
<td>Yes</td>
</tr>
<tr>
<td>Prevention</td>
<td>Dexrazoxone</td>
</tr>
<tr>
<td></td>
<td>Liposomal Doxorubicin</td>
</tr>
<tr>
<td></td>
<td>Limit dose</td>
</tr>
<tr>
<td>Treatment</td>
<td>Stop therapy</td>
</tr>
<tr>
<td></td>
<td>Cannot give more</td>
</tr>
<tr>
<td>Course</td>
<td>Irreversible</td>
</tr>
</tbody>
</table>

### 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)

- **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

#### 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**

<table>
<thead>
<tr>
<th>Squamous</th>
<th>Adeno</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>50%</td>
</tr>
<tr>
<td>Barrett’s esophagus</td>
<td>&gt;8×</td>
</tr>
<tr>
<td>Reflux symptoms</td>
<td>4 8×</td>
</tr>
<tr>
<td>Obesity</td>
<td>2 4×</td>
</tr>
<tr>
<td>Smoking</td>
<td>4 8×</td>
</tr>
<tr>
<td>Alcohol Use</td>
<td>4 8×</td>
</tr>
<tr>
<td>Caustic injury to esophagus</td>
<td>&gt;8×</td>
</tr>
<tr>
<td>Achalasia</td>
<td>4 8×</td>
</tr>
<tr>
<td>Poverty</td>
<td>2 4×</td>
</tr>
<tr>
<td>History of H&amp;N cancer</td>
<td>&gt;8×</td>
</tr>
<tr>
<td>History of breast cancer with radiation</td>
<td>4 8×</td>
</tr>
</tbody>
</table>

**PATHOPHYSIOLOGY (CONT’D)**

<table>
<thead>
<tr>
<th>Squamous</th>
<th>Adeno</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plummer Vinson syndrome</td>
<td>&gt;8×</td>
</tr>
<tr>
<td>Non epidermolytic palmpoplantar keratoderma</td>
<td>Frequent hot beverages</td>
</tr>
</tbody>
</table>

**CLINICAL FEATURES**

**Local** dysphagia (74%), odynophagia (17%), upper Gl 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 para esophageal, infraortic, 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>TisN0M0</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>I</td>
<td>T1N0M0</td>
<td>50 80%</td>
</tr>
<tr>
<td>IIa</td>
<td>T2 N0M0T</td>
<td>30 40%</td>
</tr>
<tr>
<td>IIb</td>
<td>T1 2N1M0</td>
<td>10 30%</td>
</tr>
<tr>
<td>III</td>
<td>T3N1M0 T4N0 1M0</td>
<td>10 15%</td>
</tr>
<tr>
<td>IVA</td>
<td>T@N@M1a</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>IVB</td>
<td>T@N@M1b</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

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 post operative 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
- **LEIOMYSARCOMA** (5%)
- **LYMPHOMA** mucosal associated lymphoma
- **CARCINOID**
- **GI STROMAL**

**PATHOLOGIC SUBTYPES**

<table>
<thead>
<tr>
<th></th>
<th>Diffuse type</th>
<th>Intestinal type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Proximal</td>
<td>Distal</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Gender</td>
<td>F &gt; M</td>
<td>M &gt; F</td>
</tr>
<tr>
<td>Risk factors</td>
<td>Hereditary</td>
<td>Endemic</td>
</tr>
<tr>
<td>H. pylori</td>
<td>32%</td>
<td>89%</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Peritoneal</td>
<td>Hepatic</td>
</tr>
<tr>
<td>Outcome</td>
<td>Worse</td>
<td>Better</td>
</tr>
</tbody>
</table>

**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, hema temesis), 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 Treisat 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**

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM @=any</th>
<th>Freq 5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
<td>10% 78%</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0, T1N1M0</td>
<td>58%</td>
</tr>
<tr>
<td>II</td>
<td>T3N0M0, T2N1M0, T1N2M0</td>
<td>34%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4N0M0, T3N1M0, T2N2M0</td>
<td>20%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3N2M0</td>
<td>8%</td>
</tr>
<tr>
<td>IV</td>
<td>T4N@M0, T@N3M0, T@N@M1</td>
<td>30% 7%</td>
</tr>
</tbody>
</table>

**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 test ing), 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 x 3 (epirubicin, cisplatin, infusional 5 fluorouracil) + surgery + adjuvant ECF x 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 N1 M0) 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 %)
• 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 peri gastric 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)

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 MSH2, MLH1, PMS1, PMS2, 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 ANDRECTAL CANCER

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon cancer</td>
<td>Rectal cancer</td>
</tr>
<tr>
<td>2/3</td>
<td>1/3</td>
</tr>
<tr>
<td>&gt;12 cm</td>
<td>&lt;12 cm</td>
</tr>
<tr>
<td>[&gt;4.7 in.] from anal verge or above peritoneal reflection</td>
<td>[&lt;4.7 in.] from anal verge or below peritoneal reflection</td>
</tr>
</tbody>
</table>
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 A, 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.

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).

Investigations

Basic

LABS: CBCD, lys, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, lipase, CEA, CA19-9.

Imaging: barium enema, CT abd, CXR, MRI, and endorectal US in rectal cancer.

Biopsy: Colonoscopy with biopsy, laparoscopy, laparotomy.

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.

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 differ entiated 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 x 12 if pathologic node positive (i.e. node positive); capecitabine x 8 if pathologic node negative. The type and the number of cycles of adjuvant chemotherapy are, how ever, 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

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 FU vs. control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node ve</td>
<td>17%</td>
<td>14%</td>
</tr>
<tr>
<td>Node +ve</td>
<td>40%</td>
<td>34%</td>
</tr>
</tbody>
</table>

TREATMENT ISSUES (CONT’D)

FOLFOX vs. 5 FU

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node ve</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>Node +ve</td>
<td>24%</td>
<td>24%</td>
</tr>
</tbody>
</table>

RELATIVE RISK REDUCTION FROM ADJUVANT ONLINE

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 FU benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node ve</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Node +ve</td>
<td>43%</td>
<td>38%</td>
</tr>
<tr>
<td>FOLFOX benefit</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node ve</td>
<td>39%</td>
<td>24%</td>
</tr>
<tr>
<td>Node +ve</td>
<td>59%</td>
<td>48%</td>
</tr>
</tbody>
</table>

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

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), parangangliomas, 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 ZOLINGER-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

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

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

INVESTIGATIONS
- BASIC LABS CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin, serum chromogranin A, 24 h urine 5-HIAA (sens 73%, spc 100%)

Related Topics
Wheezing (p. 1)
Chronic Diarrhea (p. 124)
MEN syndrome (p. 348)
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, 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), phenoxycbenzamine 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 peripherally 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 (pace maker cells involved in peristalsis)

LOCATIONS stomach (50%), small intestine (25%), colon (10%), esophagus, rectum, mesentry, and retroperitoneum

PATHOPHYSIOLOGY (CONT’D)

MOLECULAR BIOLOGY characteristic c kit/CD117 (90%) and/or PDGFRα mutation, CD34+ (66%)

NATURAL HISTORY clinical behavior of GIST is variable and the risk of recurrence and metastases depends on various adverse prognostic factors. Metastases most commonly involve liver, rarely regional lymph nodes and almost never lungs
**CLINICAL FEATURES**

**LOCOREGIONAL**  
GI bleed, abdominal mass, abdominal pain

**METASTATIC**  
RUQ pain, jaundice

**CONSTITUTIONAL**  
weight loss, anorexia, fatigue, hypoglycemia from secretion of IGFII (rare)

**INVESTIGATIONS**

**BASIC**
- **LABS**  
  CBC, lytes, urea, Cr, AST, ALT, ALP, bilir, INR, PTT, albumin
- **IMAGING**  
  CT abd/pelvis ± MRI, U/S abd, chest imaging, PET/CT in selected patients
- **BIOLOGY**  
  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 unresctable 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

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**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**

<table>
<thead>
<tr>
<th>T stage</th>
<th>N stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 ≤2 cm</td>
<td>N1=perirectal LN</td>
</tr>
<tr>
<td>T2 ≥2 cm but ≤5 cm</td>
<td>N2=unilateral internal iliac LN and/or inguinal LN</td>
</tr>
<tr>
<td>T3 &gt;5 cm</td>
<td>N3=perirectal and inguinal LN and/or bilateral internal iliac and/or inguinal lymph nodes</td>
</tr>
<tr>
<td>T4=involves adjacent organ(s) (involvement of sphincter muscle(s) alone is not classified as T4)</td>
<td></td>
</tr>
</tbody>
</table>

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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 duc tal adenocarcinoma, history of prior chemotherapy or radiotherapy, relatively poor prognosis
- **COLOID 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, signifi cant malignant potential, strong female predomi nance, 70–90% in pancreatic body/tail
- **SEROUS CYSTADENOMAS** cystic, benign
- **SEROUS CYSTADENOCARCINOMA** cystic, malignant behavior
- **SOLID AND PSEUDOPAPILLARY CYSTIC TUMORS** young female (childbearing) predominance, local inva sion into adjacent structures common but metas tases 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 infiltrat ing ductal carcinoma
- **MISCELLANEOUS CANCERS** liposarcomas, leiomyo sarcomas, fibrosarcomas, and lymphomas
- **OTHER LESS COMMON VARIANTS** pleomorphic, sar comatoid, and giant cell carcinomas

RISK FACTORS

- **PERSONAL** Ashkenazi Jewish origin, low socioeco nomic status, habitation of industrialized societies, obesity, and low physical activity
- **FAMILY HISTORY** hereditary non polyposis colon cancer (HNPCC), FAP, BRCA1/2 gene, hereditary pan creatitis, ataxia telangiectasia, Peutz Jeghers syn drome, 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, der matomyositis, panniculitic arthritis eosinophilia syn drome, depression

STAGING

- **TNM STAGING**
  - **T stage**
    - **T1** ≤2 cm, limited to pancreas
    - **T2** >2 cm, limited to pancreas
    - **T3** extends beyond pancreas, but not involving celiac axis or superior mesenteric artery
    - **T4** invades celiac axis or superior mesenteric artery
Hepatocellular Carcinoma

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM @=any</th>
<th>Freq.</th>
<th>Median survival (months)</th>
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<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
<td>10%</td>
<td>17</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIA</td>
<td>T3N0M0</td>
<td>20%</td>
<td>8 9</td>
</tr>
<tr>
<td>IIB</td>
<td>T1 3N1M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>T4 @M0</td>
<td>50%</td>
<td>4 6</td>
</tr>
<tr>
<td>IV</td>
<td>@N@M1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 CRITERIAa
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)

aIf in doubt, patients should be evaluated by a hepatobiliary surgeon

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

Related Topics
Cachexia (p. 397)
Cancer Pain (p. 391)
Jaundice (p. 138)
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 HEPATOCELULAR 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=multi tumors >5 cm or tumor that involves major branch of portal or hepatic vein
- T4=invades adjacent structures other than gall bladder 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

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM @=any</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1N0M0</td>
<td>55%</td>
</tr>
<tr>
<td>II</td>
<td>T2N0M0</td>
<td>37%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3N0M0</td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>T4N0M0</td>
<td>16%</td>
</tr>
<tr>
<td>IIIC</td>
<td>T@N1M0</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>T@N@M1</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

INVESTIGATIONS

BASIC

- LABS CBC, 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

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, NO, 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. Radiofrequence 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 hyper perfusion from an anomalous artery. Rarely exceeds 10 cm. Usually asymptomatic
HEPATIC ADENOMA mainly in young woman on oral contraceptive pills. May cause abdominal pain. Potential for malignant transformation. Treat initially by withdrawal of oral contraceptives and follow lesions by 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)

DIFFERENTIAL DIAGNOSIS OF SOLID RENAL MASS

RENAI 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, bilir, inr, PTT, urine analysis (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 >1.5x upper normal limit, calcium >2.5 mmol/L [<10 mg/dL], hemoglobin <lower normal limit, absence of nephrectomy.

<table>
<thead>
<tr>
<th>Factors</th>
<th>Risk group</th>
<th>Freq.</th>
<th>1 year survival</th>
<th>3 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Good</td>
<td>25%</td>
<td>71%</td>
<td>31%</td>
</tr>
<tr>
<td>1 2</td>
<td>Inter.</td>
<td>53%</td>
<td>42%</td>
<td>7%</td>
</tr>
<tr>
<td>3 5</td>
<td>Poor</td>
<td>22%</td>
<td>12%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

STAGE IV
- PALLIATIVE RESECTION: nephrectomy (particularly if primary is symptomatic), systemic therapy intended, limited metastatic disease, good per formance 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, hemangiblastomas 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.

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 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, amines such as benzidine and 2naphthylamine), drugs (cyclophosphamide), pelvic radiation
- FAMILY HISTORY: affected relatives
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, ≤2 cm
- N2 = single LN 2–5 cm, or multiple LN ≤5 cm
- N3 = any LN >5 cm

M stage (bone, liver, lungs)

- M1 = distant metastasis

STAGE GROUPINGS

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>0a</td>
<td>TaNO0M0</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>0is</td>
<td>TisNO0M0</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>T1NO0M0</td>
<td>85%</td>
</tr>
<tr>
<td>II</td>
<td>T2aN0M0, T2bN0M0</td>
<td>60%</td>
</tr>
<tr>
<td>III</td>
<td>T3aN0M0, T3bN0M0, T4aN0M0</td>
<td>35%</td>
</tr>
<tr>
<td>IV</td>
<td>T4bN0M0, T4cN0M1, T@N1, M0</td>
<td>15%</td>
</tr>
</tbody>
</table>

INVESTIGATIONS

BASIC

- LABS: CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- IMAGING: IVP or triphasic CT abd/pelvis
- URINE CYTOLOGY: sens 70%
- CYSTOSCOPY WITH BIOPSY

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) ± fulguration ± intravesicular therapy (BCG x6 [bacillus Calmette Guerin], mitomycin C, thiotepa, doxorubicin, epirubicin, Epodyl) ± intravesicular interferon. Radical cystectomy may be done if multifocal CIS

INVASIVE

- STAGE II, STAGE III radical cystectomy ± 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 INTRAPITHELIAL 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=7 10 and poorly/undifferentiated

STAGE GROUPINGS

Stage TNM 5 year survival
I T1aN0M0+G1 >95%
II T1aN0M0+G2 4 T1b cN0M0, T2N0M0 70%
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 anti-hymotrypsin 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

<table>
<thead>
<tr>
<th>RISK CATEGORIES FOR LOCALIZED DISEASE</th>
<th>PSA (ng/mL)</th>
<th>Gleason score</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (highly curable)</td>
<td>≤10</td>
<td>2, 6</td>
<td>≤T2b</td>
</tr>
<tr>
<td>Intermediate (curable)a</td>
<td>10-20</td>
<td>7</td>
<td>T2c</td>
</tr>
<tr>
<td>High (rarely curable)</td>
<td>&gt;20</td>
<td>8, 10</td>
<td>≥T3</td>
</tr>
</tbody>
</table>

*aIf 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 (CONT’D)**

**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

**MANAGEMENT (CONT’D)**

[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 anti androgen (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**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Impotence</th>
<th>Urinary incontinence</th>
<th>Urinary irritation</th>
<th>GI irritation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostatectomy</td>
<td>50 90%</td>
<td>10 20%</td>
<td>15 60%</td>
<td>2 17%</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>50%</td>
<td>1 2%</td>
<td>12 30%</td>
<td>10%</td>
</tr>
<tr>
<td>External RTc</td>
<td>50%</td>
<td>1 2%</td>
<td>2 30%</td>
<td>30%</td>
</tr>
</tbody>
</table>

a side effects at 5 years are listed  
b symptoms tend to decrease over time  
c symptoms tend to increase over time

**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, rectal bleeding), and impotence. Urethral stricture (1%), bowel obstruction (0.1%). Also risk of late onset second malignancy

**EXTERNAL BEAM RADIATION**

- **BENEFITS** 5 year disease free survival 80%
- **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

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**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 thirty to forties, pure, αFP negative 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
    - **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

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**Testicular Cancer**

EGCCCG Guidelines Ann Onc 2004 15
PATHOPHYSIOLOGY (CONT’D)
- SEX CORO 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

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

Risk group
- Good (90% 5 year survival)
- Intermediate (80% 5 year survival)
- Poor (50% 5 year survival)

Non seminoma
- Testicular or retroperitoneal tumor, S1, and absence of non pulmonary metastases
- Testicular or retroperitoneal tumor, S2, and absence of non pulmonary metastases
- Testicular, retroperitoneal, or mediastinal tumor, S3, or non pulmonary metastases

Seminoma
- Any location, any marker, and absence of non pulmonary metastases

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
- SEMEN ANALYSIS if fertility a consideration

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 E`2c m
- N2=1 or more LN 2 5 cm or >5 LN >5 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
S2 1000 10,000
S3 >10,000

STAGE GROUPINGS
Stage TNM @=any
IA T1NO0M0
IB T2 N0M0
IS T@N0M0 1
IIA T@N1M0 1
IIB T@N2M0 1
IIC T@N3M0 1
III A T@N1M1aS0 1
III B T@N@M0 1aS2
III C T@N@M0 1aS3, T@N@M1bS@

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
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 (paraortic/paracaval LN, 3-4% relapse) or adjuvant carboplatin (1-2 cycles, 3-4% relapse) or surveillance (15% relapse higher risk of recurrence if >4 cm or rete testis involvement)
- STAGE IIA orchiectomy + radiation (paraortic/ipsilateral iliac LN, 6 year RFS 95%)
- STAGE IIB orchiectomy + one of radiation (paraortic/ipsilateral iliac LN, 6 year RFS 89%) or chemotherapy (if radiation not given, BEP x3 or EP x4, 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 x2) 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 x2, 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 x2; 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 x3 or NSRP LN dissection
- STAGE IIA, MARKER POSITIVE orchiectomy + BEP x3 + resection if residual tumor
- STAGE IIB orchiectomy + BEP x3 + resection if residual tumor

ADVANCED SEMINOMA AND NON SEMINOMA (IIIA, IIIC C)
- GOOD RISK orchiectomy + chemotherapy (BEP x3 or EP x4)
- INTERMEDIATE/POOR RISK orchiectomy + chemotherapy (BEP x4)

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 x2; 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 x4, VIP x4, VeIP x4, TIP x4)
- NOTE: B=bleomycin, E/V=etoposide (VP16), P=cisplatin, I=ifosfamide, V=vinblastine, T=taxol

RELAPSED SEMINOMA if systemic relapse, consider BEP x4. If locoregional relapse, consider BEP or radiotherapy. Salvage chemotherapy regimens after first line chemotherapy include PEI x4, VIP x4, or VeIP x4 or TIP x4

RELAPSED NON SEMINOMA salvage chemotherapy regimens after first line chemotherapy include PEI x4, VIP x4, or VeIP x4 or TIP x4. 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
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, retropitoneal/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

<table>
<thead>
<tr>
<th>Stage</th>
<th>FIGO stage</th>
<th>Freq</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IA C</td>
<td>35%</td>
<td>80% 90%</td>
</tr>
<tr>
<td>II</td>
<td>IIA C</td>
<td>5%</td>
<td>60% 70%</td>
</tr>
<tr>
<td>III</td>
<td>IIIA C</td>
<td>40%</td>
<td>30% 50%</td>
</tr>
<tr>
<td>IV</td>
<td>IV</td>
<td>10%</td>
<td>20%</td>
</tr>
</tbody>
</table>

INVESTIGATIONS

BASIC
- LABS  CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, albumin, CA125, βhCG, aFP
- 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

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

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 ×), 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 (CONT’D)

**OVERALL SURVIVAL BY STAGE**

<table>
<thead>
<tr>
<th>Surgical stage</th>
<th>Freq</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA B</td>
<td>75%</td>
<td>80 90%</td>
</tr>
<tr>
<td>II</td>
<td>11%</td>
<td>70%</td>
</tr>
<tr>
<td>IIIA C</td>
<td>11%</td>
<td>50%</td>
</tr>
<tr>
<td>IVA B</td>
<td>3%</td>
<td>20 30%</td>
</tr>
</tbody>
</table>

STAGING (CONT’D)

**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 formally 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%)

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 (CONT’D)

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 TNNM 5 year survival

IA1 T1a1N0M0 95%

IA2 T1a2N0M0 80%

IB1 T1b1N0M0 60%

IB2 T1b2N0M0 30%

IIA T2aN0M0

IIB T2bN0M0

IIIA T3aN0M0

IIIB T3bN0M0, T1a1 3aN1M0

IVA T4aN0M0

IVB T4bN0M0

5%

INVESTIGATIONS

BASIC

• BLOOD TESTS CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin

• 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
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

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

IMMUNOHISTOCHEMICAL MARKERS
- CARCINOMA cytokeratin negative, common leukocyte antigen, S100, vimentin negative. Breast cancer may be ER/PR positive
- LYMPHOMA common leukocyte antigen

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

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Likely primary</th>
<th>Key history and physical</th>
<th>Investigations</th>
<th>Empiric treatment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly differentiated midline disease in young men</td>
<td>Germ cell tumor (testicular, retroperitoneal)</td>
<td>Gynecomastia suggests seminoma. Perform testicular examination</td>
<td>β-hCG, AFP. Look for isochromosome 12 which suggests tumor responsive to platinum-based therapy</td>
<td>Treat as germ cell tumor (BEP). Potentially curable</td>
</tr>
<tr>
<td>Squamous cell carcinoma with cervical lymphadenopathy</td>
<td>Head and neck cancer (hypopharynx, oropharynx, nasopharynx), skin, esophagus, lung</td>
<td>Smoker, alcohol use</td>
<td>Quadroscopy, CT chest, PET scan. Bronchoscopy and upper GI endoscopy may be considered. FNA first, then core biopsy if negative</td>
<td>Neck dissection and radiation. Potentially curable</td>
</tr>
<tr>
<td>Axillary lymphadenopathy in women</td>
<td>Breast cancer</td>
<td>Breast exam</td>
<td>Mammogram, U/S breast, MRI breast</td>
<td>Mastectomy with axillary dissection or whole breast irradiation, adjuvant chemotherapy. If lytic metastasis in postmenopausal women, consider hormonal treatment</td>
</tr>
</tbody>
</table>
MANAGEMENT (CONT’D)

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Likely primary</th>
<th>Key history and physical Investigations</th>
<th>Empiric treatment(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma with inguinal lymphadenopathy</td>
<td>Cervical/rectal cancer</td>
<td>Pelvic exam, colposcopy</td>
<td>Anoscopy, sigmoidoscopy, CT abd/pelvis, Lymph node dissection, chemoradiation</td>
</tr>
<tr>
<td>Peritoneal carcinomatosis</td>
<td>Ovarian cancer variant, primary peritoneal cancer, metastasis from colorectal or stomach cancer</td>
<td>Pelvic exam</td>
<td>Colonoscopy, gastroscopy, CT abd/pelvis, CEA, CA-125 (ratio 1/20)</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>GI (colorectal [usually otherwise well], pancreatic, esophageal, gastric, hepatic [orientals or cirrhosis], lung, breast</td>
<td>General</td>
<td>CEA, CA 19-9, CA 15-3, AFP, colonoscopy, Gemicitabine, pemetrexed</td>
</tr>
<tr>
<td>Lung nodule(s)</td>
<td>Metastasis (lower lobes, multiple), lung cancer (upper lobe, single)</td>
<td>Smoking history</td>
<td>CT chest, Platinum-based doublet chemotherapy</td>
</tr>
<tr>
<td>Malignant pleural effusion</td>
<td>Lung adenocarcinoma, mesothelioma</td>
<td>Smoking, asbestos exposure</td>
<td>Thoracentesis, Thoracentesis</td>
</tr>
<tr>
<td>Blastic bone metastasis</td>
<td>Prostate (most common), lung, breast</td>
<td>DRE</td>
<td>PSA, plain X-rays of bones, bone scan</td>
</tr>
</tbody>
</table>

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) (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)

A 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 CA 19 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 30%, stage II 50% 70%, stage IV 65–90%), ovarian cancer (46%), lung cancer (26%), liver cancer (30%)

**UTILITY IN BREAST CANCER**

- **DIAGNOSIS**: May be used sometimes to determine the presence of metastatic disease. 86 kU/L + history of breast cancer strongly suggests metastasis
- **METASTATIC SETTING**: May be used to suggest treatment failure, particularly if disease is not readily measurable

**CA 125**

**NORMAL RANGE**: <35 kU/L

**ELEVATED**: epithelial ovarian cancer (sens 50% in stage I, 85% in all), breast cancer, colorectal 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**

<table>
<thead>
<tr>
<th>Tumor marker</th>
<th>Tumor type</th>
<th>Screen</th>
<th>Diagnosis</th>
<th>Prognosis</th>
<th>Response</th>
<th>Follow up (recurrence)</th>
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<tbody>
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<td>Prostate</td>
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<tr>
<td>CA 15 3</td>
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<tr>
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<tr>
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<td>Lymphoma</td>
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</table>

=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 symptomatic 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 polypl at age <60 or two or more first degree relatives with cancer or adenomatous polypl at any age → colonoscopy every 5 years beginning at 40 or 10 years earlier than youngest index case (whichever first).

- **HNPPC, FAP, OR ATTENUATED ADENOMATOUS POLYPOSIS COLI (AAPC)** genetic counseling and special screening. For HNPPC, 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 (SIL 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

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

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A FAMILY HISTORY OF CANCER?

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
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<tbody>
<tr>
<td>Colon cancer</td>
<td>53</td>
<td>92</td>
<td>23</td>
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<tr>
<td>Breast cancer</td>
<td>82%</td>
<td>91%</td>
<td>8.9</td>
<td>0.20</td>
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<tr>
<td>Endometrial ca</td>
<td>33%</td>
<td>98%</td>
<td>14</td>
<td>0.68</td>
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<tr>
<td>Ovarian cancer</td>
<td>50%</td>
<td>99%</td>
<td>34</td>
<td>0.51</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>70%</td>
<td>94%</td>
<td>12.3</td>
<td>0.32</td>
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</table>

Accuracy of self reported family history of cancer in a first degree relative by healthy individuals

<table>
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<th>Spc</th>
<th>LR+</th>
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<tr>
<td>Colon cancer</td>
<td>57</td>
<td>96</td>
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</tr>
<tr>
<td>Breast cancer</td>
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<td>20</td>
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<td>Ovarian cancer</td>
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<td>0.21</td>
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<tr>
<td>Prostate cancer</td>
<td>69</td>
<td>93</td>
<td>24</td>
<td>0.21</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genetics</strong></td>
<td>Autosomal dominant with variable penetrance, 17q21</td>
</tr>
<tr>
<td><strong>Pathophysiology</strong></td>
<td>Tumor suppressor, granin protein family with zinc finger motif, packaging and export of peptide hormones</td>
</tr>
<tr>
<td><strong>Cancer types</strong></td>
<td>Breast (19% by age 40, 50% by age 50, 85% by age 70), ovarian (1445% lifetime risk), prostate (8 16%), colon (6%)</td>
</tr>
<tr>
<td><strong>Clinical features</strong></td>
<td>Young age of breast cancer, bilateral breast cancer, ER (70%), lobular</td>
</tr>
<tr>
<td><strong>Genetic testing</strong></td>
<td>2 common mutations</td>
</tr>
<tr>
<td><strong>Surveillance</strong></td>
<td>Breast starting at young age, clinical breast exam, mammogram, and MRI q6months</td>
</tr>
<tr>
<td><strong>Prophylaxis</strong></td>
<td><strong>Prophylactic mastectomy</strong> breast cancer risk reduction of 90%</td>
</tr>
<tr>
<td></td>
<td><strong>Hormonal</strong></td>
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</table>

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 \[\text{\#321\*, \#3 \geq 2 \text{ relatives} \geq 2 \text{ generations} \geq 1 \text{ family} \text{ diagnosed before age 50. FAP should be excluded}}\]

**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 (post surgical rectal surveillance). Discussion of prophylactic hysterectomy and salpingo oophorectomy at around age 35 or at the end of childbearing
FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

GENETICS autosome dominant, 5q21 q22

PATHOPHYSIOLOGY adenomatous 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 colorectal (risk approaches 100%)

FEATURES colon polyps (more than 100), duodenal adenomas or adenomas with villous histology and/or high grade dysplasia

SURVEILLANCE all at risk family members

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

<table>
<thead>
<tr>
<th>Chemotherapeutic agents</th>
<th>Activity</th>
<th>Myelo. supp.</th>
<th>Emetogenic risk</th>
<th>Alopecia</th>
<th>Other major toxicities</th>
<th>Dose modification</th>
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<tbody>
<tr>
<td>Cyclophosphamide (Cytoxan, IV/PO)</td>
<td>BR, GYN, NHL, BMT</td>
<td>+++</td>
<td>++(+)</td>
<td>+++</td>
<td>Hemorrhagic cystitis, muco, sterility</td>
<td>Renal, hepatic</td>
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<tr>
<td>Ifosfamide (IV)</td>
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<td>++</td>
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<td>Melphalan (PO)</td>
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<tr>
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<td>+</td>
<td>+</td>
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<td>5-Fluorouracil</td>
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<tr>
<td>Streptozocin (IV)</td>
<td>Carcino, islet cell</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>Renal, diaphrea, LFT, hypoglycemia</td>
<td>Renal, hepatic</td>
</tr>
</tbody>
</table>

Antimetabolites

| Methotrexate (IV/PO) | ALL, chorio, leptomeningeal | ++ | + | + | Muco, diaphrea, LFT, renal, pulm, neuro | Renal, hepatic |
| Pemotrexed (IV) | LU, mesothelioma, BR | ++ | + | + | Mucositis, diaphrea, hand foot | Renal |
| 5-Fluorouracil (IV) | GI, BR | ++ | + | + | Mucositis, diaphrea, LFT, fatigue | Renal |
| Cytosine arabinoside (Ara C, IV) | ALL, NHL, leptomeningeal | +++ | + | + | Muco, diaphrea, LFT, hand foot, neuro | Renal |
| Gemcitabine (IV) | GI, LU, BR, NCP, bladder | ++ | + | + | Mucositis, diaphrea, cerebella | Renal, hepatic, neuro |
| Hydroxyurea (PO, IV) | AML, CML | ++ | + | + | Mucositis, rash | Renal |
| 6-Thioguanine (6 TG, IV) | AML | ++ | + | + | Mucositis, diaphrea, LFT, hepatic | Renal |
| 6 Mercaptopurine (6 MG, IV) | AML | ++ | + | + | Mucositis, diaphrea, LFT, hepatic | Renal |
| Fluorouranine (IV, PO) | NHL, CLI | ++ | + | + | Neuro, APA, LFT | Renal |
| 2 Chlorodeoxyadenosine (cladribine, IV) | NHL, hairy cell | ++ | + | + | Constipation, fever | Renal |

Topoisomerase inhibitors

| Doxorubicin (hydroxydaunomycin, IV) | BR, SA | +++ | ++ | +++ | Cardiac | Hepatic |
| Dacarbazine (DTIC, IV) | KS, OV | ++ | + | +++ | Cardiac, infusion, skin | Hepatic |
| Daunorubicin (IV) | AML, neuroblastoma | +++ | ++ | +++ | Cardiac | Hepatic |
| Idarubucin (PO, IV) | 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 | +++ | + | +++ | Diaphrea, constipation, fever | Renal |
| Irinotecan (IV) | GI, LU, GYN | ++ | + | +++ | Diaphrea, constipation, fever | Renal |

Platinating agents

| Cisplatin (IV) | Bladder, LU, OV | ++ | ++ | ++ | Renal, neuro, ototoxicity | Renal, neuro |
| Carboplatin (IV) | Bladder, LU, OV | ++ | ++ | + | Renal, neuro, ototoxicity (less) | Renal, neuro |
| Oxaplatin (IV) | GI | + | ++ | + | Neuro, diaphrea | Neuro, renal |

Antimicrotubular agents

| Vincristine (oncospin, IV) | NHL | ++ | + | + | Neuro, constipation, diaphrea | Hepatic |
| Vinblastine (IV) | T, NHL | ++ | + | + | Neuro, constipation, diaphrea | Hepatic |
| Vindesine (navelbine, IV) | LU, BR | ++ | + | + | Neuro, constipation, diaphrea | 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

<table>
<thead>
<tr>
<th>Others</th>
<th>Activity</th>
<th>Myelo. supp.</th>
<th>Emetogenic risk</th>
<th>Alopecia</th>
<th>Other major toxicities</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin (IV)</td>
<td>Testicular</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>Pulmonary, hemorrhagic cystitis</td>
<td>Renal</td>
</tr>
<tr>
<td>Mitomycin C (IV)</td>
<td>GI, BR, GU</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>Pulmonary, GU irritation</td>
<td>Renal</td>
</tr>
</tbody>
</table>

*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

#### Monoclonal antibodies

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cytopenia</th>
<th>Other major toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (Campath) anti CD52 (SC/IV)</td>
<td>NHL, TCL</td>
<td>Infusion rx’n, infections (e.g. CMV, HSV, TB, fungal), pancytopenia</td>
</tr>
<tr>
<td>Bevacizumab (Avastin) anti VEGF (IV)</td>
<td>GI</td>
<td>Infusion rx’n, HTN, bleed, thrombosis, GI perforations, proteinuria</td>
</tr>
<tr>
<td>Cetuximab (Erbitux) anti EGFR (IV)</td>
<td>GI, H&amp;N</td>
<td>Infusion rx’n, rash, nail/hair changes, mucositis, diarrhea, hypomagnesemia</td>
</tr>
<tr>
<td>Gemtuzumab (Mylotarg) anti CD33 (IV)</td>
<td>AML</td>
<td>Infusion rx’n, N&amp;V, diarrhea, fever, LFT</td>
</tr>
<tr>
<td>Panitumumab (Vectibix) anti EGFR (IV)</td>
<td>GI</td>
<td>Rash, nail/hair changes, mucositis, diarrhea, hypomagnesemia</td>
</tr>
<tr>
<td>Rituximab (Rituxan) anti CD20 (IV)</td>
<td>NHL</td>
<td>Infusion rx’n, infections (e.g. JC virus, CMV, PJP), cardiac arrhythmia</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin) anti Her2 (IV)</td>
<td>BR</td>
<td>Infusion rx’n, cardiomyopathy</td>
</tr>
</tbody>
</table>

#### Tyrosine kinase inhibitors

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cytopenia</th>
<th>Other major toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib (Nexavar) VEGFR inhibitor (PO)</td>
<td>Renal, liver</td>
<td>Fatigue, diarrhea, acral erythema, nail/hair changes, HTN, bleed, hypothyroidism, hypophysitaptemia</td>
</tr>
<tr>
<td>Imatinib (Gleevec) bcr/abl, c kit inhibitor (PO)</td>
<td>CML, GIST</td>
<td>Periorbital edema, nausea, diarrhea, muscle cramps, bowel perforation, fatigue</td>
</tr>
<tr>
<td>Erlotinib (Tarceva) EGFR inhibitor (PO)</td>
<td>Lung</td>
<td>Rash, nail/hair changes, mucositis, diarrhea, interstitial lung dx</td>
</tr>
<tr>
<td>gefitinib (Iressa) EGFR inhibitor (PO)</td>
<td>Lung</td>
<td>Rash, nail/hair changes, mucositis, diarrhea, interstitial lung dx</td>
</tr>
</tbody>
</table>

#### LHRR agonists

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cytopenia</th>
<th>Other major toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goserelin (Zoladex) (IM)</td>
<td>Prostate, BR</td>
<td>Hot flashes, mood changes, sexual dysfunction, diarrhea, anemia, loss of muscle mass, osteoporosis</td>
</tr>
<tr>
<td>Leuprolide (Lupron) (IM)</td>
<td>Prostate, BR</td>
<td></td>
</tr>
</tbody>
</table>

#### Selective estrogen receptor modulators

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cytopenia</th>
<th>Other major toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen (Novadex)</td>
<td>BR</td>
<td>Hot flashes, mood, A, vaginal dryness/discharge, thromboembolism, hypercalcemia, endometrial cancer</td>
</tr>
</tbody>
</table>

#### Aromatase inhibitors

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cytopenia</th>
<th>Other major toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole (Arimidex) non steroidal (PO)</td>
<td>BR</td>
<td>Hot flashes, mood A, arthralgia, vaginal dryness and discharge, osteoporosis for all aromatase inhibitors</td>
</tr>
<tr>
<td>Letrozole (Femara) non steroidal (PO)</td>
<td>BR</td>
<td></td>
</tr>
<tr>
<td>Exemestane (Aromasin) steroidal (PO)</td>
<td>BR</td>
<td></td>
</tr>
</tbody>
</table>

#### Other hormonal agents

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cytopenia</th>
<th>Other major toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicalutamide (Casodex) anti androgen (PO)</td>
<td>Prostate</td>
<td>Hot flashes, mood changes, sexual dysfunction, diarrhea, anemia, loss of muscle mass, osteoporosis</td>
</tr>
<tr>
<td>Flutamide (Eulexin) antiandrogen (PO)</td>
<td>Prostate</td>
<td>Postural hypotension, sexual dysfunction, dizziness</td>
</tr>
<tr>
<td>Finasteride (Proscar) ≤5 reductase inhibitor</td>
<td>Prostate</td>
<td>Vaginal bleed and irregularities, nausea, weight gain</td>
</tr>
<tr>
<td>Megestrol (Megace) progestin (PO)</td>
<td>BR, endometrial</td>
<td>Hot flashes, nausea, diarrhea, back pain, pharyngitis</td>
</tr>
<tr>
<td>Fulvestrant (Faslodex) ER blocker (PO)</td>
<td>BR</td>
<td></td>
</tr>
</tbody>
</table>

#### Others

<table>
<thead>
<tr>
<th>Activity</th>
<th>Cytopenia</th>
<th>Other major toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide (Thalomid) antiangiogenic (PO)</td>
<td>Melasma, NHL</td>
<td>Sedation, fatigue, constipation, rash, peripheral neuropathy, thromboembolism</td>
</tr>
<tr>
<td>Bortezomib (Velcade) proteasome inhibitor (IV)</td>
<td>Melasma, NHL</td>
<td>GI symptoms, fatigue, cytopenia, rash, peripheral neuropathy</td>
</tr>
<tr>
<td>Interferon immune modulatory (IV)</td>
<td>Melasma, renal</td>
<td>Fatigue, fever, myalgia, LFT, mood changes</td>
</tr>
<tr>
<td>Temsirolimus (Torisel) mTOR inhibitor (IV)</td>
<td>Renal</td>
<td>Rash, mucositis, fatigue, hyperglycemia, hypophosphatemia, hypertriglyceridemia</td>
</tr>
</tbody>
</table>
INFUSION REACTIONS

TREAT UNDERLYING CAUSE stop infusion
ABC O₂ 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 apy 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 (hyporeflexic, 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 regard less 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, thy moma, 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

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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)₂vitD 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, PO₄, albumin, PTH, 1,25(OH)₂vitD, 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).

TUMOR LYSIS SYNDROME (CONT’D)

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 PO₄ (>1.45 mmol/L [>4.5 mg/dL]) or 25% from baseline), low Ca (<1.75 mmol/L [<7 mg/dL]) or 25% from baseline), acute renal failure, arrhythmia, and seizure.

TREATMENTS  most important is primary prophylaxis with fluids (NS 150 250 mL/h), allopurinol 300 mg PO TID and consider rasburicase (promotes uric acid degradation). Monitor urine output, K, Ca, PO₄, 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

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 (CONT’D)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated</td>
</tr>
<tr>
<td>4</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

Grade  Nausea
1  Loss of appetite without alteration in eating habits
2  Oral intake decreased without significant weight loss, dehydration, or malnutrition

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
EMETOGENIC LEVELS OF INTRAVENOUSLY ADMINISTERED ANTINEOPLASTIC AGENTS

HIGH RISK (≥90%) carmustine, cisplatin, cyclophosphamide (≥1.5 g/m²), dacarbazine, mechlorethamine, streptozocin

MODERATE RISK (31-90%) carboplatin, cyclophosphamide (≥1.5 g/m²), cytarabine (>1 g/m²), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin

LOW RISK (10-30%) bortezomib, cetuximab, cytarabine (≥1 g/m²), 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

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)

MANAGEMENT (CONT’D)

TREATMENT OVERVIEW FOR PREVENTING ACUTE AND DELAYED CINV

Risk NK1 5HT3 Steroid Etc

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 administration 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)

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)

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)
Chemotherapy-Induced Diarrhea

**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**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Chemotherapy Induced Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase of &lt;4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td>2</td>
<td>Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
</tr>
<tr>
<td>3</td>
<td>Increase of ≥7 stools per day over baseline; incontinence; hospitalization; severe increase in ostomy output compared to baseline; limiting self care ADL</td>
</tr>
<tr>
<td>4</td>
<td>Life threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
</table>

**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

**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 squash 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**

**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 squash and spit q4h q6h
INVESTIGATIONS (CONT’D)

- **MICROBIOLOGY** blood C&S (including *Mycobacterium*), sputum Gram stain/AFB/C&S, urine C&S, stool C&S, O&P, serology (HBV, HCV, HIV, mono spot, 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**

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**Fever and Rash**

**DIFFERENTIAL DIAGNOSIS**

**INFECTIONS**

- **GRAM-POSITIVE COCCI** scarlet fever, toxic shock syndrome, staphylococcal scalded skin syn drome, acute rheumatic fever (erythema mag naratum, subcutaneous nodules)
- **GRAM-NEGATIVE COCCI** meningococcemia (pur pura), disseminated gonococcal infection
- **GRAM-NEGATIVE BACILLI** *Salmonella typhi*, *Pseudomonas* (ecythema gangrenosum), *Vibrio vulnificus*
- **ENDOCARDITIS**
- **SPIROCHETES** *Borrelia burgdorferi* (Lyme erythema migrans), *Treponema pallidum* (chancre, second ary syphilis)
- **RICKETTSIAL** Rocky Mountain spotted fever, ehr liochisis, typhus
- **VIRAL EXANTHEM** acute HIV, mononucleosis, rubella, measles, roseola, erythema infectiousum, chickenpox, shingles, cossackie virus, echovirus
- **FUNGAL** Blastomyces, Coccidioides, Histoplasma

**RHEUMATOLOGIC**

- **SEROPOSITIVE** lupus, dermatomyositis
- **SERONEGATIVE** inflammatory bowel disease, reactive arthritis
- **VASCULITIS** Wegener’s, polyarteritis nodosa
- **BEHÇET’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. Mono nucelosis 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. Meningo coccus 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, pro gression, treatment), exposure (food, water, plants, animals, infected human secretions), weight loss, night sweats, travel history, sexual history, immuniza tions, past medical history (rheumatologic disorders, malignancy), medications
**PHYSICAL**
- vitals (tachycardia, tachypnea, hypoten sion, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenome galy), skin lesions (morphology, distribution), tick bite marks, joint examination

**INVESTIGATIONS**
**BASIC**
- **LABS** CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, 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 pur pura with bacterial sepsis, institute droplet and con tact isolation precautions. See p. 269 for more details

**TREAT UNDERLYING CAUSE**

**SPECIFIC ENTITIES (CONT’D)**

**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 pathogen esis. All can be treated with doxycycline
- **ROCKY MOUNTAIN SPOTTED FEVER** *Rickettsia rickettsi* 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 trans aminases; maculopapular or petechial rash in one third. Human granulocytic anaplasmosis is caused by a related *Ehrlichia* and produces similar illness with out rash. Transmitted by bodes tick and co infection with Lyme disease possible. Treat with doxycycline
- **Q FEVER** *Coxiella burnetii* transmitted by respira tory spread from infected animal body fluids (e.g. cattle, sheep, goats, cats). No rash. Fever, pneumo nitis, hepatitis, endocarditis, CNS symptoms. Treat with doxycycline

**LYME DISEASE**
- **PATHOPHYSIOLOGY** *Borrelia burgdorferi* trans mitted by tick bite after attachment for > 24 h; think about concomitant tick borne diseases
- **CLINICAL FEATURES** most common tick borne dis ease 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, hema togenous spread with neurological symptoms (facial nerve palsy, lymphocytic meningitis, ence phalitis, chorea, myelitis, radiculitis, peripheral neuropathy) and carditis (AV block, dilated cardi omyopathy); 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 muscu loskeletal pain, neurocognitive symptoms, dys esthesias and fatigue

**RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ERYTHEMA MIGRANS?**

<table>
<thead>
<tr>
<th>Sens</th>
<th>History (US studies)</th>
<th>Physical (US studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65%</td>
<td>Systemic symptoms</td>
<td>Solitary lesion</td>
</tr>
<tr>
<td>47%</td>
<td>Fatigue</td>
<td>81%</td>
</tr>
<tr>
<td>36%</td>
<td>Headache</td>
<td>Lymphadenopathy</td>
</tr>
<tr>
<td>35%</td>
<td>Myalgias</td>
<td>22%</td>
</tr>
<tr>
<td>35%</td>
<td>Arthralgias</td>
<td>Multiple lesions</td>
</tr>
<tr>
<td>33%</td>
<td>Fever</td>
<td>21%</td>
</tr>
<tr>
<td>33%</td>
<td>Pruritus</td>
<td>Central clearing of rash</td>
</tr>
<tr>
<td>31%</td>
<td>Stiff neck</td>
<td>19%</td>
</tr>
<tr>
<td>26%</td>
<td>History of a tick bite</td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td>Dysesthesia</td>
<td></td>
</tr>
<tr>
<td>11%</td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
</tbody>
</table>

**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 exam ined 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 repel lants. After tick bite (>36 h in hyperendemic area), consider doxycycline 200 mg x 1 dose within 72 h of the tick bite
- **TREATMENTS stage 1** (doxycycline 100 mg PO BID x 10 21 days, or cefuroxime 500 mg PO BID x 10 21 days). Lyme carditis (ceftriaxone 2 g IV x 14 21 days if third degree AV block; otherwise, same as stage I with oral antibiotics). Neurologic Lyme (ceftriaxone 2 g IV x 14 21 days). Lyme arthritis (doxycycline 100 mg BID x 28 days, amoxicillin)
- **JARISS–HERXHEIMER REACTION** up to 15% of patients may experience transient worsening of symptoms during first 24 h of treatment. This results from the host immune response to antigen release from dying organisms (typically Lyme and syphilis) causing fever, chills, myalgias, and exacerbation of rash

**BABESIOSIS** (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, head ache 5 33 days after, particularly in immunosup pressed individuals
- **CLINICAL FEATURES** endemic in southern New Eng land, southern New York, Wisconsin, and Minnesota
- **DIAGNOSIS** blood smear, PCR, serology
- **TREATMENTS** atovaquone plus azithromycin

**Related Topic**
Exanthematous Lesions (p. 364)

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**Fever and Joint Pain**

See JOINT PAIN AND FEVER (p. 276)

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**Sepsis**

See SEPSIS (p. 97)

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**Febrile Neutropenia**

See 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** Histi plasma, Coccidioides, Toxoplasma, Tuberculosis

**PATHOPHYSIOLOGY**

**DEFINITION** single temp >38.3°C [101°F] or >38°C [100.4°F] for >1 h, ANC <0.5 x 10⁹/L or <1.0 x 10⁹/L + expected nadir <0.5 x 10⁹/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 rela tively 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 neutro phils. If fever persists or returns after neutropenia resolves, consider hepatosplenic candidiasis
Febrile Neutropenia

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), abdominal examination (hepatosplenomegaly), skin lesions (morphology, distribution). Important (murmurs), respiratory and cardiac examination (nuchal rigidity, respiratory and cardiac examination (nuchal rigidity, respiratory and cardiac examination)

INVESTIGATIONS

BASIC

- LABS CBCD, ltes, urea, Cr, AST, ALT, ALP, bilirubin, urinalysis
- MICROBIOLOGY blood C&S x 2 (culture peripheral blood in addition to central line ports, spu tum 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 x 10^9/L, peak temperature <39°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, cindamycin 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, amphoterin 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 ≥0.5 x 10^9/L for 2 consecutive days, afebrile for ≥48 h, cultures negative, and no obvious signs of infection, or if (2) ANC <0.5 x 10^9/L by day 7, but afebrile for 5 7 days, patient initially at low risk, and no subsequent complications
  - CONTINUE ANTIBIOTICS if above criteria not met
- IF PERSISTENT FEVER ON DAY 3
  - STOP ANTIBIOTICS if ANC ≥0.5 x 10^9/L for 4 5 consecutive days
  - CONTINUE ANTIBIOTICS if ANC <0.5 x 10^9/L, reassess and continue antibiotics for 2 weeks. Consider stopping therapy if no disease site is found and condition is stable

PRE MEDICATIONS FOR AMPHOTERICIN B

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

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MALFORLD 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
primary prophylaxis was not received), in which a reduced dose may compromise disease free survival overall, 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 (<0.1×10^9/L) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multi organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of the development of fever

- **SPECIAL SITUATIONS**
  - **STEM CELL TRANSPLANT** to mobilize peripheral blood progenitor cell often in conjunction with chemotherapy. Also administered after autologous, but not allogeneic, stem cell transplantation
  - **DLBCL** prophylactic GCSF should be given for patients with diffuse aggressive lymphoma age 65 and older treated with curative chemotherapy (CHOP or more aggressive regimens)
  - **AML** may be given shortly after completion of the initial induction chemotherapy to modestly decrease the duration of neutropenia
  - **ALL** recommended after the completion of the initial first few days of chemotherapy of the initial induction or first post remission course, thus shortening the duration of neutropenia by approximately 1 week
  - **MDS** may be used to increase the ANC in neutropenic patients. Intermittent administration of CSFs may be considered in a subset of patients with severe neutropenia and recurrent infections
  - **POST-RADIATION** GCSF should be given to patients exposed to lethal doses of total body radiotherapy, but not doses high enough to lead to certain death due to injury to other organs

**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)

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**Fever with Travel History**

**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)**

**FEVER WITH EOSINOPHILIA** parasitic (acute hookworm, ascaris, strongyloides, acute schistosomiasis, visceral larva migrans, lymphatic filariasis, acute trichinosis)

**DIFFERENTIAL DIAGNOSIS (CONT’D)**

**PARASITIC** malaria, Loeffler’s syndrome (migration of larval helminths such as ascaris, strongyloides, and hookworm)

**HEMORRHAGIC FEVER**
- **BACTERIAL** rickettsial, meningococccemia, 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)

**Related Topics**
Chemotherapy (p. 226)
Neutropenia (p. 148)
Sepsis (p. 97)
Stem Cell Transplant (p. 180)
Differential Diagnosis (Cont’d)

Fever with Travel History

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History, incubation period, sexual history, immunization status, antimalarial chemoprophylaxis (medications, degree of adherence), past medical history (rheumatologic disorders, malignancy), medications

Fever with Travel History

- Bacterial
  - Enterohecic or enterohaemorrhagic 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, Trichantium coli, Trichinella spiralis

Chronic Traveler’s Diarrhea ± Fever

- Bacterial
  - Enteroaggretative or enteropathogenic E. coli, C. jejuni, Shigella, Salmonella, Yersinia enterocolitica, Aeromonas, Plesiomonas, C. difficile, Tropheryma whippellii
- 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

Investigations

Basic

- Labs: CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir, 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 x 1 within 12-24 h if initially negative result), serologies (HIV, dengue, rickettsiae, schistosomiasis, strongyloidiasis, leptospirosis, HAV, HBV, HCV, Hepatitis E)
- Imaging: CXR, US abd guided by symptoms

Special

- Lumbar puncture

Pre Travel Considerations

Vaccinations

- Standard regardless of travel (influenza, pneumococcal if age > 65, hepatitis B, MMR, DTP), 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. haemato bium, 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

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

www.phac aspc gc.ca/publicat/ccdr rmrtc/06vol32/ac5 01/index eng.php
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 3 days of return.

PATHOPHYSIOLOGY: Anopheles 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 (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 leukopenia may be present. Lymphadenopathy, leukopenia, thrombocytopenia, and jaundice are common in tropical areas. 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 during 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). Atovaquone proguanil associated with fewest side effects. Mefloquine has ease of weekly dosing. Doxycycline is the cheapest, but requires prolonged course and causes sun sensitization. CDC 2010 risk assessment and prophylaxis recommendations are available online at http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter2/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.

RICKETTSIAL INFECTIONS (OUTSIDE OF NORTH AMERICA)

PATHOPHYSIOLOGY: African tick typhus (Rickettsia africæa), 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 fresh water. 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/cefazime IV for severe disease.
<table>
<thead>
<tr>
<th>SPECIFIC ENTITIES (CONT’D)</th>
<th>SPECIFIC ENTITIES (CONT’D)</th>
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<tbody>
<tr>
<td><strong>TYPHOID FEVER</strong></td>
<td><strong>DENGUE FEVER</strong></td>
</tr>
<tr>
<td><strong>PATHOPHYSIOLOGY</strong></td>
<td><strong>BREAK BONE FEVER</strong></td>
</tr>
<tr>
<td>acquired after exposure to</td>
<td>flavivirus transmitted by mosquito</td>
</tr>
<tr>
<td>food or water contaminated by <em>Salmonella typhi</em></td>
<td>illness 4-7 days later — may develop lymphadenopathy, maculopapular/petechial rash — dengue shock syndrome and dengue hemorrhagic fever if previously exposed to other serotypes</td>
</tr>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
<td><strong>DIAGNOSIS</strong></td>
</tr>
<tr>
<td>mainly in developing coun</td>
<td></td>
</tr>
<tr>
<td>tries. Fever, chills, headache, myalgia, abdominal</td>
<td>blood cultures, serology</td>
</tr>
<tr>
<td>pain and constipation (uncommonly diarrhea),</td>
<td><strong>TREATMENTS</strong></td>
</tr>
<tr>
<td>relative bradycardia, splenomegaly, and rose</td>
<td>doxycycline plus streptomycin or rifampin</td>
</tr>
<tr>
<td>spots (faint salmon colored macules on the abdo</td>
<td><strong>PATHOPHYSIOLOGY</strong></td>
</tr>
<tr>
<td>men and trunk). Septic symptoms from intestinal</td>
<td>flavivirus transmitted by mosquito</td>
</tr>
<tr>
<td>perforation may occur in second week</td>
<td>illness 4-7 days later — may develop lymphadenopathy, maculopapular/petechial rash — dengue shock syndrome and dengue hemorrhagic fever if previously exposed to other serotypes</td>
</tr>
<tr>
<td><strong>DIAGNOSIS</strong></td>
<td><strong>CLINICAL FEATURES</strong></td>
</tr>
<tr>
<td>blood, stool, urine, or bone marrow (highest sensitivity) culture; CBC may show leukopenia</td>
<td>acquired mostly from tropical and subtropical areas. Fever, headache, retro orbital pain, severe myalgia/arthritis. Leukopenia and thrombocytopenia</td>
</tr>
<tr>
<td><strong>TREATMENTS</strong></td>
<td><strong>DIAGNOSIS</strong></td>
</tr>
<tr>
<td>fluoroquinolones, ceftriaxone, azithromycin</td>
<td>serology</td>
</tr>
<tr>
<td><strong>BRUCELLOSIS</strong> (undulant fever, Mediterranean fever)</td>
<td><strong>TREATMENTS</strong></td>
</tr>
<tr>
<td><strong>PATHOPHYSIOLOGY</strong></td>
<td>supportive</td>
</tr>
<tr>
<td>Gram negative facultative intra cellular coccobacilli</td>
<td><strong>DIAGNOSIS</strong></td>
</tr>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
<td>serology (acute and convalescent)</td>
</tr>
<tr>
<td>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</td>
<td><strong>TREATMENTS</strong></td>
</tr>
<tr>
<td><strong>DENGUE FEVER</strong> (break bone fever)</td>
<td>symptomatic with NSAIDs</td>
</tr>
<tr>
<td><strong>PATHOPHYSIOLOGY</strong></td>
<td><strong>CHIKUNGUNYA FEVER</strong></td>
</tr>
<tr>
<td>flavivirus transmitted by mosquito</td>
<td>mosquito borne viral infection acquired in Africa and Asia. Large outbreaks ongoing in Indian Ocean islands and India</td>
</tr>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
<td><strong>PATHOPHYSIOLOGY</strong></td>
</tr>
<tr>
<td>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</td>
<td>mosquito borne viral infection</td>
</tr>
<tr>
<td><strong>DIAGNOSIS</strong></td>
<td><strong>CLINICAL FEATURES</strong></td>
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</tr>
<tr>
<td><strong>TREATMENTS</strong></td>
<td><strong>DIAGNOSIS</strong></td>
</tr>
<tr>
<td>symptomatic with NSAIDs</td>
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<td><strong>CHIKUNGUNYA FEVER</strong></td>
<td><strong>TREATMENTS</strong></td>
</tr>
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<td>mosquito borne viral infection</td>
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</tr>
</tbody>
</table>

**DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS**

**DIM**

**DRUGS**
neuroleptic malignant syndrome, serotonin syndrome, sympathomimetics, alcohol withdrawal

**INFECTIOUS**
- 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

**ABSCESSES**
bacterial

**METABOLIC**
thyroid storm

**STRUCTURAL**
- subarachnoid, epidural, subdural, intracerebral
- CEREBRAL INFARCT

**Pneumonia**

See PNEUMONIA (p. 6)

**Endocarditis**

See ENDOCARDITIS (p. 52)

**Meningitis**

See Meningitis (NEJM 2006 354:1)
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*

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS ADULT PATIENT HAVE ACUTE MENINGITIS?

<table>
<thead>
<tr>
<th>History</th>
<th>Physical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Fever</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>Neck stiffness</td>
</tr>
<tr>
<td>Neck pain</td>
<td>Altered mental status</td>
</tr>
</tbody>
</table>

Jolt accentuation of headache (patient turns head horizontally at a frequency of 2–3 rotations per second. Worsening headache represents positive sign)

*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

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

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

**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
Meningitis

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 355:12)

- OPENING PRESSURE  normal is 60 250 mmH2O. Causes of elevated opening pressure include meningitis, pseudotumor cerebri, intracranial hemorrhage, tumors, and idiopathic

- CELL COUNT AND DIFFERENTIAL  normal WBC is <5/mm3. This can increase to 1000 5000/mm3 for bacterial meningitis (neutrophils mainly) and 50 1000/mm3 for viral meningitis (lymphocytes mainly). Other causes include seizure, intracerebral hemorrhage, tumor, and "traumatic tap" (correct by +1 WBC for every 500 1000 RBCs)

- XANTHOCHROMIA  lyzed 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+ 2006 296:16]

CSF analysis

CSF blood glucose ratio ≤0.4 18
CSF glucose >2.2 mmol/L (>40 mg/dL) 23
CSF WBC ≥500/mL 15
CSF lactate ≥3.5 mmol/L (≥32 mg/dL) 21

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 unconfused, 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, O2, IV, intubation. Droplet precautions for suspect N. meningitidis infection

EMPIRIC ANTIBIOTICS  steroid if acute bacterial meningitis and 15 20 min before first dose of anti biotics (dexamethasone 0.15 mg/kg or 10 mg IV q6h ×4days). Ceftriaxone 2 g IV q6h or ceftaxone 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 cefazidime 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 (ceftaxone, 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, neurosarcoïdosis, 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 neurological 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
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 neurologic 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

Related Topics
Delirium (p. 380)
Infection Control (p. 269)

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DIFFERENTIAL DIAGNOSIS OF DYSURIA

★SUV★

**SEXUALLY TRANSMITTED DISEASES** Chlamydia trachomatis, Neisseria gonorrhoeae, HSV

**URINARY TRACT INFECTIONS** (urethritis, cystitis, pyelonephritis, perinephric abscess) bacterial (★KEEPS★ Klebsiella, E. coli, Enterococci, Proteus, Staphylococcus saprophyticus)

**VAGINAL INFECTIONS** Candida albicans, Trichomonas, bacterial vaginosis

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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, cystocele, 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

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CLINICAL FEATURES OF URINARY TRACT INFECTIONS

**RATIONAL CLINICAL EXAMINATION SERIES:** DOES THIS WOMAN HAVE ACUTE UTI?

<table>
<thead>
<tr>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>1.1</td>
<td>0.9</td>
</tr>
<tr>
<td>0.3</td>
<td>3.1</td>
</tr>
<tr>
<td>0.2</td>
<td>2.7</td>
</tr>
<tr>
<td>1.6</td>
<td>0.8</td>
</tr>
</tbody>
</table>

**History**
- Dysuria
- Frequency
- Hematuria
- Fever
- Flank pain
- Lower abdominal pain
- Vaginal discharge
- Vaginal irritation
- Back pain

**Physical**
- Vaginal discharge
- CVA tenderness

**Urine dipstick**
- Leukocyte esterase or nitrite positive

**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, lyses, 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

**INCOMPPLICATED 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 monohydrate 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 3x/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 UNCOMPPLICATED PYELONEPHRITIS** treat empirically with oral fluoroquinolones × 7d (ciprofloxacin 500 mg PO BID or levofloxacin 750 mg PO daily). If isolate susceptible, may treat with trimethoprimsulfamethoxazole, amoxicillin, or amoxicillin clavulanate × 14d. 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).

**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** grey, 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 (pain less, indurated, non purulent ulcer) within 3 90 days.

**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 × 7 7 days even if asymptomatic as there is a 20 40% risk of pyelonephritis. Avoid fluoroquinolones.
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, meningoencephalitis, 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.

<table>
<thead>
<tr>
<th>Diagnostic Method</th>
<th>Test(s)</th>
<th>Utility</th>
</tr>
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<tbody>
<tr>
<td>Direct visualization</td>
<td>Dark field microscopy</td>
<td>Traditional but availability is limited</td>
</tr>
<tr>
<td>Visualization with fluorescent Ab</td>
<td>DFA</td>
<td>Diagnosis of 1st syphils</td>
</tr>
<tr>
<td>Molecular testing</td>
<td>PCR</td>
<td>Sensitive/specific but not readily available</td>
</tr>
<tr>
<td>Treponemal serology (presence of Ab</td>
<td>FTA ABS, TPPA, MHA TP, TP EIA, INNO LIA</td>
<td>Diagnosis of syphilis</td>
</tr>
<tr>
<td>against TP)</td>
<td></td>
<td>Sensitive; however, does not differentiate venereal from non venereal treponematosis</td>
</tr>
<tr>
<td>Non treponemal serology (presence</td>
<td>VDRL, RPR</td>
<td>Screening</td>
</tr>
<tr>
<td>of Ab against cardiolipin/lecithin)</td>
<td></td>
<td>RPR titer helpful in staging</td>
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<tr>
<td></td>
<td></td>
<td>Check for reinfection</td>
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<tr>
<td></td>
<td></td>
<td>Treatment monitoring</td>
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</table>

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, gummatus 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.

• 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.


• 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).
**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 swollen, 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 strep toxicocci (B, C, G, and F)
- **Surgical Wound** S. aureus, S. pyogenes
- **Human Bite** oral anaerobes, Eikenella corrodens
- **Animal Bite** Pasteurella multocida, Capnocytophaga phagocytophila
- **Tick Bite** Borrelia burgdorferi, Tularemia
- **Freshwater** Aeromonas hydrophila
- **Seawater** Vibrio vulnificus
- **Fish Exposure** Erysipelothrix rhusiopathiae, Strep toccoccus iniae
- **Hot Tub** Pseudomonas aeruginosa folliculitis

**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)
DIFFERENTIAL DIAGNOSIS

OSTEOMYELITIS

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, sterno clavicular, sacroiliac) and sometimes long bones (femur, tibia, humerus)

CONTIGUOUS SPREAD FROM SOFT TISSUE INFECTIONS trauma, surgery, orthopedic prosthesis, decubitus ulcer

CONTIGUOUS SPREAD FROM SOFT TISSUE INFECTIONS WITH GENERALIZED VASCULAR INSUFFICIENCY ischemic ulcers, diabetic ulcers

RISK FACTORS FOR OSTEOMYELITIS

SYSTEMIC diabetes, sickle cell disease (Salmonella)

LOCAL vascular compromise (arterial insufficiency, neuropathy venous stasis), orthopedic surgery

CLINICAL FEATURES

DIABETIC FOOT ULCER either probing of bone or ulcer area above 2 cm² is associated with ~90% chance of having underlying osteomyelitis (sens 66%, spc 85%, PPV 89%, NPV 56%). Further non invasive testing is unlikely to improve accuracy of diagnosis

CLINICAL FEATURES (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 ta zobactam 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)
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 (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 ± *cefazidime* 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

<table>
<thead>
<tr>
<th>PATHOPHYSIOLOGY</th>
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<tbody>
<tr>
<td><strong>ORGANISMS</strong> genus <em>Mycobacterium</em> consists of &gt;50 species. TB is caused by <em>M. tuberculosis</em> complex including <em>M. tuberculosis</em>, <em>M. bovis</em>, and others. The cell envelope contains mycolic acid → resists destaining by acid alcohol, thus termed acid fast bacilli</td>
</tr>
<tr>
<td><strong>TRANSMISSION</strong> TB transmission is almost exclusively airborne through inhalation of minute droplet nuclei. Therefore, lungs are the primary focus. How ever, any organs can become infected during the bacteremia that follows initial lung infection</td>
</tr>
<tr>
<td><strong>LATENT TB INFECTION (LTBI)</strong> 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</td>
</tr>
<tr>
<td><strong>FACTORS THAT INCREASE THE RISK OF INFECTION</strong> 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)</td>
</tr>
<tr>
<td><strong>FACTORS INCREASING THE RISK OF REACTIVATION</strong> 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</td>
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<table>
<thead>
<tr>
<th>PATHOPHYSIOLOGY (CONT’D)</th>
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<tbody>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
</tr>
<tr>
<td><strong>PRIMARY TB</strong></td>
</tr>
<tr>
<td>• <strong>SYMPTOMS</strong> fever, night sweats, pleuritic chest pain, chronic cough, anorexia, weight loss, fatigue, erythema nodosum</td>
</tr>
<tr>
<td>• <strong>SIGNS</strong> 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</td>
</tr>
<tr>
<td><strong>REACTIVATION TB</strong> (active pulmonary)</td>
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<tr>
<td>• <strong>SYMPTOMS</strong> cough, yellow green sputum (increases over time), hemoptysis (25%), chest pain/dyspnea (33%), fever/night sweats (50%), fatigue (50–66%), weight loss</td>
</tr>
<tr>
<td>• <strong>SIGNS</strong> 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)</td>
</tr>
<tr>
<td><strong>ELDERLY WITH REACTIVATION TB</strong> presents with fever, night sweats, or hemoptysis less often. Lesions less often cavitary and less often TST positive</td>
</tr>
</tbody>
</table>
CLINICAL FEATURES (CONT’D)

COMPLICATIONS OF PULMONARY TB
hemothysis (rarely massive), pneumothorax (more common in endemic countries), bronchiectasis, and pulmonary destruction (rare)

Related Topic
Tuberculosis in Pregnancy (p. 412)

INVESTIGATIONS

BASIC
- LABS  CBCD, lyes, 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

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 regard less 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 isonia zid 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

DRUG MONITORING

- **BASELINE** platelet, Cr, AST, ALP, bilirubin, uric acid
- **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. lugdunensis, S. schleiferi

PAIRS/CHAINS (catalase negative)
- **α-HEMOLYTIC STREPTOCOCCI** S. pneumoniae, viridans 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 (CONT‘D)**

- **ACID FAST** (mycobacterium) M. tuberculosis, M. leprae, M. avium intracellulare complex, or non tuberculous Mycobacteria (NTM, also known as mycobacterium 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**

ACID FAST (mycobacterium) M. tuberculosis, M. leprae, M. avium intracellulare complex, or non tuberculous Mycobacteria (NTM, also known as mycobacterium 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, Garden ella, Nocardia
  - **ANAEROBIC** Actinomyces, Propionibacterium, Eubacterium

- **BRANCHING BACILLI ★ABCD LMN★** Actinomyces (acid fast negative), Bacillus, Clostridium, Diptheroids, Listeria, Lactobacillus, Mycobacterium (Modified and Ziehl Neelsen acid fast), Nocardia (modified acid fast)

**GRAM NEGATIVE COCCI**

NEISSERIA N. meningitidis (diplococci), N. gonorrhoeae (diplococci), other Neisseria

MORAXELLA M. catarrhalis

**GRAM NEGATIVE BACILLI**

AEROBIC
- **GLUCOSE FERMENTING AND LACTOSE FERMENTING** a number of Enterobacteriaceae including E. coli, Citrobacter, Enterobacter, Klebsiella, Serratia
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

S. AUREUS (MSSA) may develop resistance to penicillin by β-lactamase

PEUSDOMONAS: 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, oxacillin). In general, hospital MRSA strains have broader resistance (e.g. clindamycin, trimethoprim sulfamethoxazole, tetracyclines) than community associated MRSA strains (CA MRSA). Risk factors for hospital MRSA infections include frequent hospital visits and contact with MRSA infected individuals; CA MRSA is associated with crowding, acute and chronic skin disease, poor hygiene, sharing of contaminated items, contact sports, and IDU

β LACTAMASE RESISTANT BACTERIA constitutive (E. coli*, Klebsiella*, Haemophilus, Neisseria, bacteroides), inducible (S. aureus, Serratia*†, Providencia*†, Pseudomonas, Indole positive Proteus*†, Citrobacter*†, Enterobacter*†, Morganella*†)

†★SPIRE M★ organisms with inducible, chromosomally mediated cephalosporinases (AmpC type β-lactamases) resistant to penicillins, first and second generation cephalosporins, cephemycins, and β-lactamase inhibitors

*these organisms may have extended spectrum β-lactamase (ESBL) resistant to all β-lactams except carbapenems
<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Mechanism</th>
<th>Gram positive</th>
<th>Gram negative</th>
<th>Anaerobes</th>
<th>Others</th>
<th>Renal adjustments</th>
</tr>
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<tbody>
<tr>
<td><strong>Penicillins</strong></td>
<td>Bactericidal, cell wall synthesis inhibition and lysis</td>
<td>++ Strep</td>
<td>Meningococcus</td>
<td>++ Syphilis</td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td>Penicillin G 2–4 M units IV q4–6h</td>
<td></td>
<td>++ Strep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin V 250–500 mg PO TID/QID</td>
<td></td>
<td>++ S. aureus</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Cloxacillin/nafoxacillin/oxacillin 1–2 g IV q4–6h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amino-Penicillins</strong></td>
<td>Bactericidal, cell wall synthesis inhibition and lysis</td>
<td>+/+Strep/Entero</td>
<td>+/– H. flu, +/– E. coli</td>
<td>Listeria</td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Amoxicillin 250–1000 mg PO TID</td>
<td></td>
<td>++ Strep/Entero</td>
<td>+/– H. flu, +/– E. coli</td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Amox/clavulanate 875/125 mg PO BID</td>
<td></td>
<td>++ Strep/Entero</td>
<td>+H. flu, E. coli</td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td><strong>Anti-pseudomonal Penicillins</strong></td>
<td>Bactericidal, cell wall synthesis inhibition and lysis</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pip/tazo 3.375 g q6h–4.5 g IV q8h</td>
<td></td>
<td>++ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tcarcillin 3–4 g IV q4–6h</td>
<td></td>
<td>++</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Tcarcillin/clavulanate 3.1 g IV q4–6h</td>
<td></td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monobactam and Carbapenems</strong></td>
<td>Bactericidal, cell wall synthesis inhibition and lysis</td>
<td>++ ++</td>
<td>++ Pseudo</td>
<td>+++</td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td>Aztreonam 1–2 g IV q6–8h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (dose)</td>
</tr>
<tr>
<td>Imipenem 500 mg IV q6h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td>Meropenem 1 g q8h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td>Ertapenem 1 g IV q24h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td>Doripenem 500 mg IV q8h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td><strong>First-Generation Cephalosporins</strong></td>
<td>Bactericidal, cell wall synthesis inhibition and lysis</td>
<td>++ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin 1–2 g IV q8h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Cephalexin 250–1000 mg PO QID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td><strong>Second-Generation Cephalosporins</strong></td>
<td>Bactericidal, cell wall synthesis inhibition and lysis</td>
<td>++ ++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime 750–1500 mg IV q8h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Cefuroxime 125–500 mg PO BiD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Cefprozil 250–500 mg PO q12h</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Yes (interval)</td>
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<tr>
<td>Cefaclor 250–500 mg PO BID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td><strong>Third/Fourth Generation Cephal.</strong></td>
<td>Bactericidal, cell wall synthesis inhibition and lysis</td>
<td>+++ +</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefoxitin 1–2 g IV q6–8h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Cefotaxime 1–2 g IV q6–8h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Ceftriaxone 1–2 g IV q24h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Cefazidime 1 g IV q8–12h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Ceftazime 1–2 g IV q12h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Ceftrime 400 mg PO daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>Cefotibiprole 500 mg IV q8–12h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (interval)</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td>Bactericidal, binds to 30S and 50S ribosomes</td>
<td>Entero (syn)</td>
<td>+/– Entero (syn)</td>
<td></td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td>Gentamicin 5–7 mg/kg IV q24h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td>Tobramycin 5–7 mg/kg IV q24h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td>Amikacin 7.5 mg/kg q12h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td>Streptomycin 15 mg/kg IM or IV q24h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes (dose + interval)</td>
</tr>
<tr>
<td>Antibiotics (cont’d)</td>
<td>Mechanism</td>
<td>Gram positive</td>
<td>Gram negative</td>
<td>Anaerobes</td>
<td>Others</td>
<td>Renal adjustments</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------</td>
<td>---------------</td>
<td>---------------</td>
<td>-----------</td>
<td>--------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>Fluoroquinolones</strong></td>
<td>Bactericidal, inhibit DNA synthesis through inhibition of DNA gyrase and topoisomerase</td>
<td>+++</td>
<td>+++Pseudo</td>
<td>AFB</td>
<td>Yes (interval)</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin 500 mg PO/400 mg IV BID</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Norfloxacin 400 mg PO BID</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin 200–400 mg PO BID</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin 500–750 mg PO/IV daily</td>
<td>++</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin 400 mg PO/IV daily</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Gemifloxacin 320 mg PO daily</td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Macrolides</strong></td>
<td>Bacteriostatic, binds to 50S ribosomes</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Azithromycin 250 mg PO daily</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin 250–500 mg PO BID</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Erythromycin 250–500 mg PO q6–12h</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td>Bacteriostatic, binds to 30S ribosomes</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Doxycycline 100 mg PO/IV q12h</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Minocycline 50–100 mg PO daily–BID</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Tigecycline 100 mg IV, then 50 mg q12h</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Sulfa</strong></td>
<td>Bactericidal, blocks DNA synthesis</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole/Trimethoprim 1–2 SS/DS tab PO BID (also available IV)</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Clindamycin</strong></td>
<td>Bacteriostatic, binds to tRNA complex</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Clindamycin 150–450 mg PO QID or 300–600 mg IV q6–12h</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Metronidazole</strong></td>
<td>Bactericidal, DNA breakage</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Metronidazole 500 mg PO/IV q12h</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Glycopeptides</strong></td>
<td>Bactericidal, interferes with peptidoglycan and RNA synthesis</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Vancomycin 15 mg/kg IV q12h</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Oxazolidinones</strong></td>
<td>Bactericidal (Strep) and bacteriostatic (Staph, enteric)</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Linezolid 600 mg PO/IV q12h</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Streptogramins</strong></td>
<td>Inhibits late + early protein synthesis</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Quinupristin/dalfopristin 7.5 mg/kg IV q8h via central line</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td><strong>Lipopeptides</strong></td>
<td>Bactericidal, disrupts cell membrane</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Daptomycin 4–6 mg/kg q24h</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
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 ototoxic agents (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 [22–46 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)

VANCYCLINE TOXICITY AND DOSING

TOXICITY  rash, infusion related red man syndrome, rarely nephrotoxicity (especially combined with aminoglycoside), and ototoxicity. However, 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**

- **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 carbapenem or fluoroquinolone or amoxicillin. For intra abdominal source, piperacillin tazobactam plus amoxicillin. 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 piperacillin/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 highly variable. See p. 123 for details

PERITONITIS/INTRA ABDOMINAL SEPSIS (coli forms, anaerobes) piperacillin/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, 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

HEPATITIS B

See HEPATITIS B (p. 130)

HEPATITIS C

See HEPATITIS C (p. 131)

HERPES SIMPLEX VIRUS INFECTION

See HERPES SIMPLEX VIRUS (p. 366)
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/mm³ 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 8 weeks if change of HAART)

AIDS CD4 <200/mm³ or any AIDS defining diseases

• BACTERIAL MAC, TB, recurrent Salmonella sepsis

• VIRAL CMV retinitis, chronic HSV, PML

CD4 COUNT AND PATHOLOGIES IN HIV PATIENTS

CD4 count (>500 200 500 100 200 <100 (mm³)

Kaposi sarcoma + + + + +

Bacterial + + + + +

TB + + + + +

HSV + + + + +

Candida + + + + +

Coccidioides + + + + +

Histoplasma + + + + +

PJP + + + + +

Cryptococcus + + + + +

Toxoplasma + + + + +

CMV + + + + +

MAC + + + + +

CNS lymphoma + + + + +

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

DISENTAL DIAGNOSIS

• BRAIN ABSCCESS toxoplasma (CD4 <100/mm³, usually multiple ring enhancing lesions), tuberculosis (any CD4), Cryptococcus (CD4 <100/mm³), Histoplasma (CD4 <500/mm³), aspergillosis

• CNS LYMPHOMA (CD4 <100/mm³)

• PROGRESSIVE MULTIFOCALEUKOENCEPHALOPATHY (PML, CD4 <100/mm³) 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 antibody dies, and (3) lack of toxoplasma prophylaxis in an HIV patient with CD4 count <100/mm³ has 90% PPV for diagnosing toxoplasma

TREATMENT OF TOXOPLASMA pyrimethamine plus either sulfadiazine or clindamycin
**CHRONIC MENINGITIS IN HIV PATIENTS**

**DIFFERENTIAL DIAGNOSIS**
- **CRYPTOCOCCUS** (CD4 <100/mm³) ubiquitous fun.
- **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 ×2 months for consolidation, followed by fluconazole 200 mg PO daily as maintenance. Man agement 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× increased risk in HIV patients. May be extrapolunmonary
- **NON-TB MYCOBACTERIUM** MAC (CD4 <100/mm³, pulmonary involvement alone is rare, usually disseminated)
- **FUNGAL** (CD4 <500/mm³) *Histoplasma, Coccioides, Cryptococcus*
- **PNEUMOCYSTIS JIROVECII PNEUMONIA** (PJP, CD4 <200/mm³)

**DIAGNOSIS** CBCD, lytes, urea, Cr, LDH (↑ 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 8/6 daily ×21 days. If severe disease (PaO₂ <70 mmHg), add *prednisone* 40 mg PO BID ×5 days, then 40 mg PO daily ×5 days, then 20 mg PO daily ×11 days. Alter natives to *trimethoprim sulfamethoxazole* include dapsone plus trimethoprim, or clindamycin plus pri maquine, pentamidine IV. Use atovaquone if G6PD deficiency

**ESOPHAGITIS IN HIV PATIENTS**

**DIFFERENTIAL DIAGNOSIS**
- **INFECTIONS**
  - **CANDIDA** (CD4 <500/mm³) 50 70%
  - **HSV** (any CD4) 5 10%
  - **CMV** (CD4 <100/mm³) 5 15%
  - **NON-INFECTIONOUS** 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/mm³) *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/mm³) *M. avium, M. intracellulare*
  - **CMV** (CD4 <100/mm³)
  - **PARASITIC** *Microsporidium, Entamoeba histolytica, Giardia, Isospora, Cryptosporidium*
  - **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/mm³)

**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/mm³) dif fuse large B cell lymphoma, primary effusion lymphoma (associated with HHV8 and EBV), and plas mablastic lymphomas. Treat with combination chemotherapy (CHOPR)
- **Primary CNS lymphoma** (CD4 <100/mm³) strongly associated with EBV. Treat with radiation and/or high dose methotrexate or intrathecal chemotherapy
- **Cervical carcinoma** (any CD4) strongly associated with HPV. Treat with surgery, radiation, and/or chemotherapy (cisplatin)
AIDS ASSOCIATED MALIGNANCIES (CONT’D)

NON AIDS DEFINING MALIGNANCIES increased incidence of Hodgkin’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/mm³. Trimethoprim sulfamethoxazole SS 1 tab PO daily, or trimethoprim sulfamethoxazole DS 1 tab PO daily, or trimethoprim sulfamethoxazole DS 1 tab PO three times a week. If allergic, desensitize or use dapsone.

TOXOPLASMOsis PROPHYLAXIS for patients with positive Toxoplasma serology and CD4 <100/mm³. Trimethoprim sulfamethoxazole DS 1 tab PO daily. If allergic, dapsone plus pyrimethamine plus folinic acid are alternatives.

MAC PROPHYLAXIS for patients with CD4 <50/mm³. Azithromycin 1200 mg PO once weekly.

HISTOPLASmosis PROPHYLAXIS for patients with CD4 <150/mm³ and living in endemic area. Itraconazole 200 mg PO daily.

TB PROPHYLAXIS for patients with positive tuberculin skin test reaction (induration ≥5 mm) and not treated for TB previously. Isoniazid 5 mg/kg/day PO daily to max 300 mg/day, or 900 mg TIW x 9 months. Rifampin 600 mg PO daily x 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 (ddl), lamivudine (3TC), abacavir (ABC), tenofovir (TFD), 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).

CCRS 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.

APPRAOCH start treatment in all symptomatic patients and in asymptomatic patients if CD4 <350/mm³. Treatment should be considered for CD4 between 350 and 500/mm³ and is optional for those >500/mm³. Rapidly declining CD4 counts (>100/mm³/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 ↓ by 2 logs after 8 weeks and ↓ to <50 copies/mL after 6 months of therapy. Need to continue therapy or may develop viral load rebound/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 HBeAb, 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. ddl is contra indicated and AZT use is discouraged in those on ribavirin

Influenza

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.
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.

<table>
<thead>
<tr>
<th>DISTINGUISHING FEATURES BETWEEN INFLUENZA A, B, AND C</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hosts</strong></td>
</tr>
<tr>
<td>Humans, Birds, Mammals</td>
</tr>
<tr>
<td>Antigenic shift</td>
</tr>
<tr>
<td>Antigenic drift</td>
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<tr>
<td>Epidemics</td>
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<td>Pandemics</td>
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</table>

**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.

**COMPLICATIONS** respiratory (bacterial pneumonia), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, aseptic meningitis, transverse myelitis, Guillain Barre syndrome).

<table>
<thead>
<tr>
<th>RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE INFLUENZA?</th>
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</thead>
<tbody>
<tr>
<td><strong>All age groups</strong></td>
</tr>
<tr>
<td>Sens</td>
</tr>
<tr>
<td>Fever</td>
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<tr>
<td>Feverishness</td>
</tr>
<tr>
<td>Cough</td>
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<tr>
<td>Myalgia</td>
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<tr>
<td>Malaise</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Sore throat</td>
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<tr>
<td>Sneezing</td>
</tr>
<tr>
<td>Nasal congestion</td>
</tr>
<tr>
<td>Chills</td>
</tr>
<tr>
<td>Vaccine history</td>
</tr>
<tr>
<td>Fever and cough</td>
</tr>
<tr>
<td>Fever, cough, and acute onset</td>
</tr>
<tr>
<td><strong>Age ≥60</strong></td>
</tr>
<tr>
<td>Sens</td>
</tr>
<tr>
<td>Fever</td>
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<tr>
<td>Feverishness</td>
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<tr>
<td>Cough</td>
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<tr>
<td>Myalgia</td>
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<td>Malaise</td>
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<td>Sore throat</td>
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<tr>
<td>Sneezing</td>
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<tr>
<td>Nasal congestion</td>
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</table>
CLINICAL FEATURES (CONT’D)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE INFLUENZA?

<table>
<thead>
<tr>
<th></th>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
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</thead>
<tbody>
<tr>
<td>Chills</td>
<td>46%</td>
<td>82%</td>
<td>2.6</td>
<td>0.66</td>
</tr>
<tr>
<td>Vaccine history</td>
<td></td>
<td></td>
<td>0.63</td>
<td>1.1</td>
</tr>
<tr>
<td>Fever and cough</td>
<td>30%</td>
<td>94%</td>
<td>5.0</td>
<td>0.75</td>
</tr>
<tr>
<td>Fever, cough, and acute onset</td>
<td>27%</td>
<td>95%</td>
<td>5.4</td>
<td>0.77</td>
</tr>
</tbody>
</table>

**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, bilir unib, 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 (CONT’D)

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 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

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 rimantidine are inactive against influenza B and C and resistance is now widespread 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

<table>
<thead>
<tr>
<th>Antiviral agents</th>
<th>Mechanism</th>
<th>HSV, VZV</th>
<th>CMV</th>
<th>Influenza A</th>
<th>Influenza B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir 200–800 mg PO BID 5x/day, 5–10 mg/kg IV q8h</td>
<td>Nucleoside analogues—activated by viral thymidine kinase, inhibit viral DNA polymerase (vDNAp); also incorporated into viral DNA and act as a chain terminator</td>
<td>++</td>
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<tr>
<td>Valacyclovir 500–1000 mg PO daily–TID</td>
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<tr>
<td>Famciclovir 250–1000 mg PO BID</td>
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<tr>
<td>Penciclovir 10 mg/g topically q2h x4 days</td>
<td>Applied topically for treatment of oral cold sores</td>
<td>++</td>
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</tr>
<tr>
<td>Ganciclovir 5 mg/kg IV q12h or 1000 mg PO TID (maintenance)</td>
<td>Nucleoside analogue that inhibits viral DNA polymerase</td>
<td>++ ++</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Valganciclovir 900 mg PO daily–BID</td>
<td></td>
<td>++ +++</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Foscarnet 90 mg/kg IV q12–24h</td>
<td>Pyrophosphate analogue that inhibits viral DNA polymerase</td>
<td>++ +++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cidofovir 5 mg/kg IV qweek</td>
<td>Nucleoside analogue that inhibits viral DNA polymerase</td>
<td>++ +++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine 100 mg PO BID</td>
<td>Inhibit M2 Protein (ion channel) of influenza A, blocking uncoating of virus genome within newly infected cells</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rimantadine 100 mg PO BID</td>
<td></td>
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</tr>
<tr>
<td>Zanamivir 10 mg INH q12–24h</td>
<td>Neuraminidase Inhibitors. Block release of influenza virus from infected cells</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oseltamivir 75 mg PO daily–BID</td>
<td></td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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*, *zygomyces*, *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 par enchymal 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)

#### PATHOLOGY

**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 hematologic 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, neone nates, 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. alibicans*. Echinocandin and lipid formulation of amphotericin B are preferred for initial therapy in neutropenic patients. Almost all (>95%) *C. alibicans* are sensitive to fluconazole. Some laboratories report *C. alibicans* 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 aspergillosma (“fungal ball”), allergic bronchopul monary 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 fun gal 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 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 *Cunninghamamella*

PATHOPHYSIOLOGY mostly affecting immunocompromised patients and those with diabetes. Prognosis extremely poor

CLINICAL FEATURES CNS, pulmonary, GI, and cutaneous involvement. Infection can cause devastating rhino orbital cerebral and pulmonary infections

TREATMENTS antifungal therapy frequently needs to be combined with surgical debridement. Empiric treatment options include lipid formulations of amphotericin B and posaconazole. Note that susceptibility testing of Zygomycetes is not always reliable, and that caspofungin and “azoles” (apart from posaconazole) 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, pan cytopenia, 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/mm³, transplantation, hematologic malignancies, chronic kidney diseases, diabetes mellitus, cirrhosis, or corticosteroid use. This pathogen is inhaled, then disseminates with predilection for CNS with meningitis more common than focal parenchymal infections
- C. GATTII  seen more commonly in immunocompetent hosts and paradoxically uncommon in immunosuppressed hosts. Symptomatic infection is usually pulmonary ± focal parenchymal brain infection

CLINICAL FEATURES  CNS, pulmonary, and cutaneous involvement (but may involve any organ)

TREATMENTS  CNS infection (lumbar puncture to lower intracranial pressure, amphotericin B plus fluconazole), pulmonary or cutaneous infection (fluconazole or itraconazole)

Coccidioidomycosis (Cont’d)

lesions. Radiologically, unilateral infiltrate and hilar adenopathy are common. Cutaneous symptoms include erythema nodosum and erythema multiforme. Most common sites of dissemination are skin, bone, and meninges

DIAGNOSIS  fungal culture and serology. Note that Coccidioides is a level 3 pathogen. Therefore, cultures should be processed in high level isolation unit and labeled carefully. 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

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Candida</th>
<th>Cryptococcus</th>
<th>Aspergillus</th>
<th>Other molds</th>
<th>Dimorphic Zygomycota</th>
<th>Renal adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azoles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td><strong>Inhibits CP450</strong></td>
<td>++C. alb</td>
<td>+++</td>
<td>+</td>
<td>Yes (dose)</td>
<td></td>
</tr>
<tr>
<td>100–400 mg PO/IV daily</td>
<td>(convert lanosterol to ergosterol on cell membrane)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Voriconazole</td>
<td>+++</td>
<td>+++</td>
<td>++Fusa/ Scedo</td>
<td>++</td>
<td>No but avoid IV form</td>
<td></td>
</tr>
<tr>
<td>4 mg/kg IV q12h or 200 mg PO BID</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++Fusa</td>
<td>++</td>
<td>+++</td>
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<tr>
<td>200 mg PO QID</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Amphotericin B</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Amphotericin B</td>
<td><strong>Binds to ergosterol on cell wall, causing cell leakage</strong></td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>0.3–1 mg/kg IV q24h</td>
<td></td>
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<tr>
<td>Liposomal Amphotericin B</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>3–5 mg/kg IV q24h</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>AmphoB colloidal dispersion</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>Yes (interval)</td>
</tr>
<tr>
<td>AmphoB lipid complex 5 mg/ kg IV q24h</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>Yes (interval)</td>
</tr>
<tr>
<td><strong>Echinocandins</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Caspofungin</td>
<td><strong>Inhibits synthesis of β-1,3-d-glucan on cell wall</strong></td>
<td>+++</td>
<td>+++</td>
<td>+Scedo</td>
<td>+/-</td>
<td>No</td>
</tr>
<tr>
<td>70 mg then 50 mg IV q24h</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Micafungin</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>150 mg IV q24h</td>
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<tr>
<td>Anidulafungin</td>
<td>+++</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
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<tr>
<td>200 mg then 100 mg IV q24h</td>
<td></td>
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</tr>
<tr>
<td><strong>5-Flucytosine</strong></td>
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<td></td>
</tr>
<tr>
<td>Flucytosine</td>
<td><strong>Inhibits synthesis of DNA (thymidylate synthetase)</strong></td>
<td>+++</td>
<td>+++</td>
<td></td>
<td>++</td>
<td>Yes (dose)</td>
</tr>
</tbody>
</table>

*Other than Aspergillus, Fusarium, Scedosporium, and Pseudallescheria boydii are all examples of molds*

*Dimorphic fungi include Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Paracoccidioides brasiliensis, and Sporothrix schenckii*

*Zygomycota fungi include Rhizopus, Mucor, and Absidia*

*Flucytosine is ineffective against some Candida, Molds, and Zygomycetes*

*Itraconazole is ineffective against some Candida, Scedosporium, and Zygomycetes. It has activity against Cryptococcus, but has less CSF penetration than fluconazole*

*Voriconazole is ineffective against some Candida, Scedosporium, and Zygomycetes. It has activity against Cryptococcus, but has less CSF penetration than fluconazole*

*Amphotericin B is ineffective against some Candida, Scedosporium, Trichosporum, Aspergillus terreus, C. guilliermondii and C. lusitaniae*

*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)

**FUNGEMIA** empiric treatment for fungi not yet speciated where neither amphotericin B nor fluconazole can be used

**FEVRILE 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 nephrotoxic drugs, 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/
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

**NEEDLE STICK INJURY (CONT’D)**

**PROPHYLAXIS FOR OTHER INFECTIOUS AGENTS**
diphtheria (penicillin or erythromycin), meningococcal (rifampin, ciprofloxacin, ceftriaxone), pertussis (trimethoprim sulfamethoxazole), syphilis (penicillin), rabies (rabies immune globulin, vaccine), varicella zoster (varicella zoster immune globulin, vaccine), hepatitis A (immune globulin, vaccine)

### Immunization for Adults

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Vaccine</th>
<th>Immunization Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles SC</td>
<td>Live</td>
<td>0, +1 months (if high risk)</td>
<td>All adults not previously immunized in childhood</td>
<td>Preg, immunocomp.</td>
</tr>
<tr>
<td>Mumps SC</td>
<td>Live</td>
<td>0, +1 months (if high risk)</td>
<td>All adults not previously immunized in childhood</td>
<td>Preg, immunocomp.</td>
</tr>
<tr>
<td>Rubella SC</td>
<td>Live</td>
<td>0, +1 months (if high risk)</td>
<td>All adults not previously immunized in childhood</td>
<td>Preg, immunocomp.</td>
</tr>
<tr>
<td>Polio IM/SC</td>
<td>Inactivated</td>
<td>–</td>
<td>Not routinely recommended for adults</td>
<td>–</td>
</tr>
<tr>
<td>HBV IM</td>
<td>Recombinant</td>
<td>0, +1 months, +6 months</td>
<td>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</td>
<td>–</td>
</tr>
<tr>
<td>HAV IM</td>
<td>Inactivated</td>
<td>0, +6 months</td>
<td>Travelers (esp. developing world), chronic liver disease (e.g. chronic HCV/HBV), men who have sex with men, food handlers</td>
<td>–</td>
</tr>
<tr>
<td>Influenza IM</td>
<td>Inactivated</td>
<td>Annually (Oct)</td>
<td>Adults &gt;50 years, &gt;6 months 50 years with chronic disease, pregnancy, healthcare workers</td>
<td>–</td>
</tr>
<tr>
<td>Varicella SC</td>
<td>Live</td>
<td>0, 1–2 months</td>
<td>All who have not had chicken pox by adulthood, especially healthcare workers</td>
<td>Preg, immunocomp.</td>
</tr>
<tr>
<td>Herpes zoster SC</td>
<td>Live</td>
<td>1 dose</td>
<td>Adults &gt;60 years. Note this vaccine has higher dose of attenuated virus than varicella vaccine</td>
<td>Preg, immunocomp, no history of Varicella</td>
</tr>
<tr>
<td>HPV IM</td>
<td>Recombinant</td>
<td>0, +1–2 months, +6 months</td>
<td>Females aged 9–26 years (licensed also for males in some countries)</td>
<td>–</td>
</tr>
</tbody>
</table>

**Bacterial vaccines**

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Vaccine</th>
<th>Immunization Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertussis</td>
<td>Cellular</td>
<td>1 dose</td>
<td>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>
<td>–</td>
</tr>
<tr>
<td>Td (tetanus, diphtheria) IM</td>
<td>Toxoid, inactivated</td>
<td>0, +2 months, +6–12 months, q10year</td>
<td>All adults not previously immunized in childhood (see Tdap under Pertussis)</td>
<td>–</td>
</tr>
<tr>
<td>Pneumococcal IM/SC</td>
<td>Polysaccharide</td>
<td>0, +5year</td>
<td>Adults &gt;65 years, &gt;6 months 50 years with chronic disease, pregnancy, splenectomy, malignancy, smokers</td>
<td>–</td>
</tr>
<tr>
<td><em>Haemophilus</em> type B</td>
<td>Conjugated</td>
<td>1 dose</td>
<td>Splenectomy</td>
<td>–</td>
</tr>
<tr>
<td>Meningococcal SC</td>
<td>Polysaccharide</td>
<td>1 dose</td>
<td>Splenectomy, college dormitory students, lab workers, travelers to endemic areas</td>
<td>–</td>
</tr>
</tbody>
</table>
RISK FACTORS FOR SPECIFIC ORGANISMS
- **HBV** household contacts/sexual partners of hepatitis patients, IDU, homosexual, multiple sexual partners, tattoo, piercing, transfusions, health care 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

CONTRAINDICATIONS
- **ALL VACCINES** anaphylaxis, severe illness
- **LIVE VACCINES** pregnancy, immunocompromised (steroids, AIDS but not HIV, malignancies)

SIDE EFFECTS local erythema, fever
RHEUMATOLOGY
Section Editor: Dr. Elaine Yacyshyn

Septic Arthritis

DIFFERENTIAL DIAGNOSIS OF MONOARTHRITIS

★ ICU RN ★

INFECTIONS

- **VIRAL** HIV, HBV, Parvovirus, rubella, mumps, enterovirus, adenovirus
- ** FUNGAL ** *Cryptococcus*, *Blastococcus*
- **OSTEOMYELITIS/OSTEONECROSIS EXTENDING TO JOINT**
- **CRYSTAL** gout, pseudogout, hydroxyapatite, basic calcium phosphate
- **UNCLASSIFIED**

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, episceritis, 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?

<table>
<thead>
<tr>
<th>History</th>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
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</thead>
<tbody>
<tr>
<td>Age &gt;80</td>
<td>19%</td>
<td>95%</td>
<td>3.5</td>
<td>0.86</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12%</td>
<td>96%</td>
<td>2.7</td>
<td>0.93</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>68%</td>
<td>73%</td>
<td>2.5</td>
<td>0.45</td>
</tr>
</tbody>
</table>


9

273
## Clinical Features (Cont’d)

<table>
<thead>
<tr>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent joint surgery</td>
<td>24%</td>
<td>96%</td>
<td>6.9</td>
</tr>
<tr>
<td>Hip/knee prosthesis</td>
<td>35%</td>
<td>89%</td>
<td>3.1</td>
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<tr>
<td>Skin infection</td>
<td>32%</td>
<td>88%</td>
<td>2.8</td>
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<tr>
<td>HIV infection</td>
<td>79%</td>
<td>50%</td>
<td>1.7</td>
</tr>
<tr>
<td>Joint pain</td>
<td>85%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint edema</td>
<td>78%</td>
<td></td>
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<tr>
<td>Fever</td>
<td>57%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweats</td>
<td>27%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigors</td>
<td>19%</td>
<td></td>
<td></td>
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</tbody>
</table>

### 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/C2: 90% 73% 28 0.71

### 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 fluid analysis provides 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.*

### Investigations

#### Basic
- CBC, lymphocytosis, Cr, uric acid, ANA, RF, ESR, CRP, INR, PTT

#### Imaging
- Joint XR (chondrocalcinosis in pseudogout)

#### Arthrocentesis
- Cell count with diff, Culture and Gram stain, Crystal

#### Special
- Infection Workup
- Urethral/rectal swabs, blood C&S

### Diagnostic Issues (Cont’d)

#### 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

<table>
<thead>
<tr>
<th></th>
<th>Non</th>
<th>Infectious</th>
<th>Infectious</th>
<th>Septic</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (cells/mm³)</td>
<td>&lt;200</td>
<td>200</td>
<td>2000</td>
<td>50,000</td>
</tr>
<tr>
<td>PMNs (%)</td>
<td>&lt;25%</td>
<td>&lt;25%</td>
<td>25%</td>
<td>50%</td>
</tr>
</tbody>
</table>

#### 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 halluces 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

CAUSES

DECREASED URATE EXCRETION (90%)
- RENAL DISEASE
- DRUGS ★ CAN'T LEAP ★ Cyclosporine, Alcohol, Nicotinic Acid, Thiazides, Loop diuretics, Ethambutol, ASA (low dose), Pyrazinamide

INCREASED URATE PRODUCTION (10%)
- METABOLIC SYNDROME obesity, hyperlipidemia, hypertension
- INCREASED METABOLISM alcohol, hemolytic anemia, psoriasis, Lesch Nyhan syndrome
- NEOPLASTIC myeloproliferative disease, lymphoproliferative disease, chemotherapy

PATHOPHYSIOLOGY

IMBALANCE decreased urate excretion and/or increased urate production → uric acid crystals deposited in joints, skin, and kidneys → arthritis, tophi, and renal failure. Gout almost never occurs in pre menopausal women

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 col lection 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 sug gests ↓ excretion)
- IMAGING joint XR

INVESTIGATIONS (CONT'D)
- ARTHROCENTESIS ★ 3C ★ (Cell count with diff, Culture and Gram stain, Crystal, for gout, sens 85%, spc 100%)
- 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 intracel lular 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). Probencid 250 1000 mg PO BID (first line, ↓ renal urate reabsorption. Ensure normal renal func tion). 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 (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, hemo chromatosis, diabetes, hypothyroidism, hypomagne semia, 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

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-INFECCIOUS/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 (CONT’D)

DISTINGUISHING FEATURES
• TEMPERATURE >40°C (>104°F) Still’s disease, bacterial arthritis, SLE

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
• ARTHROCENTESIS ★3C★ (Cell count with diff [>2000 WBC/mm³], Culture and Gram stain, Crystal)

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★ Polymyositis, Palindromic rheumatism, SLE, Scleroderma, Sjogren’s syndrome, Rheumatoid arthritis
• SERONEGATIVE ★PEAR★ Psoriatic arthritis, Enteric arthritis, Ankylosing spondylitis, Reactive arthritis, undifferentiated disease
• 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-INFECTION/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 poly myalgia 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), auto antigens (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 halluc valgus, cock up toes
• LEGS knees (80%), ankles (80%), hips (50%)
• ARMS shoulders (60%), elbows (50%), acromio clavicular (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

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<tr>
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<th>Inflammatory</th>
<th>Non inflammatory</th>
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<tbody>
<tr>
<td>Classic example</td>
<td>RA</td>
<td>OA</td>
</tr>
<tr>
<td>Morning stiffness</td>
<td>&gt; 1 h</td>
<td>+/-</td>
</tr>
<tr>
<td>Resting</td>
<td>Worsens</td>
<td>Improves</td>
</tr>
<tr>
<td>Activity</td>
<td>Improves</td>
<td>Worsens</td>
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<tr>
<td>Synovitis, redness</td>
<td>+</td>
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</tr>
<tr>
<td>Fever, weight loss</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>ESR, CRP, platelets</td>
<td>↑</td>
<td>No change</td>
</tr>
</tbody>
</table>

INVESTIGATIONS

BASIC
- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, ESR, CRP, RF (lgM), 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★ (Cell count with diff [>2000 WBC/mm³], Culture and Gram stain, Crystal. 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


SPECIFIC ENTITIES

PALINDROMIC RHEUMATISM episodic arthritis with one or more joints being affected sequentially for hours to days, and symptom free periods in
between for days to months. May be anti CCP positive and occasionally progresses to other rheumatic disorders (RA, SLE). Treatment with hydroxychloroquine can be useful.

**Sjogren’s Syndrome** (Keratoconjunctivitis sicca)

- **Pathophysiology**
  - CD4 lymphocytic infiltration of salivary and lacrimal glands

- **Causess**
  - Primary (sicca plus episodic, non deform ing 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

**Loefgren’s Syndrome**

A benign self limited form of sarcoidosis. Tetrad of erythema nodosum, hilar lymphadenopathy, arthritis (ankles and sometimes knees), and uveitis

**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
  - Renal: proteinuria > 0.5 g/day or ≥ 3+, or cellular casts
  - Arthritis ≥ 2 peripheral joints, non erosive
  - Serositis: pleuritis, pericarditis
  - Hematologic: hemolytic anemia, leukopenia < 4.0 x 10^9/L, lymphopenia < 1.5 x 10^9/L, thrombocytopenia < 100 x 10^9/L
  - Excitation: seizures, psychosis
  - Serology: 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 criterion) 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 (dys pnea, pleuritic chest pain, progressive reduction in lung volume, elevated diaphragms)
  - Cardiac: pericarditis (sens 30%), myocarditis, Libman Sacks endocarditis
SEROLOGIC ANA (sensitivity (steroids), and embolisms other causes such as infections, medication side effects (especially in pregnancy, associated with neonatal lupus and congenital complete 

WHO CLASSIFICATION OF LUPUS NEPHRITIS

- NORMAL (class I) asymptomatic
- MESANGIAL PROLIFERATIVE (class II) mild hematuria or proteinuria
- FOCALE PROLIFERATIVE (class III) nephritic syndrome, proteinuria
- DIFFUSE PROLIFERATIVE (class IV) nephritic syndrome, nephrotic syndrome
- MEMBRANOUS GLOMERULONEPHRITIS (class V) nephrotic syndrome
- GLOMERULOSCLEROSIS (class VI) uremia

CONSTITUTIONAL SYMPTOMS

- VI > IV > III > V > II, consider aggressive treatment for class III, IV

GI mesenteric thrombosis and vasculitis, transmural mastitis/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, psychic depression, peripheral neuropathy

DERMATOLOGIC photosensitivity (sensitivity 50%), malar rash (nasolabial folds spared, sensitivity 50%), discoid lupus (erythematosus papules/plaques with central hypopigmentation, atrophic scarring involving scalp and exposed skin, sensitivity 25%), mucosal ulcers (oral, vaginal, nasal septal), alopecia, livedo reticularis, palpable purpura, Raynaud’s

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 adherance, infections, and pregnancy. Always consider other causes such as infections, medication side effects (steroids), and embolisms

INVESTIGATIONS

BLOOD TESTS CBCD, lymphocytes, 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

INVESTIGATIONS (CONT’D)

- WHO CLASSIFICATION OF LUPUS NEPHRITIS
  - NORMAL (class I) asymptomatic
  - MESANGIAL PROLIFERATIVE (class II) mild hematuria or proteinuria
  - FOCALE PROLIFERATIVE (class III) nephritic syndrome, proteinuria
  - DIFFUSE PROLIFERATIVE (class IV) nephritic syndrome, nephrotic syndrome
  - MEMBRANOUS GLOMERULONEPHRITIS (class V) nephrotic syndrome
  - GLOMERULOSCLEROSIS (class VI) uremia

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 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, ulcera-
tions, 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, amloidipine 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 (Calcinosis, Raynaud’s phenomenon, Esophageal dysmotility, Sclerodactyly, Telangiectasias), 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, hypo pigmentation, hyperpigmentation, “coup de sabre deformity”, purse lip, telangiectasia), and GI hypo motility (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

**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 SCI 70) seen more in diffuse systemic sclerosis and antibody to centro meme 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 [erythemathous rash over upper chest/back/shoulders], periangual 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**

<table>
<thead>
<tr>
<th>History</th>
<th>Steroid myopathy</th>
<th>Inflammatory myopathies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid use</td>
<td>Other steroid related symptoms</td>
<td>Other inflammatory myopathy symptoms</td>
</tr>
<tr>
<td>Physical</td>
<td>Neck flexor normal</td>
<td>Neck flexor weaker</td>
</tr>
<tr>
<td>Tests</td>
<td>CK less often ↑</td>
<td>CK often ↑, anti Jo1/anti Mi2 Ab</td>
</tr>
<tr>
<td>EMG</td>
<td>Normal</td>
<td>Abnormal activity</td>
</tr>
<tr>
<td>Stop steroid</td>
<td>Improves</td>
<td>Worsens</td>
</tr>
</tbody>
</table>
Seronegative Spondyloarthropathies

DIFFERENTIAL DIAGNOSIS OF OLIGOARThRITIS

★ RICE ★

RHEUMATOLOGIC (>6 weeks)

• SEROPositive ★ PSSR ★ Polymyositis, Palindromic rheumatism, SLE, Scleroderma, Rheumatoid arthritis

• SERONEgATIVE ★ PEAR ★ Psoriatic arthritis, Enteric arthritis, Ankylosing spondylitis, Reactive arthritis, undifferentiated

VASCULITIS 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 enteral 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, polyarthritis

CARDINAL FEATURES

DISTRIBUTION male preponderance, age 20-40

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

• INFECTION 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 ★ (Cell count with diff, Culture and Gram stain, Crystal)

DIAGNOSTIC ISSUES

EUROPEAN SPONDYLOARTHROPATHY STUDY GROUP CRITERIA one of inflammatory spinal pain or synovitis (asymmetric or predominantly in the lower limbs) plus one of positive family history, psoriasis, inflammatory bowel disease, urethritis/cervicitis/acute diarrhea (within 1 month prior to arthritis), alternating buttock pain, enthesopathy, sacroiliitis (sens 75%, spc 87%)
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, sacroilitis, 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  sacroilitis with more than minimum abnormality bilaterally or unequivocal abnormality unilaterally
  - DIAGNOSIS  one clinical plus one radiologic criterion = probable AS; three clinical criteria or one diagnostic 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, sacroilitis, 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), aphtous ulcers (Crohn's mainly), arthritis, erythema nodosum, pyoderma gangrenosum, DVT, and amyloidosis
- TREATMENTS
  - TYPE I ARTHROPATHY  acute, pauciarticular peripheral arthritis ± spondylitis and sacroilitis, 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, sacroilitis, morning stiffness, arthritis (distal DIP joints, asymmetric oligoarthritis of lower limbs, symmetric polyarthritis, arthritis mutilans), enthesitis (Achilles tendinitis, 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, sacroilitis, morning stiffness, lower limb arthritis (asymmetric oligoarthritis of lower limbs), and enthesitis (Achilles tendinitis, 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, uni lateral, photophobia, pain, redness, impaired vision)), bowel inflammation (acute enterocolitis, chronic ileocolitis), and cardiac abnormalities (aortic regurgitation, conduction abnormalities). Plain film reveals fluffy erosions, periostal 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%)

- TREATMENTS NSAIDs (pain control), sulfasalazine, anti TNF agents, methotrexate, azathioprine, leflunomide

Related Topics
Inflammatory Bowel Disease (p. 120)
Psoriasis (p. 362)

DIFFERENTIAL DIAGNOSIS

MECHANICAL
- TRAUMA sprain, straın, 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 (CONT’D)

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,

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

<table>
<thead>
<tr>
<th>Feature</th>
<th>Inflammatory</th>
<th>Mechanical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Older</td>
</tr>
<tr>
<td>Onset</td>
<td>Insidious</td>
<td>Abrupt</td>
</tr>
<tr>
<td>Duration</td>
<td>&gt;3 months</td>
<td>Shorter</td>
</tr>
<tr>
<td>AM stiffness</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Resting</td>
<td>Worsens</td>
<td>Improves</td>
</tr>
<tr>
<td>Activity</td>
<td>Improves</td>
<td>Worsens</td>
</tr>
<tr>
<td>Sacroiliac joints</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

MANAGEMENT

SYMPTOM CONTROL pain control
TREAT UNDERLYING CAUSE flexion and extension exercises

Back Pain

NEJM 2005 353:4
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 lumbo sacral 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 achinging 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 vertebral column 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

<table>
<thead>
<tr>
<th>Disc/Root</th>
<th>Pain</th>
<th>Sensory</th>
<th>Weakness</th>
<th>Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4 5 (C5)</td>
<td>Medial scapula, lateral upper arm</td>
<td>Shoulder</td>
<td>Deltoid, supraspinatus, infraspinatus</td>
<td>Supinator</td>
</tr>
<tr>
<td>C5 6 (C6)</td>
<td>Lateral forearm, thumb, and index finger</td>
<td>Thumb and index finger</td>
<td>Biceps, brachioradialis, wrist extension</td>
<td>Biceps</td>
</tr>
<tr>
<td>C6 7 (C7)</td>
<td>Medial scapula, posterior arm, dorsum of forearm, third finger</td>
<td>Posterior forearm, third finger</td>
<td>Triceps, wrist flexion, finger extension</td>
<td>Triceps</td>
</tr>
<tr>
<td>C7 1 (C8)</td>
<td>Shoulder, ulnar side of forearm, fifth finger</td>
<td>Fifth finger</td>
<td>Intrinsic hand muscles, thumb flexion, and abduction</td>
<td>None</td>
</tr>
<tr>
<td>L3 4 (L4)</td>
<td>Anterior thigh</td>
<td>Lateral leg to medial malleolus</td>
<td>Hip flexion, dorsiflexion, and inversion</td>
<td>Knee</td>
</tr>
<tr>
<td>L4 5 (L5)</td>
<td>Posterior lower limb</td>
<td>Lateral leg, dorsal foot including first web space</td>
<td>Hip extension and abduction, dorsiflexion, plantarflexion, and ankle eversion and inversion</td>
<td>None</td>
</tr>
<tr>
<td>L5 6 (L6)</td>
<td>Posterior lower limb, often to ankle</td>
<td>Posterior leg</td>
<td>Hip extension and abduction, dorsiflexion, plantarflexion, and ankle eversion</td>
<td>Ankle</td>
</tr>
<tr>
<td>S2 4</td>
<td>Sacral or buttock, radiate to posterior leg or perineum</td>
<td>Perineum (sacral paresthesia)</td>
<td>Bowel and bladder dysfunction</td>
<td>None</td>
</tr>
</tbody>
</table>

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

NEJM 2008 358:8
Osteoarthritis

**DIFFERENTIAL DIAGNOSIS**

**PRIMARY OSTEARTHRITIS**
- **GENERALIZED** primary generalized, diffuse idiopathic skeletal hyperostosis
- **ISOLATED** nodal, hips, erosive

**SECONDARY OSTEARTHRITIS**
- **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 OSTEARTHRITIS** age, female, obesity, high bone mass, mechanical factors (previous joint injury, excessive varus, or valgus), smoking, genetics

**CLINICAL FEATURES**

**SUBTYPES OF PRIMARY OSTEARTHRITIS**
- **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 ≥4 vertebrae. Also known as Forester disease. X rays are diagnostic. May mimic ankyllosing 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 OSTEARTHRITIS** 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**

- **HIP OSTEOARTHRITIS**
  - **ACR DIAGNOSTIC CRITERIA FOR HIP OSTEOARTHRITIS**
    - hand pain, aching, or stiffness and three or four of the following features (hard tissue enlargement of 2 or more of 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%

**MANAGEMENT**

**CONSERVATIVE MEASURES** patient education, weight reduction, exercise, physiotherapy, assistive devices

**SYMPTOM CONTROL** acetaminophen 325 650 mg PO q4 6h, 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, acu puncture, 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 OSTEARTHRITIS** 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 vertebral more commonly
- **ASSOCIATIONS** alcohol, steroids, sepsis, storage disease (Gaucher), sickle cell disease, emboli (fat, cholesterol), post radiation, trauma, idopathy, connective tissue disease (SLE, rheumatoid arthritis, vasculitis), cancer, hypercoagulable states
**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.

**Treatments**

---

**Fibromyalgia**

**Differential Diagnosis of Diffuse Body Pain**

<table>
<thead>
<tr>
<th>Differential Diagnosis</th>
<th>Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibromyalgia</td>
<td>Diffuse soft tissue pain, sleep disturbances, fatigue.</td>
<td>CBCD, lytes, urea, Cr, Ca, Mg, PO₄, ESR, TSH, CK</td>
</tr>
<tr>
<td>Myopathy</td>
<td></td>
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<tr>
<td>Metabolic (hypothyroidism), drug induced, myofascial pain syndrome (more localized)</td>
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<tr>
<td>Neuromyelitis</td>
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<tr>
<td>Multiple Sclerosis</td>
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<tr>
<td>Myofascial pain syndrome (more localized)</td>
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<tr>
<td>Psychiatric</td>
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<tr>
<td>Depression</td>
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</tbody>
</table>

**Pathophysiology**

Increased Pain Perception Associations:
- Irritable bowel syndrome, irritable bladder syndrome, chronic headaches, mood disorders (depression, anxiety), sleep disorders.

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**Clinical Features**

**Generalized Symptoms**
- Diffuse soft tissue pain, sleep disturbances, fatigue.

**Specific Tender Points**
- 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, PO₄, ESR, TSH, CK
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, multiple 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

SPECIFIC ENTITIES (CONT’D)

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 THROMBOANGITIS OBLITERANS  Buerger’s disease

VASCULITIS IMIMCS

- 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/polyangiitis, 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 meningococemia), iatrogenic (drugs)

- **CLINICAL FEATURES** bright to dark red purpuric papules/plaques

- **DIAGNOSIS** skin biopsy shows leukocytoclastic vasculitis

**WHEN TO SUSPECT VASCULITIS** multi system or ischemic vascular disease, palpable purpura, glomerulonephritis, mononeuritis multiplex, myalgia/arthralgia/arthritis, abdominal/testicular pain, unexplained constitutional symptoms. Greater likelihood of vasculitis if combination

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**DIAGNOSTIC ISSUES**

**DIAGNOSIS BY ORGAN INVOLVEMENT**

<table>
<thead>
<tr>
<th>Head (stroke, visual Δ)</th>
<th>Peripheral neuropathy</th>
<th>Lung (dyspnea, hemoptysis)</th>
<th>Kidneys (GN)</th>
<th>Abdomen (pain)</th>
<th>Skin (palpable purpura)</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takayasu aortitis</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Giant cell arteritis</td>
<td>+</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Microscopic polyangiitis</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>p-AnCA</td>
</tr>
<tr>
<td>Wegener’s granulomatosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Churg–Strauss syndrome</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henoch–Schonlein purpura</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Behcet’s disease</td>
<td>+</td>
<td></td>
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<tr>
<td>Cryoglobulinemia</td>
<td>+</td>
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<td>++</td>
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</tr>
</tbody>
</table>

++ 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/24 h monthly

**SECONDARY VASCULITIDES** treat underlying cause

**SPECIFIC ENTITIES (CONT’D)**

**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

**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
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. Extra cranial 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?

<table>
<thead>
<tr>
<th>History</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaw claudication</td>
<td>4.2</td>
<td>0.72</td>
</tr>
<tr>
<td>Diplopia</td>
<td>3.4</td>
<td>0.95</td>
</tr>
<tr>
<td>Temporal headache</td>
<td>1.5</td>
<td>0.82</td>
</tr>
<tr>
<td>Any headache</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Unilateral visual loss</td>
<td>0.85</td>
<td>1.2</td>
</tr>
<tr>
<td>Any visual symptom</td>
<td>1.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Vertigo</td>
<td>0.71</td>
<td>1.1</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.2</td>
<td>0.87</td>
</tr>
<tr>
<td>Weight loss</td>
<td>1.3</td>
<td>0.89</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.1</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.2</td>
<td>0.94</td>
</tr>
<tr>
<td>Fever</td>
<td>1.2</td>
<td>0.92</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0.93</td>
<td>1.1</td>
</tr>
<tr>
<td>Polymyalgia rheumatic</td>
<td>0.97</td>
<td>0.99</td>
</tr>
</tbody>
</table>

### 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   |
- Synovitis                                   | 0.41| 1.1 |
- Male gender                                 | 0.83| 1.1 |
- 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."
**SPECIFIC ENTITIES (CONT’D)**

**POLYARTERITIS NODOSA (PAN)**
- **PATHOPHYSIOLOGY** necrotizing vasculitis of med ium and small arteries with no glomerulonephritis. Associated with HIV, CMV, Parvovirus B19, HBV, HCV
- **CLINICAL FEATURES** mononeuritis multiplex (parti cularly the peroneal and tibial branches of sciatic nerve), orchitis, skin (palpable purpura, livedo reti cularis, subcutaneous nodules, distal gangrene), Gl (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 tender ness, mononeuropathy or polyneuropathy, dia stolic 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, arter iographic abnormality (aneurysms or occlusions of the visceral arteries, not due to arteriosclero sis, fibromuscular dysplasia, or other non inflam matory causes), biopsy of small or medium sized artery containing PMN. Need 3 of 10 criteria (sens 82%, spc 87%)
- **TREATMENTS** steroids, cyclophosphamide

**M ICROSCOPIC POLYANGIITIS (MPA)**
- **PATHOPHYSIOLOGY** necrotizing vasculitis of the small vessels. Frequent glomerulonephritis and lung involvement
- **CLINICAL FEATURES** renal (RPGN), pulmonary (hemoptysis, hemorrhage). Gl, skin, and neurologic symptoms as in PAN. p ANCA positive
- **TREATMENTS** steroids, cyclophosphamide

**WEGENER’S GRANULOMATOSIS**
- **PATHOPHYSIOLOGY** systemic vasculitis of the med ium 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 pro teinase 3)
- **CLINICAL FEATURES** ★ELKS★★ Ears and nose, Lungs, Kidneys, and Skin involvement
- **ACR DIAGNOSTIC CRITERIA** nasal or oral inflamma tion/ulcers, abnormal CXR (nodules, fixed infl trates, 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, metho trexate, rituximab

**SPECIFIC ENTITIES (CONT’D)**

**CHURG STRAUSS SYNDROME**
- **PATHOPHYSIOLOGY** systemic vasculitis of the med ium and small arteries, typically involving the lung and skin. Also vascular and extravascular granulo matosis with necrosis. Associated with asthma and p ANCA (autoantibodies against myeloperox idase), 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 infil trates (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, granulo cytes in walls of arterioles or venules on biopsy. Need two of four criteria (sens 87%, spc 88%)
- **TREATMENTS** usually resolves spontaneously. Con sider steroids (prednisone 85 mg PO daily, taper by 5 mg/week) for symptom control. Consider cyclo phosphamide plus high dose steroids if crescentic glomerulonephritis

**BEHÇET’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**

**ERYTHROCYTESEDIMENTATION 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)**
- **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
  - **HOMOGENEOUS** 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 Schönlein purpura
- **UTILITY** associated with lupus nephritis and disease activity in SLE and cryoglobulinemic vasculitis

**SCLERODERMA**

**ANTI SCL 70 (TOPOISOMERASE I)** (very specific)
- **DISORDERS** scleroderma (sens 20 30%, very spc)
- **UTILITY** associated with disease activity

**ANTICENTROMERE**
- **DISORDERS** CREST (sens 90%), idiopathic Raynaud’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 tRNA 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**

<table>
<thead>
<tr>
<th>Axis</th>
<th>Examination</th>
<th>ROM (Active and Passive)</th>
<th>Palpation (SWAT&lt;sup&gt;b&lt;/sup&gt;)</th>
<th>Special tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shoulder</strong></td>
<td>Winging of scapulae</td>
<td>Abduction (180°)</td>
<td>Clavicle, AC joint, coracoid process, acromion, spine of scapula, greater and lesser tuberosity of humerus, biceps tendon</td>
<td><strong>Initial abduction against resistance</strong> (supraspinatus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adduction (50°)</td>
<td></td>
<td><strong>External rotation against resistance</strong> (infraspinatus and teres minor)</td>
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<tr>
<td></td>
<td></td>
<td>Flexion (180°)</td>
<td></td>
<td><strong>Internal rotation against resistance</strong> (subscapularis)</td>
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<tr>
<td></td>
<td></td>
<td>Extension (60°)</td>
<td></td>
<td><strong>Relocation and anterior release tests</strong> (shoulder instability)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Internal rotation (90°)</td>
<td></td>
<td><strong>Biceps load I and II</strong> (labrum tear)</td>
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<tr>
<td></td>
<td></td>
<td>External rotation (90°)</td>
<td></td>
<td><strong>Biceps tendonitis</strong></td>
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<td></td>
<td>Also examine C-spine and upper limb (neurological testing)</td>
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<td></td>
<td><strong>Tinel’s test, Phalen’s test</strong> (carpel tunnel syndrome)</td>
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<td></td>
<td><strong>Finkelstein’s test</strong> (de Quervain’s tenosynovitis)</td>
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<td></td>
<td>Hand grip strength and function (write)</td>
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<td></td>
<td>Neurological testing of hand</td>
</tr>
<tr>
<td><strong>Hand and wrist</strong></td>
<td>Boutonniere, Swan neck, subluxation @ MCP, and wrist, ulnar deviation @ MCP, radial deviation @ carpus, rheumatoid nodules, Heberden’s and Bouchard’s nodes</td>
<td>Thumb flexion, extension, abduction, and adduction</td>
<td>Wrist</td>
<td><strong>FABER test</strong> (groin pain=hip joint, buttck pain=SI joint)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Finger flexion/extension</td>
<td>Carpal joints</td>
<td><strong>Thomas test</strong> (hip flexion contracture)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opposition</td>
<td>MCP joints</td>
<td><strong>Trendelenburg test</strong> (weakness of gluteus medius on standing side)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wrist flexion/extension</td>
<td>PIP joints</td>
<td><strong>Leg length discrepancy</strong> (true and false)</td>
</tr>
<tr>
<td></td>
<td>Lumbral lordosis</td>
<td>Abduction (50°)</td>
<td>ASIS</td>
<td><strong>Anterior drawer test, Lachman test, pivot shift</strong> (anterior cruciate ligament)</td>
</tr>
<tr>
<td></td>
<td>Gait&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Adduction (20°)</td>
<td>Iliac crest</td>
<td><strong>Posterior drawer test</strong> (posterior cruciate ligament)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Internal rotation (35°)</td>
<td>SI joint</td>
<td><strong>Collateral ligaments</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>External rotation (45°)</td>
<td>Greater trochanter</td>
<td><strong>McMurray test, medial–lateral grind test</strong> (meniscal)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flexion (120°)</td>
<td>Ischial tuberosity</td>
<td><strong>Anterior drawer test</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Extension (20–30°)</td>
<td></td>
<td><strong>Lateral/medial stability</strong></td>
</tr>
<tr>
<td><strong>Knee</strong></td>
<td>Varus</td>
<td>Flexion (135°)</td>
<td>Patella, tibial tuberosity</td>
<td><strong>Subtalar complex stability</strong></td>
</tr>
<tr>
<td></td>
<td>Valgus</td>
<td>Extension (10°)</td>
<td>Head of tibia/fibula</td>
<td><strong>Achilles tendon rupture</strong></td>
</tr>
<tr>
<td></td>
<td>Genu recurvatum</td>
<td>Eversion (10°)</td>
<td>Joint line tenderness</td>
<td><strong>Ankle and foot</strong></td>
</tr>
<tr>
<td></td>
<td>Baker cyst</td>
<td>Inversion (10°)</td>
<td>Femoral condyles</td>
<td><strong>Varus</strong></td>
</tr>
<tr>
<td></td>
<td>Gait&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>Bursas (suprapatellar, subpatellar, infrapatellar, anserine)</td>
<td><strong>Valgus</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bulge test, balloon test, patella tap</td>
<td><strong>Achilles tendon</strong></td>
</tr>
<tr>
<td><strong>Ankle and foot</strong></td>
<td>Varus</td>
<td>Dorsiflexion (20°)</td>
<td>Achilles tendon</td>
<td><strong>Malleolus</strong></td>
</tr>
<tr>
<td></td>
<td>Valgus</td>
<td>Plantarflexion (50°)</td>
<td>Malleolus</td>
<td><strong>Achilles tendon</strong></td>
</tr>
<tr>
<td></td>
<td>Achilles tendon</td>
<td>Subtalar joint inversion</td>
<td>Anterior talofibular ligament</td>
<td><strong>Lateral/medial stability</strong></td>
</tr>
<tr>
<td></td>
<td>Nails, bunion</td>
<td>and eversion (5°)</td>
<td>Deltoid ligament</td>
<td><strong>Subtalar complex stability</strong></td>
</tr>
<tr>
<td></td>
<td>Hallux valgus</td>
<td>Forefoot joints</td>
<td>Calcaneus</td>
<td><strong>Achilles tendon rupture</strong></td>
</tr>
<tr>
<td></td>
<td>Metatarsus varus</td>
<td>Joints of toes</td>
<td>Base of MTP</td>
<td><strong>Anterior drawer test</strong></td>
</tr>
<tr>
<td></td>
<td>Pes planus</td>
<td></td>
<td>Calcaneus</td>
<td><strong>Lateral/medial stability</strong></td>
</tr>
<tr>
<td></td>
<td>Shoes</td>
<td></td>
<td>Navicular</td>
<td><strong>Subtalar complex stability</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup> SEADS—Symmetry/swelling, Erythema, Atrophy, Deformity, and Surgeries/scars  
<sup>b</sup> SWAT—Swelling/synovitis, Warmth, Anatomic landmarks, Tenderness  
<sup>c</sup> 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.

**Clinical tests for shoulder instability**
- Relocation test applying pressure to shoulder anteriorly causes relief
  - Sens: 85%  
  - Spec: 87%  
  - LR+: 6.5
- Anterior release releasing anterior pressure causes pain
  - Sens: 92%  
  - Spec: 89%  
  - LR+: 8.3
- Apprehension test applying pressure to shoulder posteriorly causes pain
  - Sens: 88%  
  - Spec: 50%  
  - LR+: 1.8

**Clinical tests for labral tears**
- Biceps load I and II tests flexion of elbow against resistance causes pain
  - Sens: 83%  
  - Spec: 98%  
  - LR+: 29
- Pain provocation of Mimori passive movement from maximally supinated to pronated causes pain
  - Sens: 100%  
  - Spec: 90%  
  - LR+: 7.2
- Internal rotation resistance strength internal rotation against resistance causes pain
  - Sens: 88%  
  - Spec: 96%  
  - LR+: 25

**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?

**Clinical tests for anterior cruciate ligament tear**
- Anterior drawer test
  - LR+: 3.8
- Lachman test
  - LR+: 42
- Lateral pivot shift test
  - LR+: 25

**Clinical tests for posterior ligament tear**
- Composite assessment
  - LR+: 21

**Clinical tests for meniscal tear**
- McMurray test
  - LR+: 1.3
- Joint line tenderness
  - LR+: 0.9
- Joint effusion
  - LR+: 5.7
- Medial lateral grind
  - LR+: 4.8
- Apley apprehension test
  - LR+: 2.7

**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
Brain Tumors

**PATHOPHYSIOLOGY**

**CLASSIFICATION BY HISTOLOGY**
- **NEUROEPITHELIAL**
  - **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**
- **EPENDYMOMA** (2%)
- **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, plasma cytoma, 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** para ganglioma, 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 palsies, 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
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, bilir unib, 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 recur rence 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 OLIGODENDROGLIOMAS

<table>
<thead>
<tr>
<th>Oligodendrogloma</th>
<th>1p19q deletion</th>
<th>No 1p19q deletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>15 years</td>
<td>5 years</td>
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<tr>
<td>High grade</td>
<td>5 10 years</td>
<td>2 years</td>
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</tbody>
</table>

MANAGEMENT (CONT’D)

4 week break and then adjuvant temozolomide d1 5 q28d × 6

- 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  nitro soures, bevacizumab, etoposide, carboplatin, procarbazine

- EPENDYMOMA  resection ± radiation. Palliative chemotherapy may be provided with recurrence

- PRIMARY NEUROECTODERMAL TUMORS  (medulloblastoma, supratentorial, pineoblastoma) resection plus craniosinal radiation for low risk tumors may be curative. Add adjuvant chemotherapy (cisplatin, etoposide, cyclophospha mide 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 accumu lative 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 displace ment of the hemispheres, causing impaction of the diencephalon and midbrain into the tentorial notch → rostrocaudal deterioration with decorti cate 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, and melanoma, and primary unknown cancers. About 10x 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%

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

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

HEMMORRHAGIC 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 (cocaïne)

STROKE MIMICS  (usually global rather than focal neurological symptoms) ★DIMS★

- DRUG INTOXICATION
- INFECTIONS
- INSANITY  conversion disorder
- METABOLIC  hypoglycemia, renal failure, hepatic failure
- MIGRAINES
- SYCONE
- SEIZURES  Todd’s paralysis
- STRUCTURAL  trauma, tumors, subdural hemorrhage

PATHOPHYSIOLOGY (CONT’D)

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?

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 mid dle basilar artery, origin of vertebral arteries

2. SMALL VESSEL STROKE  (lacunar/penetrating vessels) most commonly due to lipohyalinotic occlusion related to hypertension and occasional atheroma at the origin of vessels. Found at penetrating branches of the anterior, middle, and posterior cerebral and basal 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

Acute Stroke Syndromes

NEJM 2007 357:6
NEJM 2008 359:13
AHA/ASA Stroke Guidelines 2009
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, hyper tension, family history, male, history of heart disease (valvular, AF, endocarditis)
- **ICH** hypertension, trauma, bleeding diatheses, illicit drugs, vascular malformations, blacks, Asians

**COMPLICATIONS OF 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

**PATHOPHYSIOLOGY (CONT’D)**

**SAH** illicit drugs, bleeding diatheses

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**
  - Age 1=age >60 years,
  - Blood pressure 1=hypertension at the acute evaluation >140/90 mmHg)
  - Clinical features 2=unilateral weakness, 1=speech disturbance without weakness
  - Duration of symptom 1=10-59 min, 2=>60 min
  - Diabetes 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
  - **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 Features (Cont’d)**

- **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

**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
- **MIDDLE CEREBRAL ARTERY** left dominant hemispheric, embolic >thrombotic) anosognosia, left motor and sensory deficit (face, arm >leg), left spatial neglect, left homonymous hemianopia, impaired left conjugate gaze

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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+

<table>
<thead>
<tr>
<th>Pre hospital assessment</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of any one of acute facial paresis, arm drift, or abnormal speech</td>
<td>5.5</td>
<td>0.39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>In hospital clinical assessment</th>
<th>LR+</th>
<th>Prob. stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal neurological deficit, persistent neurological deficit, acute onset during prior week, no history of head trauma</td>
<td>0.14</td>
<td>1.5% ≥10%</td>
</tr>
<tr>
<td>4 factors</td>
<td>40</td>
<td>80%</td>
</tr>
</tbody>
</table>

**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 hemianopia, 2=complete hemianopia, 3=bi lateral hemianopia), **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)
RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A CLINICALLY IMPORTANT CAROTID BRUIT?

<table>
<thead>
<tr>
<th>Sens</th>
<th>Spc</th>
<th>LR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>29%</td>
<td>88%</td>
<td>2.4</td>
</tr>
<tr>
<td>76%</td>
<td>76%</td>
<td>3.2</td>
</tr>
<tr>
<td>62%</td>
<td>61%</td>
<td>1.6</td>
</tr>
</tbody>
</table>

**ABILITY OF CAROTID BRUITS TO INDICATE CAROTID STENOSIS IN SYMPTOMATIC PATIENTS**

TIA patients with >50% stenosis

Anterior circulation TIA patients with 75-99% stenosis

Anterior circulation TIA patients with 70-99% stenosis

**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
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 second ary to postictal phenomenon, suspicion of SAH, acute MI/post MI pericarditis, persistent hyperten sion ≥185/110), **labs** (platelet <100 × 10^9/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 simi lar 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Primary prophylaxis</th>
<th>Secondary prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Anti HTN 20%</td>
<td>Anti HTN 28%</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Statins</td>
<td>Statins</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>ASA 20 30%</td>
<td>ASA 20 30%</td>
</tr>
<tr>
<td>Post MI</td>
<td>ASA 31%</td>
<td>ASA 30%</td>
</tr>
<tr>
<td>Post stroke</td>
<td>No needed if no previous stroke</td>
<td>Clopidogrel 43%</td>
</tr>
</tbody>
</table>

The percentages in this table represent relative risk reduction

CRITERIA FOR CAROTID ENDARTERECTOMY

<table>
<thead>
<tr>
<th>Carotid stenosis</th>
<th>Symptomatic</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70%</td>
<td>Yes (NNT 6.3)</td>
<td>Yes for men with stenosis ≥60% only (NNT 33)</td>
</tr>
<tr>
<td>50–69%</td>
<td>Yes for men only (NNT 22)</td>
<td>No</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Upper motor neuron</th>
<th>Lower motor neuron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspect</td>
<td>Atrophy after long term</td>
</tr>
<tr>
<td>Tone</td>
<td>Spasticity</td>
</tr>
<tr>
<td>Strength</td>
<td>Upper limbs flexors &gt;extensors pronation &gt;supination</td>
</tr>
<tr>
<td>Reflex</td>
<td>Increased with clonus</td>
</tr>
<tr>
<td>Pronator drift</td>
<td>Present</td>
</tr>
<tr>
<td>Lower limbs extensors &gt;flexors</td>
<td>Nerve root/peripheral nerve distribution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Upper motor neuron</th>
<th>Lower motor neuron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inspect</td>
<td>Atrophy and fasciculations</td>
</tr>
<tr>
<td>Tone</td>
<td>Flaccidity</td>
</tr>
<tr>
<td>Strength</td>
<td>Nerve root/peripheral nerve distribution</td>
</tr>
<tr>
<td>Reflex</td>
<td>Decreased</td>
</tr>
<tr>
<td>Pronator drift</td>
<td>Babinski upgoing</td>
</tr>
</tbody>
</table>

SPECIFIC ENTITIES (CONT’D)

- **APHASIA (LANGUAGE IMPAIRMENT)**
  - **TESTING PHRASES**
    - **COMPREHENSION WITHOUT REPLY** “Touch your chin, then your nose, then your ear”
    - **COMPREHENSION WITH ANSWERS** “Do you put your shoes on before your socks?”
    - **FLUENCY** “Describe your daily activities.”
    - **NAMING** “Name this object.” (e.g. pen)
    - **REPETITION** “No ifs, ands, or buts.”
**DISTINGUISHING FEATURES BETWEEN DIFFERENT TYPES OF APHASIA**

<table>
<thead>
<tr>
<th>Wernicke</th>
<th>Broca’s</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comprehension</td>
<td>No</td>
<td>Normal</td>
</tr>
<tr>
<td>Fluency</td>
<td>Normal</td>
<td>No</td>
</tr>
<tr>
<td>Naming</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Repetition</td>
<td>No</td>
<td>no</td>
</tr>
<tr>
<td>Others</td>
<td>Contralat. sensory/ motor Δ</td>
<td></td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Types of dysarthria</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic (hemispheric stroke cranial nerves LMN)</td>
<td>Harsh, strained voice Low pitch voice</td>
</tr>
<tr>
<td>Hyperkinetic (basal ganglia lesion)</td>
<td>Harsh, strained voice Low pitch voice</td>
</tr>
<tr>
<td>Hypokinetic (Parkinson’s)</td>
<td>Low volume</td>
</tr>
<tr>
<td>Ataxic (cerebellar lesion)</td>
<td>Explosive, scanning speech</td>
</tr>
<tr>
<td>Flaccid (cranial nerves VII, IX, X)</td>
<td>Breathy, nasal, low volume Wheezing</td>
</tr>
</tbody>
</table>

**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
- **SNOT Reflex**: gentle pressure over the nasal philtrum results in puckering of lips
- **GLABELLAR TAP REFLEX**: repeated tapping forehead produces persistent blinking

---

**Cranial Nerve Examination**

<table>
<thead>
<tr>
<th>CN</th>
<th>Nucleus location</th>
<th>Skull exit</th>
<th>Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Olfactory tract</td>
<td>Cribriform plate</td>
<td>Sensory smell (coffee, vanilla, peppermint)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensory visual acuity and color, visual fields, blind spot, fundoscopy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reflex pupillary reflex (afferent)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Motor ptosis and eye deviated downward and outward. Poor medial elevation and accommodation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reflex pupillary reflex (afferent)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parasympathetic pupillary dilation</td>
</tr>
<tr>
<td>II</td>
<td>Thalamus</td>
<td>Optic foramen</td>
<td>Motor patient tilts head to contralateral side, vertical diplopia worst looking to one side and down</td>
</tr>
<tr>
<td>III</td>
<td>Midbrain</td>
<td>Superior orbital fissure</td>
<td>Sensory light touch, pain and temperature over V1, V2 and V3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Motor wasting of temporal and masseter muscles, weakness of jaw movement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reflex corneal reflex (afferent) and jaw jerk (afferent and efferent)</td>
</tr>
<tr>
<td>IV</td>
<td>Midbrain</td>
<td>Superior orbital fissure</td>
<td>Motor crossed eyes, impaired lateral gaze</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sensory numbness around the ear canal and altered taste (anterior 2/3 of tongue)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Motor difficulty raising eye brows, closing eyes, frowning, blowing out cheeks and showing teeth. Altered speech (‘Pa Pa Pa’) and hyperacusis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reflex corneal reflex (afferent)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Parasympathetic lacrimation and saliva production</td>
</tr>
<tr>
<td>V</td>
<td>Principal Pons</td>
<td>V1 superior orbital fissure</td>
<td>Motor crossed eyes, impaired lateral gaze</td>
</tr>
<tr>
<td></td>
<td>Spinal Medulla</td>
<td>V2 foramen rotundum</td>
<td>Sensory numbness around the ear canal and altered taste (anterior 2/3 of tongue)</td>
</tr>
<tr>
<td></td>
<td>Mesencephalic Pons/ midbrain</td>
<td>V3 foramen ovale</td>
<td>Motor difficulty raising eye brows, closing eyes, frowning, blowing out cheeks and showing teeth. Altered speech (’Pa Pa Pa’) and hyperacusis</td>
</tr>
<tr>
<td></td>
<td>Motor Pons</td>
<td>Superior orbital fissure</td>
<td>Motor crossed eyes, impaired lateral gaze</td>
</tr>
<tr>
<td>VI</td>
<td>Pons</td>
<td>Motor internal acoustic meatus and stylomastoid foramen</td>
<td>Sensory numbness around the ear canal and altered taste (anterior 2/3 of tongue)</td>
</tr>
<tr>
<td>VIIa</td>
<td>Motor, solitary, superior salivatory Pons</td>
<td>Taste stylomastoid foramen</td>
<td>Motor difficulty raising eye brows, closing eyes, frowning, blowing out cheeks and showing teeth. Altered speech (’Pa Pa Pa’) and hyperacusis</td>
</tr>
</tbody>
</table>

---

**SPECIFIC ENTITIES (CONT’D)**

<table>
<thead>
<tr>
<th>Types of dysarthria</th>
<th>Quality</th>
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<tr>
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</tr>
<tr>
<td>Flaccid (cranial nerves VII, IX, X)</td>
<td>Breathy, nasal, low volume Wheezing</td>
</tr>
<tr>
<td>CN</td>
<td>Nucleus location</td>
</tr>
<tr>
<td>----</td>
<td>------------------</td>
</tr>
<tr>
<td>VII</td>
<td>Vestibular, cochlear medulla</td>
</tr>
<tr>
<td>IX</td>
<td>Nucleus ambiguous, inferior salivatory, solitary medulla</td>
</tr>
<tr>
<td>X</td>
<td>Nucleus ambiguous, dorsal motor vagal, solitary medulla</td>
</tr>
<tr>
<td>XI</td>
<td>Nucleus ambiguous medulla</td>
</tr>
<tr>
<td>XII</td>
<td>Medulla</td>
</tr>
</tbody>
</table>

---

**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

**CAVERNOUS SINUS LESIONS** (tumor, aneurysm, and thrombosis) may lead to III, IV, V1 and VI palsies

**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)

**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)

**FACIAL (VII) NERVE LESIONS** for details on localization, please refer to p. 307

---

**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 quadrantanopia and eventually complete bitemporal hemianopia
- **HOMONYMOUS HEMIANOPIA** lesion is located post optic chiasm
- **FORMAL VISUAL FIELD TESTING** Goldman perimeter

**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)
### Distinguishing Features Between Papilledema, Optic Atrophy, and Optic Neuritis

<table>
<thead>
<tr>
<th></th>
<th>Papilledema</th>
<th>Optic atrophy</th>
<th>Optic neuritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>↑ ICP</td>
<td>Neuritis</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>Tumors</td>
<td>Glaucoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Congenital</td>
<td></td>
</tr>
<tr>
<td><strong>Symp</strong></td>
<td>Headaches</td>
<td>↓ vision</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N&amp;V, ↓ level of consciousness</td>
<td>↓ color</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Focal deficits</td>
<td>Eye pain</td>
<td></td>
</tr>
<tr>
<td><strong>Optic disc</strong></td>
<td>Swollen optic disc</td>
<td>Gray white optic disc</td>
<td>Swollen optic disc</td>
</tr>
<tr>
<td></td>
<td>Disc margins obscured</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other signs</strong></td>
<td>Flame hemorrhages</td>
<td>↓ acuity</td>
<td>↓ acuity</td>
</tr>
<tr>
<td></td>
<td>Cotton wool spots</td>
<td>↓ color vision</td>
<td>↓ color vision</td>
</tr>
<tr>
<td></td>
<td>↑ blind spot</td>
<td>↓ pupil reflex</td>
<td>↓ pupil reflex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑ blind spot</td>
<td></td>
</tr>
</tbody>
</table>

### Medullary Syndromes

<table>
<thead>
<tr>
<th></th>
<th>Medial (Dejerine syndrome)</th>
<th>Lateral (Wallenberg syndrome)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Artery supply</strong></td>
<td>Anterior spinal artery</td>
<td>Posterior inferior cerebellar artery</td>
</tr>
<tr>
<td><strong>Cranial nerve (ipsilateral)</strong></td>
<td>XII</td>
<td>V ↓ facial sens.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VIII nystagmus, vertigo, nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IX, X dysphagia, hoarseness, altered taste</td>
</tr>
<tr>
<td><strong>Motor (contralateral)</strong></td>
<td>UMN weakness</td>
<td>None</td>
</tr>
<tr>
<td><strong>Sensory (contralateral)</strong></td>
<td>↓ vibration, proprioception</td>
<td>↓ pain and temperature</td>
</tr>
<tr>
<td><strong>Cerebellum (ipsilateral)</strong></td>
<td>Normal</td>
<td>Affected</td>
</tr>
</tbody>
</table>

### 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

### 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)

### Pathophysiology

#### Extraocular Eye Movements

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Nerve</th>
<th>Movement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior rectus</td>
<td>III</td>
<td>Upward</td>
</tr>
<tr>
<td>Inferior rectus</td>
<td>III</td>
<td>Downward</td>
</tr>
<tr>
<td>Lateral rectus</td>
<td>VI</td>
<td>Lateral</td>
</tr>
<tr>
<td>Medial rectus</td>
<td>III</td>
<td>Medial</td>
</tr>
<tr>
<td>Superior oblique</td>
<td>IV</td>
<td>Downward medial</td>
</tr>
<tr>
<td>Inferior oblique</td>
<td>III</td>
<td>Upward medial</td>
</tr>
</tbody>
</table>

### Specific Entities (Cont'd)
## 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

### 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

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### DISTINGUISHING FEATURES BETWEEN UPPER AND LOWER MOTOR NEURON FACIAL NERVE LESIONS

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Central (stroke)</th>
<th>Peripheral (Bell’s palsy)</th>
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<tbody>
<tr>
<td>Upper facial muscles</td>
<td>Contralateral cortex or corticobulbar fibers</td>
<td>Ipsilateral facial nerve nucleus or facial nerve</td>
</tr>
<tr>
<td>Lower facial muscles</td>
<td>Unable to show teeth</td>
<td>Unable to show teeth</td>
</tr>
<tr>
<td>Salivation, taste, and lacrimation</td>
<td>Normal</td>
<td>Varies depending on lesion location*</td>
</tr>
<tr>
<td>Other findings</td>
<td>Hemiplegia (same side as palsy)</td>
<td>Hyperacusis</td>
</tr>
</tbody>
</table>

* 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 Guiltain 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 optica, combination of optic neuritis and cervical myelopathy, acute disseminated encephalomyelitis, SLE, PAN, Sjogren’s, Behçet’s disease, granulomatosis angitis, 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, adrenomyeloneuropathy
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 (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 pseudopenesthesia (loss of sensory feedback from arm causing involuntary writhing movements of fingers and wrist when eyes closed)
TONE spasms spells (maybe painful), spontaneous clonus
MOTOR weakness, spasticity, and hyperreflexia. Upper motor neuron weakness in lower extremities characteristic of multiple sclerosis
AUTONOMIC bladder, bowel, and erectile dysfunction
CEREBELLAR loss of balance, action tremor, slurred speech, and incoordination
COGNITIVE inattention, slowed information processing, memory loss, and difficulties with abstract concepts and complex reasoning
FATIGUE, DEPRESSION

INVESTIGATIONS
BASIC
• LABS CBC, ltes, urea, Cr, Ca, Mg, PO₄, CK, quantitative Ig, ANA, ENA
• IMAGING MRI head/spine (sens 90%)
• LUMBAR PUNCTURE with CSF IgG index and oligoclonal bands (mild lymphocytosis <50/mm³, mild ↑ protein with ≥2 oligoclonal bands)

SPECIAL
• EVOKED POTENTIAL STUDIES

DIAGNOSTIC AND PROGNOSTIC ISSUES
DIAGNOSTIC CRITERIA 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 Avonex (interferon β 1a 30 µg IM weekly), Betaseron.

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.

MANAGEMENT (CONT’D) (interferon β 1b 250 µg SC q2days), Copaxone (glatiramer acetate 20 mg SC daily), Rebif (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

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)

• 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

NEJM 2008 359:2
PATHOPHYSIOLOGY

TERMS
- SIMPLE conscious
- COMPLEX impaired consciousness
- PARTIAL part of cortex
- GENERALIZED bilateral cortex, unconscious
- CLONIC jerky contractions, rhythmic
- TONIC muscle stiffening
- EPILEPSY ≥ 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

EPILEPSY
- 2 unprovoked seizures
- STATUS EPILEPTICUS > 30 min of seizures

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
- Past history Seizures, head injury, stroke, tumor
- Pre event Awake or sleep
- No warning
- Aura
- Event Vocalization at onset
- Tonic clonic convulsions
- Cyanotic/gray
- Incontinence frequent
- Tongue biting (side)
- Frequent injuries (fall on face, #, dislocations)
- Longer ↓ level of consciousness
- Post event Confused, tired, sleepy
- Muscle ache

Vasovagal syncope
- No strong history
- Usually upright
- Usually warning
- Lightheaded
- No vocalization
- Occasionally clonic movements, hypotonia
- Pale
- Incontinence occasionally
- Tongue biting rare (tip)
- Less commonly injured
- Short ↓ level of consciousness
- Alert
- Diaphoretic

INVESTIGATIONS

BASIC
- LABS CBCD, lytes, urea, Cr, glucose, Ca, Mg, PO₄, 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 Ja kob disease
- PROGNOSTIC useful for anoxic brain injury (burst suppression, alpha coma, and electrocerebral silence suggests very poor prognosis)

MANAGEMENT

STATUS EPILEPTICUS ABC, O₂, IV, stat investigations (ABG, CBCD, lytes, Cr, glucose, Mg, Ca, PO₄, 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, multivitamin 1 tab IV/PO daily)

LONG TERM MANAGEMENT valproic acid 200–500 mg or 10–15 mg/kg PO daily, increase by 250–500 mg/week, typical daily dose is 750–2000 mg; lamotrigine 25 mg PO daily, increase by 25–50 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 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 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 reinstating driver’s license (varies with jurisdiction). Some places may also restrict driving for 6 months after antiepileptic dose adjustments. More stringent rules may exist for commercial drivers

TREATMENT ISSUES (CONT’D)

recurrence after first seizure is 30–60%. Risk after second seizure is 80–90%

ANTEPIELECTIC CHOICES

- BROAD-SPECTRUM ANTEPIELECTIC DRUGS in decreasing order of efficacy, include valproic acid, lamo trigine, topiramate, levetiracetam, and zonisamide. These antiepileptic medications represent reasonable first line therapy for most seizure types

- NARROW-SPECTRUM ANTEPIELECTIC 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

<table>
<thead>
<tr>
<th>P</th>
<th>C</th>
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<td>Myoclonic</td>
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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 ANTEPIELEPTICS 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

★ SYNCOPE ★

- Micturition, defecation, coughing, laughing

VASOVAGAL

- Painful, emotional stimulus, head turning

NEUROGENIC

- Vestibular stroke, seizures, autonomic insufficiency

CARDIOGENIC

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

VALVULAR

- Aortic stenosis, mitral stenosis, pulmonary embolism

PERICARDIAL

- Tamponade

MYOCARDIAL

- Myocardial infarction, hypertrophic cardiomyopathy

ORTHOSTATIC

PHYSIOGENIC

ETC

- Drugs

INVESTIGATIONS (CONT’D)

SPECIAL

- EEG if suspect seizures

- STRESS TEST

- TILT TABLE TEST to confirm vasovagal syncope

MANAGEMENT

ACUTE

ABC, O₂, 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 the 5 risk factors: CHESS

- C: HF history, H: Hct <30, E: ECG abnormality, S: SBP <90 mmHg, or S: Shortness 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 (spec 90%), implantable loop recorders

TREATMENTS

- Lie down if pre syncope, adequate fluids and salt intake, SSRI (paroxetine 20 mg PO daily), vasoconstrictor (midodrine 2.5–10 mg PO TID), permanent cardiac pacing if recurrent.

NEJM 2005 352:10

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

NEUROGENIC ORTHOSTATIC HYPOTENSION

PATHOPHYSIOLOGY

- Standing leads to pooling of blood (500–1000 mL) in legs → decreased venous return
Migraine Headaches

**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

**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

**DIAGNOSIS**

SBP drop of \( \geq 20 \text{ mmHg} \) or DBP drop of \( \geq 10 \text{ mmHg} \) 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

**Related Topics**

Arrhythmia (p. 39)
Dizziness (p. 315)
Falls (p. 382)
Stroke (p. 299)
Valvular Heart Disease (p. 47)

**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**

Pulsating, duration of 4–72 hours, Unilateral, Nausea, Disabling (LR+ 24 if 4 criteria, LR+ 3.5 if 3 criteria, LR+ 0.41 if \( \leq 2 \) criteria)

<table>
<thead>
<tr>
<th>LR+</th>
<th>LR</th>
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<tr>
<td>Chronic headache features suggestive of serious intracranial abnormality requiring neuroimaging</td>
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<tr>
<td>Cluster type headache</td>
<td>11</td>
</tr>
<tr>
<td>Abnormal findings on neurologic examination</td>
<td>5.3</td>
</tr>
<tr>
<td>Undefined headache</td>
<td>3.8</td>
</tr>
<tr>
<td>Headache with aura</td>
<td>3.2</td>
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<tr>
<td>Headache aggravated by exertion or a Valsalva like maneuver</td>
<td>2.3</td>
</tr>
<tr>
<td>Headache with vomiting</td>
<td>1.8</td>
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</tbody>
</table>

**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)**

**ALARMS SYMPTOMS** (suggesting secondary causes) “thunderclap headache,” progressive headache over days to months, new onset after age 40, precipitated by Valsalva maneuver or exertion, noc turnal 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. Char acterizes 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** CBC, Cr, ESR (temporal arteritis), INR, PTT
- **IMAGING** CT head, MRI head

**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 (CONT’D)**

**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.

**HYPNOCHE 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 child bearing age → headache worse upon awakening and with change of position, associated with transient visual changes, papilledema and sometimes sixth nerve palsy.

**DIAGNOSIS** MRI/MRV (to exclude other causes such as cerebral vein thrombosis), lumbar puncture with ↑ opening pressure (>250 mmHg)

**TREATMENTS** weight loss, NSAIDs for pain, furosemide, acetazolamide 250 mg PO QID, lumbar puncture, toneal 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 lopontine angle tumor, cerebellar hemorrhage, subclavian steal
- **Peripheral**
  - benign positional vertigo (30%), acute labyrinthitis/vestibular neuritis (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?**

<table>
<thead>
<tr>
<th></th>
<th>PPV</th>
<th>NPV</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive head hanging maneuver plus either vertigo or vomiting predict peripheral vertigo</td>
<td>85%</td>
<td>68%</td>
<td>7.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Absence of vertigo or age &gt;69 or presence of neurological deficit predict serious causes of dizziness</td>
<td>40%</td>
<td>88%</td>
<td>1.5</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**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,

**Clinical Features (Cont’d)**

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

<table>
<thead>
<tr>
<th></th>
<th>Central</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>More gradual</td>
<td>More sudden</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Purely horizontal, vertical, rotational</td>
<td>Usually horizontal and rotational</td>
</tr>
<tr>
<td></td>
<td>Not inhibited by fixation onto object</td>
<td>Inhibited by fixation of eyes onto object</td>
</tr>
<tr>
<td></td>
<td>Persists for a longer period</td>
<td>Shorter duration</td>
</tr>
<tr>
<td>N&amp;V</td>
<td>Varies</td>
<td>More severe</td>
</tr>
<tr>
<td>Others</td>
<td>Severe imbalance</td>
<td>Tullio’s phenomenon (nystagmus and vertigo caused by loud noises at a particular frequency)</td>
</tr>
<tr>
<td></td>
<td>Other non auditory cranial nerve symptoms usually present</td>
<td>Tinnitus, hearing loss</td>
</tr>
</tbody>
</table>

#### 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.

### MANAGEMENT

**SYMPTOM CONTROL**
- Benzodiazepines (diazepam 2–10 mg IV), anticholinergic (meclizine 25 mg PO q8 12h, diphenhydramine 25–50 mg q6 8h, 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 some times 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)

#### 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 neuritis secondary to viral infection
- **CLINICAL FEATURES** vertigo (typically days, sporadically) that may be precipitated by change in position (labyrinthitis) or spontaneous (vestibular neuritis), severe N&V
Hearing Impairment

DIFFERENTIAL DIAGNOSIS

SENSORINEURAL (inner ear to cortex) CVA, presbycusis, multiple sclerosis, Meniere’s disease, trauma (noise exposure, barotraumas, pene trating trauma), tumor (acoustic neuroma, menin gioma), infectious (viral cochleitis, meningitis, syphilis), congenital (viral infections, malforma tions, hereditary hearing loss), iatrogenic (5 FU, bleomycin, nitrogen mustard, erythromycin, vanco mycin, tetracycline, aminoglycoside, ASA, otologic surgery), autoimmune, thyrotoxicosis

CONDUCTIVE

• MIDDLE EAR trauma ( tympanic membrane per foration, temporal bone trauma), tumor (choles teatoma, otosclerosis, glomus tumors), infec tious (otitis media), congenital ( congenital atresia, ossicular chain malformation)

• OUTER EAR trauma (canal), tumor ( squamous cell cancer, exostosis, osteoma), infectious (external otitis), congenital ( congenital micro tia, atresia), others (cerumen, psoriasis)

MIXED conductive and sensorineural hearing loss

CLINICAL FEATURES

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE HEARING IMPAIRMENT?

<table>
<thead>
<tr>
<th></th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>2.5</td>
<td>0.13</td>
</tr>
<tr>
<td>Asking patients whether they have hearing impairment</td>
<td>3.8</td>
<td>0.38</td>
</tr>
<tr>
<td>Hearing handicap inventory for the elderly (screening version) score of ≥8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Weber</th>
<th>Rinne</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductive loss</td>
<td>Good ear</td>
<td>Quieter</td>
</tr>
<tr>
<td>Bad ear</td>
<td>Louder</td>
<td>BC &gt; AC</td>
</tr>
<tr>
<td>Sensorineural loss</td>
<td>Good ear</td>
<td>Louder</td>
</tr>
<tr>
<td>Bad ear</td>
<td>Quieter</td>
<td>AC &gt; BC</td>
</tr>
</tbody>
</table>

NOTE: AC=air conduction, BC=bone conduction

WEBER TEST 256 Hz tuning fork on bridge of fore head. 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 unilat
eral), Horner’s syndrome (usually unilateral), myasthe
nia gravis (bilateral or unilateral), botulism (usually
bilateral), myotonic dystrophy (usually bilateral)

PATHOPHYSIOLOGY

ANTIBODY AGAINST POST SYNAPTIC ACETYLCHOL
LINE RECEPTOR  leads to decreased neurotransmis
sion and muscle weakness (ocular, bulbar, and skeletal)
ASSOCIATIONS  thymic diseases (hyperplasia, thy
moma, 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 differ
ential 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),

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE MYASTHENIA GRAVIS?

<table>
<thead>
<tr>
<th></th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Food in mouth after swallowing</td>
<td>13.0</td>
<td>0.70</td>
</tr>
<tr>
<td>Speech becoming unintelligible during prolonged speaking</td>
<td>4.5</td>
<td>0.61</td>
</tr>
<tr>
<td>Physical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peek sign</td>
<td>30</td>
<td>0.88</td>
</tr>
<tr>
<td>Ice test</td>
<td>24</td>
<td>0.16</td>
</tr>
<tr>
<td>Sleep test</td>
<td>53</td>
<td>0.01</td>
</tr>
<tr>
<td>Special tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edrophonium test</td>
<td>15</td>
<td>0.11</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>Horner’s syndrome</th>
<th>Third nerve palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptosis</td>
<td>Partial. Never complete</td>
<td>Partial or complete</td>
</tr>
<tr>
<td>Pupil size</td>
<td>Constricted</td>
<td>Dilated</td>
</tr>
<tr>
<td>Pupil asymmetry</td>
<td>Worse in darkness</td>
<td>Worse in light</td>
</tr>
<tr>
<td>Pupil reflex</td>
<td>Normal</td>
<td>Sluggish or absent</td>
</tr>
<tr>
<td>Others</td>
<td>Anhydrosis</td>
<td>Affected eye downward and outward</td>
</tr>
<tr>
<td></td>
<td>Enophthalmos</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Absent ciliospinal reflex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterochromia</td>
<td></td>
</tr>
</tbody>
</table>
INVESTIGATIONS

BASIC
- LABS  TSH, ANA, RF
- IMAGING CT chest (thymoma, malignancy), CT/ MR head (if third nerve palsy)

SPECIAL
- EDROPHONIUM/TENSILON TEST  injection of acetyl cholinesterase inhibitor, improvement may be detected in 30 s and lasts <5 min
- ANTIBODIES  anti acetylcholine receptor anti body (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. Thyrectomy (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 morn ing 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

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)

<table>
<thead>
<tr>
<th>Cerebellar ataxia</th>
<th>Tabes dorsalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Sensory Δ</td>
</tr>
<tr>
<td>Speech Δ</td>
<td>Bowel/bladder Δ</td>
</tr>
<tr>
<td>Incoordination</td>
<td>Impotence, pain</td>
</tr>
<tr>
<td>Gait difficulties</td>
<td>Dementia if neurosyphilis</td>
</tr>
<tr>
<td>Inspection</td>
<td>Argyll Robertson pupils</td>
</tr>
<tr>
<td>Normal cognition</td>
<td>Optic atrophy</td>
</tr>
<tr>
<td>Ataxic speech</td>
<td></td>
</tr>
<tr>
<td>H&amp;N</td>
<td>Normal tone</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Heel shin test</td>
</tr>
<tr>
<td>Scanning speech</td>
<td>Absent reflexes (Westphal’s sign)</td>
</tr>
<tr>
<td>Explosive speech</td>
<td>Extensor plantar</td>
</tr>
<tr>
<td>Motor</td>
<td>Hypotonia, dysmetria, dysdiadochokinesia, heel shin test, pendular reflexes</td>
</tr>
</tbody>
</table>
Distinguishing Features Between Cerebellar Disorder and Tabes Dorsalis (see p. 244)

<table>
<thead>
<tr>
<th>Cerebellar ataxia</th>
<th>Tabes dorsalis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Vibration and proprioception</td>
</tr>
<tr>
<td>Gait</td>
<td>Slap foot gait</td>
</tr>
<tr>
<td>Truncal ataxia</td>
<td>Wide based gait</td>
</tr>
<tr>
<td>Wide based gait</td>
<td>Positive with eyes closed only</td>
</tr>
<tr>
<td>Romberg</td>
<td>Positive with eyes closed and open</td>
</tr>
</tbody>
</table>

HISTORY characterize ataxia (truncal or limb, ting, 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. Ballism is large amplitude, proximal chorea, e.g. Huntington’s chorea
- Pseudathetosis: 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 Hyperkplexia, Stiff-Person Syndrome: continuous isometric contractions of somatic muscles

Pathophysiology

Parkinsonism ✔ Trap ✔ any 2 of Tremor, Rigidity, Akinesia/bradykinesia, and Postural instability.
Parkinson’s disease is primary or idiopathic parkinsonism. Secondary or acquired parkinsonism may be due to head trauma, cerebrovascular disease, drugs, or hydrocephalus.

**PATHOPHYSIOLOGY (CONT’D)**

**PARKINSONISM PLUS SYNDROMES** progressive supranuclear palsy, multiple system atrophy, Lewy body dementia, cortico basal ganglia degeneration

**CLINICAL FEATURES**

**PHYSICAL EXAMINATION FOR PARKINSON’S DISEASE**
- resting tremor (4-6/s), rigidity, bradykinesia, 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.

**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?**

<table>
<thead>
<tr>
<th>History</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>1.3</td>
<td>0.24 0.60</td>
</tr>
<tr>
<td>Rigidity</td>
<td>1.3</td>
<td>0.12 0.93</td>
</tr>
<tr>
<td>Difficulty rising from chair</td>
<td>1.9</td>
<td>0.39 0.58</td>
</tr>
<tr>
<td>Loss of balance</td>
<td>1.6</td>
<td>0.29 0.35</td>
</tr>
<tr>
<td>Shuffling gait</td>
<td>3.3</td>
<td>0.32 0.50</td>
</tr>
<tr>
<td>Difficulty opening jars</td>
<td>6.1</td>
<td>0.26</td>
</tr>
<tr>
<td>Difficulty turning in bed</td>
<td>13</td>
<td>0.56</td>
</tr>
<tr>
<td>Micrographia</td>
<td>2.8</td>
<td>0.30 0.44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>1.3</td>
<td>0.47 0.61</td>
</tr>
<tr>
<td>Rigidity</td>
<td>0.5</td>
<td>0.38 1.6</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>0.4</td>
<td>1.67 3.7</td>
</tr>
<tr>
<td>Heel to toe difficulties</td>
<td>2.9</td>
<td>0.32</td>
</tr>
<tr>
<td>Glabellar tap</td>
<td>4.5</td>
<td>0.13</td>
</tr>
</tbody>
</table>

**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**

<table>
<thead>
<tr>
<th>Tremor</th>
<th>Parkinson</th>
<th>Essential</th>
<th>Cerebellar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hertz</td>
<td>4 6</td>
<td>5 9</td>
<td>3 5</td>
</tr>
<tr>
<td>Head direction</td>
<td>Up down (“yes”)</td>
<td>Side to side (“no”)</td>
<td>None</td>
</tr>
<tr>
<td>Legs involved</td>
<td>Yes</td>
<td>Rare</td>
<td>Yes</td>
</tr>
<tr>
<td>Effect of alcohol</td>
<td>No change</td>
<td>Improved</td>
<td>No change</td>
</tr>
</tbody>
</table>

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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, 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 (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 (mid stance), heel off (lift off), toes off (swing)

- **GAIT MOVEMENTS** comment on pace length, width, coordination, and stability (see table below for specific pathologies)

- **NEUROLOGICAL EXAMINATION** lower limb motor and sensory examination. Also include Romberg test

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic gait</td>
<td>Upper motor neuron lesion (stroke)</td>
</tr>
<tr>
<td>Scissor gait</td>
<td>Bilateral upper motor neuron disease</td>
</tr>
<tr>
<td>Apraxic/magnetic gait</td>
<td>Frontal lobe (NPH, stroke)</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shuffling gait</td>
<td>Extrapyramidal lesion (Parkinson’s)</td>
</tr>
<tr>
<td>Broad based gait</td>
<td>Cerebellar vermis</td>
</tr>
<tr>
<td>Ataxic gait</td>
<td>Cerebellar anterior (alcohol)</td>
</tr>
<tr>
<td>Unsteady, sensory ataxia gait</td>
<td>Posterior column (Tabes dorsalis, B12 deficiency, Friedreich’s ataxia)</td>
</tr>
<tr>
<td>Trendelenburg gait (waddling)</td>
<td>Hip adductor muscle weakness (gluteus medius)</td>
</tr>
<tr>
<td>Steppage gait</td>
<td>Foot drop (peroneal nerve palsy)</td>
</tr>
</tbody>
</table>

### Related Topics
- Dementia (p. 378)
- Orthostatic Hypotension (p. 312)

### Pathophysiology

**Foraminal Encroachment of the Spinal Nerve**  
usually due to a combination of decreased disc height and degenerative changes of the unco vertebrae 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 (Cont’d)

**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, unrelenting 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

### Pathology

**Shuffling Gait**  
Extrapyramidal lesion (Parkinson’s)

**Broad Based Gait**  
Cerebellar vermis

**Ataxic Gait**  
Cerebellar anterior (alcohol)

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Posterior column (Tabes dorsalis, B12 deficiency, Friedreich’s ataxia)

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Hip adductor muscle weakness (gluteus medius)

**Steppage Gait**  
Foot drop (peroneal nerve palsy)

### Pathomorphology

**Pathophysiology**

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### Clinical Features

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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, unrelenting night pain, previous cancer, immunosuppression, and IDU) which may suggest tumor or infections

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**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
<table>
<thead>
<tr>
<th>Root</th>
<th>Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3,4,5</td>
<td>Diaphragm</td>
</tr>
<tr>
<td>C5</td>
<td>Deltoid (shoulder abduction)</td>
</tr>
<tr>
<td>C6</td>
<td>Biceps and brachioradialis (elbow flexion), radial wrist extensors (wrist extension)</td>
</tr>
<tr>
<td>C7</td>
<td>Triceps (elbow extension), ulnar wrist extensors (wrist extension), wrist flexors, finger extensors</td>
</tr>
<tr>
<td>C8</td>
<td>Intrinsic muscles of hand</td>
</tr>
<tr>
<td>T1</td>
<td>Intrinsic muscles of hand</td>
</tr>
<tr>
<td>T2 12</td>
<td>Chest wall and abdominal muscles</td>
</tr>
<tr>
<td>L2</td>
<td>Iliopsoas (hip flexion)</td>
</tr>
<tr>
<td>L3</td>
<td>Quadriceps (knee extension), adductor longus (hip adduction)</td>
</tr>
<tr>
<td>L4</td>
<td>Quadriceps (knee extension), tibialis anterior (dorsiflexion and inversion)</td>
</tr>
</tbody>
</table>

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### MYOTOMES (CONT'D)

<table>
<thead>
<tr>
<th>Root</th>
<th>Muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>L5</td>
<td>Extensor hallucis longus (big toe extension), tibialis posterior (plantarflexion and eversion), gluteus medius (hip abduction)</td>
</tr>
<tr>
<td>S1</td>
<td>Gluteus maximus (hip extension), gastrocnemius, soleus, peroneus longus (plantar flexors, eversion)</td>
</tr>
<tr>
<td>S2,3,4</td>
<td>Bowel, bladder, sexual organs, anal other pelvic muscles</td>
</tr>
</tbody>
</table>

### BRACHIAL PLEXUS

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Root/origin</th>
<th>Muscle function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal scapular</td>
<td>C5/root level</td>
<td>Rhomboids (retracts scapula)</td>
</tr>
<tr>
<td>Long thoracic</td>
<td>C567/root</td>
<td>Serratus anterior (scapula abduction)</td>
</tr>
<tr>
<td>Suprascapular</td>
<td>C56</td>
<td>Supraspinatus (arm abduction)</td>
</tr>
<tr>
<td>Lateral anterior</td>
<td>C67</td>
<td>Infraspinatus (arm external rotation)</td>
</tr>
<tr>
<td>Medial anterior thoracic</td>
<td>C8</td>
<td>Pectoralis major (arm adduction, internal rotation)</td>
</tr>
<tr>
<td>Subscapular</td>
<td>C56</td>
<td>Pectoralis minor (protracts scapula)</td>
</tr>
<tr>
<td>Thoracodorsal</td>
<td>C78</td>
<td>Latissimus dorsi (arm extension, adduction, internal rotation)</td>
</tr>
<tr>
<td>Axillary</td>
<td>C5</td>
<td>Deltoid (arm abduction)</td>
</tr>
<tr>
<td>Musculo cutaneous</td>
<td>C56</td>
<td>Teres major (arm extension, ext. rotation)</td>
</tr>
<tr>
<td>Median</td>
<td>C567T1</td>
<td>Brachioradialis (supination)</td>
</tr>
<tr>
<td>Radial</td>
<td>C67</td>
<td>See tables below</td>
</tr>
<tr>
<td>Ulnar</td>
<td>C8T1</td>
<td>See tables below</td>
</tr>
</tbody>
</table>

### MUSCLE NERVE FUNCTION CORRELATION

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Innervation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibialis anterior</td>
<td>Deep peroneal n. (L4L5S1)</td>
<td>Inversion, dorsiflexion</td>
</tr>
<tr>
<td>Tibialis posterior</td>
<td>Tibial n. (L4L5)</td>
<td>Inversion, planterflexion</td>
</tr>
<tr>
<td>Peroneus longus</td>
<td>Superficial peroneal n. (L5S1)</td>
<td>Eversion, planterflexion</td>
</tr>
<tr>
<td>Peroneus brevis</td>
<td>Superficial peroneal n. (L5S1)</td>
<td>Eversion, planterflexion</td>
</tr>
</tbody>
</table>

### DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS

<table>
<thead>
<tr>
<th>C6 VS. MEDIAN NERVE LESION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensory</strong></td>
</tr>
<tr>
<td>C6</td>
</tr>
<tr>
<td>Sensory surface of 1st 2nd fingers Lateral surface of arm/forearm</td>
</tr>
</tbody>
</table>

*LOAF* Lateral lumbricals (1st and 2nd), Opponens pollicis (opposition), Abductor pollicis brevis (abduction of thumb), Flexor pollicis brevis (flexion of thumb/fingers)
## DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT’D)

### C7 VS. RADIAL NERVE LESION

<table>
<thead>
<tr>
<th></th>
<th>Radial nerve (C5, T1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensory</strong></td>
<td>Dorsal surface of 1&lt;sup&gt;st&lt;/sup&gt; lateral 4&lt;sup&gt;th&lt;/sup&gt; fingers</td>
</tr>
<tr>
<td></td>
<td>Dorsal surface of arm/forearm</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td>Triceps (normal if high lesion)</td>
</tr>
<tr>
<td></td>
<td>Wrist extensors</td>
</tr>
<tr>
<td><strong>Reflex</strong></td>
<td>Triceps</td>
</tr>
</tbody>
</table>

| **Sensory**| Palmer surface of 3<sup>rd</sup> finger                                                |
|            | Dorsal surface of arm/forearm                                                          |
| **Motor**  | Wrist extensors and flexors                                                           |
|            | Finger and thumb extensors                                                            |
| **Reflex** | Triceps                                                                               |

### C8/T1 VS. ULNAR NERVE LESION

<table>
<thead>
<tr>
<th></th>
<th>Ulnar nerve (C8T1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensory</strong></td>
<td>Palmar and sometimes dorsal surface of 4&lt;sup&gt;th&lt;/sup&gt; and 5&lt;sup&gt;th&lt;/sup&gt; fingers</td>
</tr>
<tr>
<td></td>
<td>Medial surface of arm and forearm</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td>Lumbricals (3&lt;sup&gt;rd&lt;/sup&gt;, 4&lt;sup&gt;th&lt;/sup&gt;), interossei</td>
</tr>
<tr>
<td></td>
<td>5&lt;sup&gt;th&lt;/sup&gt; finger opposition, abduction, and flexion.</td>
</tr>
<tr>
<td></td>
<td>Thumb adductor</td>
</tr>
<tr>
<td><strong>Reflex</strong></td>
<td>Triceps (radial n.)</td>
</tr>
</tbody>
</table>

| **Sensory**| LOAF muscles (median n.)                                                               |
|            | Wrist flexion and abduction                                                           |
| **Motor**  | Lumbricals (3<sup>rd</sup>, 4<sup>th</sup>), interossei                               |
|            | 5<sup>th</sup> finger opposition, abduction and flexion.                              |
|            | Thumb adductor                                                                        |
| **Reflex** | Triceps                                                                               |

### L3 VS. OBTURATOR NERVE LESION

<table>
<thead>
<tr>
<th></th>
<th>Obturator nerve (L34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensory</strong></td>
<td>Medial thigh/knee</td>
</tr>
<tr>
<td></td>
<td>Hip adduction</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td>Hip adduction</td>
</tr>
<tr>
<td><strong>Reflex</strong></td>
<td>Adductor</td>
</tr>
</tbody>
</table>

| **Sensory**| Thigh/knee and medial leg                                                             |
| **Motor**  | Hip adduction                                                                         |
| **Reflex** | Knee, adductor                                                                        |

### L4 VS. FEMORAL NERVE LESION

<table>
<thead>
<tr>
<th></th>
<th>Femoral nerve (L234)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensory</strong></td>
<td>Lateral leg to medial malleolus</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td>Knee extension</td>
</tr>
<tr>
<td><strong>Reflex</strong></td>
<td>Knee</td>
</tr>
</tbody>
</table>

| **Sensory**| Dorsiflexion (deep peroneal n.)                                                        |
| **Motor**  | Dorsiflexion and eversion                                                               |
|            | Great toe dorsiflexion                                                                  |
| **Reflex** | Knee                                                                                   |

### L5 VS. PERONEAL NERVE LESION

<table>
<thead>
<tr>
<th></th>
<th>Common peroneal n. (L45S1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensory</strong></td>
<td>Lateral leg, dorsal foot including first web space</td>
</tr>
<tr>
<td><strong>Motor</strong></td>
<td>Dorsiflexion (deep peroneal n.) and eversion</td>
</tr>
<tr>
<td></td>
<td>(superficial peroneal n.)</td>
</tr>
<tr>
<td></td>
<td>Great toe dorsiflexion</td>
</tr>
</tbody>
</table>

| **Sensory**| Lateral leg, dorsal foot including first web space                                     |
| **Motor**  | Dorsiflexion and eversion                                                               |
|            | Great toe dorsiflexion                                                                  |
| **Reflex** | Kneeflexion                                                                            |
DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT’D)

**S1 VS. SCIATIC NERVE LESION**

<table>
<thead>
<tr>
<th>S1</th>
<th>Sciatic nerve (L4 S3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Lateral foot including 5th toe</td>
</tr>
<tr>
<td>Motor</td>
<td>Plantarflexion</td>
</tr>
<tr>
<td>Reflex</td>
<td>Ankle</td>
</tr>
</tbody>
</table>

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).

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Abductor pollicis brevis</th>
<th>1st dorsal interosseous</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 radiculopathy</td>
<td>Weak</td>
<td>Weak</td>
</tr>
<tr>
<td>Median nerve</td>
<td>Weak</td>
<td>Spared</td>
</tr>
<tr>
<td>Ulnar nerve</td>
<td>Spared</td>
<td>Weak</td>
</tr>
</tbody>
</table>

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

- **DEMELINATING** Guillain Barre, neoplastic (carcinoma, lymphoma, MGUS IgM), drugs (taxanes), chronic inflammatory demyelinating polyradiculoneuropathy

**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

**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)
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)

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

<table>
<thead>
<tr>
<th>History</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic/probable Katz diagram</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Age &gt;40</td>
<td>1.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Nocturnal paresthesia</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Bilateral symptoms</td>
<td>1.4</td>
<td>0.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypalgesia (↓ pain sensation) in the median nerve territory</td>
<td>3.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Abnormal vibration</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Weak thumb abduction strength</td>
<td>1.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Thenar atrophy</td>
<td>1.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Square wrist sign</td>
<td>2.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Closed fist sign</td>
<td>7.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Flick sign</td>
<td>21.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Tinel’s sign</td>
<td>1.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Phalen’s sign</td>
<td>1.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Vitals</th>
<th>Sympathetic dysfunction</th>
<th>Parasympathetic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Orthostatic hypotension</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Skin</td>
<td>Warm and moist</td>
<td>Cool and dry</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>H&amp;N</th>
<th>Sympathetic dysfunction</th>
<th>Parasympathetic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horner’s</td>
<td>Dry eyes + mouth</td>
<td>Dilated pupil</td>
</tr>
<tr>
<td>Heart</td>
<td>No respiratory variation</td>
<td>Constipation</td>
</tr>
<tr>
<td>GI/GU</td>
<td>Distended bladder</td>
<td>Impotence</td>
</tr>
<tr>
<td>MSK, gait</td>
<td>Postural instability</td>
<td></td>
</tr>
</tbody>
</table>

Related Topics
Diabetic neuropathy (p. 337)
Radiculopathy (p. 323)
GUILLAIN-BARRE SYNDROME (GBS)

- **PATHOPHYSIOLOGY** precipitants (*Campylobacter jejuni*, upper 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 cmH₂O, maximum expiratory pressure <40 cmH₂O, 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)
<table>
<thead>
<tr>
<th>MONONEUROPATHIES</th>
<th>Pathophysiology</th>
<th>Signs and symptoms</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axi ary nerve (C5–6)</td>
<td>Lesion usually near shoulder joint. Affects deltoid and teres minor.</td>
<td>Motor: weakness of shoulder abduction, shoulder atrophy. Sensory: deficit similar to C5 lesion.</td>
<td>Saturday night palsy (acute compression) is frequent cause. Cheiralgia paresthetica (entrapment of superficial branch of radial nerve to dorsum of hand).</td>
</tr>
<tr>
<td>Ulnar nerve (C8–T1)</td>
<td>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.</td>
<td>Motor: weakness of finger adduction, abduction and thumb adduction (Froment’s sign), claw-hand and interosseous atrophy. Sensory: changes in both dorsal and palmar surfaces of 4th and 5th fingers. May have pain over median proximal forearm (cubital tunnel). Tests: Tinel sign positive.</td>
<td>Cycist’s palsy.</td>
</tr>
<tr>
<td>Nerve (origin)</td>
<td>Pathophysiology</td>
<td>Signs and symptoms</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------</td>
<td>---------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Anterior interosseous branch of median nerve (C7–T1)</td>
<td>Lesion usually just below the elbow. Affects long flexors of thumb and index and middle fingers.</td>
<td>Motor: weakness of pinch, pain in voluntary forearm. Sensory: intact.</td>
<td></td>
</tr>
<tr>
<td>Femoral nerve (L2–4)</td>
<td>Lesion usually proximal to inguinal ligament. Affects iliopsoas (hip flexor) and quadriceps femoris (knee extensor).</td>
<td>Motor: bucking of knee, absent knee jerk, weak anterior thigh muscles with atrophy. Obturator nerve (hip adduction) not affected. Sensory: changes in anterior leg to medial thigh.</td>
<td></td>
</tr>
<tr>
<td>Tibial nerve (L5–S2)</td>
<td>Lesion usually at tarsal tunnel or near medial malleolus. Affects calf muscles (proximal), toe flexor, and other intrinsic foot muscles.</td>
<td>Motor: weak toe flexors. Sensory: pain and numbness of sole.</td>
<td>Tarsal tunnel syndrome.</td>
</tr>
</tbody>
</table>
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)

**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/multifocal neuropathy), 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**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>no contraction</td>
</tr>
<tr>
<td>1</td>
<td>flicker</td>
</tr>
<tr>
<td>2</td>
<td>possible only with gravity eliminated</td>
</tr>
<tr>
<td>3</td>
<td>against gravity only</td>
</tr>
<tr>
<td>4</td>
<td>power decreased but muscle contraction possible against resistance</td>
</tr>
<tr>
<td>5</td>
<td>normal power resistance</td>
</tr>
</tbody>
</table>

**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** CBC, lytes, urea, Cr, Ca, Mg, PO4, CK, aldolase, LDH, AST, ALT, ANA, ANCA, HBV/HBC serology, cryoglobulin, RF, TSH

Related Topics
- Critical Illness Weakness (p. 89)
- Dermatomyositis (p. 279)
- Eaton Lambert Syndrome (p. 319)
- Myasthenia Gravis (p. 318)
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

AMYOTROPHIC LATERAL SCLEROSIS (ALS)
- PATHOPHYSIOLOGY combined upper and lower motor neuronal degeneration → spread to involve multiple myotomes in multiple regions (bulbar, cervical, and lumbarosacral). 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, intra cerebral), 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 (sub acute 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 (crecent like), especially along the edges of the intracranial cavity

BONE AND AIR SPACES  check for fractures in bone window and fluid in sinuses
SKIN AND SUBCUTANEOUS TISSUES check for swelling of extracranial soft tissues in subdural window.

HEAD CT FINDINGS IN THE ELDERLY

SMALL VESSEL DISEASE diffuse brain atrophy, hypodense periventricular white matter due to gliosis, and lacunar infarcts within the basal ganglia.

LARGER VENTRICLES AND SUBARACHNOID SPACES due to brain atrophy.

FOCAL CALCIFICATION common within the basal ganglia in the elderly and should not be confused with hemorrhage.

HEAD CT FINDINGS IN STROKE

LOCALIZATION the presenting symptoms can help focus evaluation. The majority of infarcts involve the MCA territory or subcortical region. Early signs of infarction include the following:

- **HYPERDENSE MCA** the suspected MCA must be significantly denser than the contralateral MCA or basilar artery.
- **EDEMA OF THE BASAL GANGLIA AND/OR INSULAR CORTEX** involved lentiform nucleus will appear hypodense with indistinct lateral border. The insular cortex will appear swollen compared to the contralateral side.
- **SULCAL EFFACEMENT** the sulci along the cerebral convexity on the involved side will appear smaller than the other side.

EVOLUTION hypodense lesions may not appear until after 24 h. MRI is superior to CT for identifying acute stroke. Lesions may become more hypodense over time. Old infarcts are very black.
# Endocrinology

## Section Editor: Dr. Laurie Mereu

### Diabetes Mellitus

**Canadian Diabetes Association Guidelines 2008**

## Classification

<table>
<thead>
<tr>
<th>Type of Diabetes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1 Diabetes</td>
<td>Autoimmune destruction of β cells, prone to DKA</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td>Insulin resistance and a relative or absolute insulin deficiency</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>Glucose intolerance diagnosed during pregnancy</td>
</tr>
</tbody>
</table>

### 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, pancreatocystic duct dilation
- **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 2-4x higher risk of 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

### Reasons Why Blood Sugar Fluctuates
- **Lifestyle**
  - Diet (quantity/quality, timing), exercise
- **Blood Sugar Testing**
  - Accuracy, timing
- **Neuropathy**
  - Hypoglycemic unawareness, gastroparesis
- **Illness**
  - Infections, stress
- **Insulin**
  - Injection site, technique, dose
- **Decreased Insulin Requirement**
  - Renal failure, Addison’s
- **Medications**
  - Interactions
- **Other Endocrine Causes of Hyperglycemia**
  - Cushings, 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,
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 stalkig 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

**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, O₂, 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 DSW. 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 euvoletic 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 HCO₃ over 1-2 h. If pH 6.9 7.0, giving HCO₃ is optional. If pH >7.0, giving HCO₃ is not necessary

**DIAGNOSTIC ISSUES**

**DIAGNOSTIC CRITERIA FOR DIABETES**

<table>
<thead>
<tr>
<th></th>
<th>Fasting BS</th>
<th>GTT (75 g, 2hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;5.6 mmol/L</td>
<td>&lt;7.8 mmol/L</td>
</tr>
<tr>
<td>Impaired Fasting</td>
<td>5.6-6.9 mmol/L</td>
<td>[100-125 mg/dL]</td>
</tr>
<tr>
<td>Impaired Glucose</td>
<td>7.8-11.0 mmol/L</td>
<td>&lt;11.1 mmol/L</td>
</tr>
<tr>
<td>Diabetic*</td>
<td>≥7.0 mmol/L</td>
<td>≥11.1 mmol/L</td>
</tr>
<tr>
<td>GTT=glucose tolerance test</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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

**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)
**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, lites, 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)**

**ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS**  
(CONT’D)

**SPECIFIC ENTITIES**

**NON KETOTIC HYPEROSMOLAR HYPERGLYCEMIA**

- **PATHOPHYSIOLOGY** occurs in patients with type 2 diabetes
- **CLINICAL FEATURES** characterized by profound dehydration, increased osmolal 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.

**LONG TERM MANAGEMENT**

- **RISK REDUCTION ★ ABCDEFG★

  - **ASA/ACE INHIBITOR** ASA 81 mg PO daily for sec ondary prevention, controversial for primary pre vention. 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. Con sider fibrates (↑ triglycerides, ↑ HDL), HMG CoA

**SPECIFIC ENTITIES (CONT’D)**

**NON KETOTIC HYPEROSMOLAR HYPERGLYCEMIA**

<table>
<thead>
<tr>
<th>Hydration</th>
<th>1 NS (i.e. 15–20 mL/kg/h)</th>
<th>500 mL/h NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV #1</td>
<td>Use 1/2NS if corrected Na &gt;145 mmol/L (for every 10 mmol/L [182 mg/dL] ↑ in blood glucose, correct Na by 1 mmol/L)</td>
<td>500 mL/h NS</td>
</tr>
<tr>
<td>IV #2</td>
<td>Mix 25 units reg insulin in 250 mL DW (1 unit=10 mL)</td>
<td>250 mL/h NS</td>
</tr>
</tbody>
</table>

**SPECIFIC ENTITIES**

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Bolus 0.1 units/kg regular IV insulin (e.g. 7 units for 70 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Then 0.1 unit/kg initially followed bolus (e.g. 5–10 units/h)</td>
</tr>
<tr>
<td></td>
<td>Hold for 2 h if hypotensive or K &lt;3.5 mEq/L.</td>
</tr>
<tr>
<td>Target</td>
<td>glucose &lt;15 mM [&lt;270 mg/dL] increases risk of cerebral edema (mostly in children)</td>
</tr>
</tbody>
</table>

**Glucose**

<table>
<thead>
<tr>
<th>mM</th>
<th>mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt;90</td>
</tr>
<tr>
<td>1–5</td>
<td>91–180</td>
</tr>
<tr>
<td>6–10</td>
<td>181–270</td>
</tr>
<tr>
<td>11–15</td>
<td>271–360</td>
</tr>
<tr>
<td>16–20</td>
<td>361–437</td>
</tr>
<tr>
<td>&gt;20</td>
<td>&gt;438</td>
</tr>
</tbody>
</table>

**Potassium**

<table>
<thead>
<tr>
<th>Serum potassium</th>
<th>&lt;3 mEq/L, give 40 mEq/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium replace</td>
<td>3–4 mEq/L, give 30 mEq/h</td>
</tr>
<tr>
<td></td>
<td>4–5 mEq/L, give 20 mEq/h</td>
</tr>
<tr>
<td></td>
<td>5–6 mEq/L, give 10 mEq/h</td>
</tr>
</tbody>
</table>

**Laboratory**

| Baseline: glucose, β-OH butyurate, ABG, urinalysis, CBCD, electrolytes, Cr, PO4, Mg, ±lase, CK, cultures, toponin, ECG | Glucose (C/S), lites (VBG) |
|                                                            | ABGs if pH <7.0 |
|                                                            | Glucose (C/S) hourly, lites (VBG), PO4 |
|                                                            | ABGs if pH <7.0 |
|                                                            | lites q4–8h |

**Alkaline replacement**

| Rarely indicated unless severe acidosis (pH <6.8) with inop in circulatory collapse |
| Dose 50–100 mEq, NaHCO3 in 1/2NS over 30–60 mins |
| Extra potassium may be needed in bicarbonate therapy |

**Phosphate replacement**

| Consider if serum phosphorus <0.85 mmol/L [<2.0 mg/dL] and give if serum phosphorus <0.35 mmol/L [<1.1 mg/dL] |
| 2.6–8 mEq/L (9–25 mmol/L) [11 mmol of phosphate + 31 mg of elemental phosphorus] |
| (e.g. 10 mL of KPO4 in 1 L NaCl over 6 h) |

**General measures**

| Make flow sheet (ABG’s, glucose, lites, bicarb, AG, CO2, urine output), q1h vials |
| Foley to uromerter f 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
LONG TERM MANAGEMENT (CONT’D)

- **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 post prandial 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. Gastroparesis (sensitizes tissues to insulin, ↓ hepatic glucose production) pioglitazone 15–45 mg PO daily; adverse effects include glucose absorption) acarbose 25–100 mg TID ac meals; adverse effects include bloating and diarrhea.

- **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, Buproprion 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, had 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.
  - **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 0.5–4.0 mg PO TID ac meals; adverse effects include hypoglycemia.

**SULFONYLUREA** (↑ pancreatic insulin release) gliptin 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, pro motes 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**

### 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 Leve mir. 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 Leve mir

### 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 bed time basal insulin would have to be decreased. If the 3 AM glucose is high, then increase the bed time 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 sup per insulin R dose

### TYPES OF INSULIN

<table>
<thead>
<tr>
<th>Insulin type/action</th>
<th>Trade names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting (clear)</td>
<td>Humalog (insulin lispro)</td>
</tr>
<tr>
<td>Onset: 10-15 min</td>
<td>Humulin R</td>
</tr>
<tr>
<td>Peak: 1.5 h</td>
<td>\</td>
</tr>
<tr>
<td>Duration: 3-5 h</td>
<td>\</td>
</tr>
<tr>
<td>Short acting (clear)</td>
<td>\</td>
</tr>
<tr>
<td>Onset: 30 min</td>
<td>\</td>
</tr>
<tr>
<td>Peak: 2-3 h</td>
<td>\</td>
</tr>
<tr>
<td>Duration: 6.5 h</td>
<td>\</td>
</tr>
<tr>
<td>Intermediate acting (cloudy)</td>
<td>Humulin N</td>
</tr>
<tr>
<td>Onset: 1-3 h</td>
<td>\</td>
</tr>
<tr>
<td>Peak: 5-8 h</td>
<td>\</td>
</tr>
<tr>
<td>Duration: up to 18 h</td>
<td>\</td>
</tr>
<tr>
<td>Long acting basal insulin analogues (clear)</td>
<td>Insulin detemir (Lememir)</td>
</tr>
<tr>
<td>Onset: 90 min</td>
<td>\</td>
</tr>
<tr>
<td>Duration: up to 24 h</td>
<td>\</td>
</tr>
<tr>
<td>Premixed</td>
<td>Humulin 30/70</td>
</tr>
<tr>
<td>Premixed regular insulin</td>
<td>Novolin 40/60</td>
</tr>
<tr>
<td>NPH (cloudy)</td>
<td>Humalog Mix 25</td>
</tr>
<tr>
<td>Premixed insulin analogues (cloudy)</td>
<td>\</td>
</tr>
</tbody>
</table>

**Canadian Diabetes Association Guidelines 2008**
SAMPLE SLIDING SCALE TEMPLATE

**INSULIN SLIDING SCALE**

Glucose meter QID with insulin SC QID

<table>
<thead>
<tr>
<th>Blood sugar</th>
<th>Regular or rapid insulin SC TID ac meals</th>
<th>NPH or basal insulin SC qhs</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4</td>
<td>give juice, call MD</td>
<td>give juice, call MD</td>
</tr>
<tr>
<td>4.1–6</td>
<td>Individualized</td>
<td>Individualized</td>
</tr>
<tr>
<td>6.1–8</td>
<td>dosing</td>
<td>dosing</td>
</tr>
<tr>
<td>8.1–10</td>
<td>Individualized</td>
<td></td>
</tr>
<tr>
<td>10.1–12</td>
<td>dosing</td>
<td></td>
</tr>
<tr>
<td>12.1–16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16.1–18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.1–20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;20</td>
<td>Notify MD</td>
<td>Notify MD</td>
</tr>
</tbody>
</table>

**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

**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 ultra sound, 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 carotenemia), carpal 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 (CONT’D)

<table>
<thead>
<tr>
<th>TSH</th>
<th>fT4</th>
<th>fT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sick euthyroid syndrome</td>
<td>N/↑/↓</td>
<td>N/↓</td>
</tr>
<tr>
<td>Secondary or tertiary hypothyroidism, nephrotic syndrome, anticonvulsants (phenytoin, carbamazepine), and some sick euthyroid syndrome</td>
<td>N</td>
<td>↓</td>
</tr>
</tbody>
</table>

MANAGEMENT

MYXEDEMA COMA ABC, O\(_2\), IV. Levotyroxine 200 500 \(\mu\)g IV, then 100 \(\mu\)g 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 \(\mu\)g PO daily (1.6 \(\mu\)g/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 \(\mu\)g daily and titrate up by 25 \(\mu\)g/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

INTERPRETATION

Subclinical hypothyroidism  ↑ N N
Primary hypothyroidism  ↑ ↓ ↓
Secondary hypothyroidism  ↓ ↓ ↓

Related Topic
Hypothyroidism in Pregnancy (p. 414)
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 similiar 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 over production 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 pleuropericardial 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 orbit. 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

Classification of Graves’ Ophthalmopathy

<table>
<thead>
<tr>
<th>Class</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms or signs</td>
</tr>
<tr>
<td>I</td>
<td>Only symptoms of ocular irritation (dryness, grittiness)</td>
</tr>
<tr>
<td>II</td>
<td>Soft tissue involved (peri orbital edema)</td>
</tr>
<tr>
<td>III</td>
<td>Proptosis</td>
</tr>
<tr>
<td>IV</td>
<td>Extraocular muscle involved (ophthalmoplegia)</td>
</tr>
<tr>
<td>V</td>
<td>Corneal involvement</td>
</tr>
<tr>
<td>VI</td>
<td>Sight loss</td>
</tr>
</tbody>
</table>

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, ALT 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

<table>
<thead>
<tr>
<th></th>
<th>TSH</th>
<th>fT4</th>
<th>fT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subclinical hyperthyroidism</td>
<td>↓</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Primary hyperthyroidism</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>T3 thyrotoxicosis</td>
<td>↓</td>
<td>N</td>
<td>↑</td>
</tr>
<tr>
<td>Secondary hyperthyroidism</td>
<td>↑/N</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

MANAGEMENT

THYROID STORM ABC, O2, IV. **Propylthiouracil** 1000 mg PO/NG stat, then 300 mg PO q6h. **Lodine 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 I131 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

Solitary Thyroid Nodule

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

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, phe nothiazines, 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 (CONT’D)

**affect hormone production in this order**: ↓ GH, ↓ LH and FSH, ↓ TSH, ↓ ACTH, and ↑ Prolactin

**PRLACTINOMA IN** ♀ infertility, oligomenorrhea, galactorrhea

**PRLACTINOMA IN** ♂ erectile dysfunction, infertility

**FSH/LH ADENOMA** asymptomatic/mass effect

INVESTIGATIONS

**BASIC** 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)

**DIFFERENTIAL DIAGNOSIS OF HYPERPROLACTINEMIA**

**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

**MACROADENOMA (>1 cm [0.4in])** should investigate anterior pituitary function (IGF 1, LH, FSH, TSH, ACTH, prolactin, AM cortisol, free T4, estrogen, pro gesterone, AM testosterone), and formal visual field testing

**PHYSIOLOGIC** pregnancy, exercise, stress

**TUMORS** pituitary (prolactinoma, other functional tumors [acromegaly], non functional tumor with stalk compression), non pituitary

**DRUGS** metoclopramide, domperidone, phe nothiazines, butyrophenones, risperidone, MAOI, TCA, SSRI, verapamil, estrogen, narcotics

**OTHERS** hypothyroidism (↑ TRH), chronic kidney disease

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**CLINICAL FEATURES**

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**DIFFERENTIAL DIAGNOSIS OF HYPERPROLACTINEMIA**

**PHYSIOLOGIC** pregnancy, exercise, stress

**TUMORS** pituitary (prolactinoma, other functional tumors [acromegaly], non functional tumor with stalk compression), non pituitary

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**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
MANAGEMENT

PROLACTINOMA dopamine agonists (bromocriptine 2.5 mg PO daily, cabergoline 0.25 mg PO 2/week). Transsphenoidal resection (only if visual field compromise). Indications for treatment of prolactinoma include infertility, galactorrhea, hypogonadism and macroadenoma

ACROMEALY 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

ANTEOR 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

ACROMEALY

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 hemianopia, 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).

NEJM 2006 355:24

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)

PSYCHOFIC 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)

Adrenal Incidentaloma

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

NEJM 2007 356:6

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, hyper tensive retinopathy, moon face, plethora, acne, hirsutism, supravacular and dorsocervical fat pad, supravacular 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, lysates 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 metaiodobenzyl guanidine 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 wash out ≥50% at 10 min
- PHEOCHROMOCYTOMA cystic, hemorrhagic, variable size, may be bilateral, high enhanced attenuation
DIAGNOSTIC ISSUES (CONT'D)

- ADRENOCORTICAL CARCINOMA irregular, heterogenous 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%

Adrenal Insufficiency

DIFFERENTIAL DIAGNOSIS

PRIMARY (Addison’s disease)

- AUTOIMMUNE
- INFECTIONS TB, histoplasmosis, coccidioidomycosis, AIDS
- HEMORRHAGE anticoagulants, sepsis (Water house Friderichen syndrome, associated with meningococcemia), trauma, antcardiolipin antibodies
- INFLITRATION cancer, sarcoidosis, amyloidosis

SECONDARY (↓ ACTH secretion) exogenous glu
corticoid therapy, pituitary or hypothalamus tumor, infarction, infection, infiltration, irradiation

-DISTINGUISHING FEATURES BETWEEN PRIMARY
ADRENAL INSUFFICIENCY

<table>
<thead>
<tr>
<th>Addison’s disease</th>
<th>Secondary adrenal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>↑</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>↓ Na, ↑ K</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Hyper pigmentation</td>
</tr>
<tr>
<td>Adrenal hormones affected</td>
<td>Cortisol, DHEA</td>
</tr>
</tbody>
</table>

- SPECIFIC ENTITIES (CONT'D)

- 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)

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, con sider medical therapy (spironolactone 12.5 mg PO BID or amiloride 5 10 mg PO daily)

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)
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 cosyn tropin 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 cosyn tropin 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, O2, IV. Fluids (DNS 2 3L IV bolus). Corticosteroid (hydrocortisone

Differential Diagnosis

IATROGENIC (↑ ACTH)
PITUITARY (↑ ACTH) Cushing’s disease
ECTOPIC (↑ ACTH) small cell lung cancer
ADRENAL (↓ ACTH) adenoma, carcinoma

Clinic Features

SIGNs AND SYMPTOMs OF CUSHING’S SYNDROME
• NEUROLOGICAL euphoria, depression, psychosis, restlessness, irritability, insomnia
• OPHTHALMATIC 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

MANAGEMENT (CONT’D)

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 anesthesia) 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 x 24 h postop, then regular daily dose
• HIGH STRESS (e.g. intraabdominal operations, car diac surgery) hydrocortisone 100 mg IV, followed by 50 mg IV q8h x 24 h, and taper by 50% per day until regular daily dose

Cushing’s Syndrome

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. Partial suppression of cortisol confirms pituitary Cushing’s. Failure to suppress cortisol confirms ectopic or adrenal Cushing’s

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

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**

<table>
<thead>
<tr>
<th>Glucocorticoids</th>
<th>Half life (h)</th>
<th>Equivalent anti inflammatory potencya</th>
<th>Equivalent mineralocorticoid potencya</th>
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<tr>
<td>Short acting</td>
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<tr>
<td>Cortisone</td>
<td>8 12</td>
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<td>2</td>
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<tr>
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<tr>
<td>Fludrocortisone</td>
<td>12 24</td>
<td>0.5</td>
<td>125</td>
</tr>
</tbody>
</table>

*aHigher number indicates greater potency as compared to prednisone
**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 dermato logic 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

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**Hypocalcemia**

**DIFFERENTIAL DIAGNOSIS**

**PTH ABNORMALITIES (PO₄⁻)**
- **HYPOPARATHYROIDISM** surgery, irradiation, autoimmune, congenital, infiltrative, DiGeorge’s syndrome
- **FUNCTIONAL HYPOPARATHYROIDISM** Mg deficiency
- **PTH RESISTANCE** pseudohypoparathyroidism

**VITAMIN D ABNORMALITIES (PO₄⁻)**
- **VITAMIN D DEFICIENCY** nutritional, malabsorption
- **ALTED 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 D₃ may be obtained via diet as well) → liver → 25OH D₃ (used to determine vitamin D status) → kidney (stimulated by PTH or hypo PO₄⁻) → 1,25(OH)₂D₃ (also known as calcitriol, the active form of vitamin D)
- **1,25(OH)₂D₃** ↑ Ca reabsorption at gut, kidney, and bone, ↑ PO₄ reabsorption at gut and kidney
- **PTH ACTION** ↑ Ca reabsorption at distal tubule and bone, ↓ PO₄ reabsorption at proximal tubule, ↑ 1,25(OH)₂D₃

**CLINICAL FEATURES**
- **HISTORY** tetany, stridor (laryngospasm), seizures, confusion, weakness, past medical history (thyroid

**TREAT UNDERLYING CAUSE**

**Related Topic**
Hypophosphatemia (p. 83)

**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 transsphe noidal surgery or irradiation before development of macroadenoma. Consult endocrinology

**CLINICAL FEATURES (CONT’D)**

**PHYSICAL** hypotension, Trousseau’s sign, Chvostek’s sign, carpal/pedal spasm, weakness

**INVESTIGATIONS**

**BASIC**
- **LABS** Ca, albumin, Mg, PO₄⁻, PTH, ALP, 25OH D₃, 1,25(OH)₂D₃, lyes, 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 MgSO₄ 2 g IV over 2 h. If mild symptoms, **CaCO₃** 1 2 g PO TID, **calcitriol** (1,25(OH)₂D₃) 0.25 1 μg daily

**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, immunosup pressants and HAART may lead to increased inactivation of 1,25(OH)₂D₃), chronic kidney disease (decreased activation), liver failure (decreased activation)
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, ↓ PO₄ reabsorption at proximal tubule, ↑ 1,25(OH)₂D₃

Malignancy related mechanisms local osteolytic bone lesions, humor al hypercalcemia of malignancy (PTH related peptide), 1,25(OH)₂D₃ secretion (lymphomas), ectopic hyperparathyroidism (very rare)

Sarcoidosis mechanism unregulated synthesis of 1,25(OH)₂D₃, 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, PO₄, PTH, ALP, 1,25(OH)₂D₃, 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

<table>
<thead>
<tr>
<th>Primary</th>
<th>PTH</th>
<th>Sarcoïdosis</th>
<th>PTHrP</th>
<th>FHH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>↑↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>PO₄</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>PTH</td>
<td>↑↑/N</td>
<td>↓</td>
<td>↑</td>
<td>↑/N</td>
</tr>
<tr>
<td>PTHrP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitriol</td>
<td></td>
<td>↑</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine Ca</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td></td>
</tr>
</tbody>
</table>

Management

Symptom control NS 200 500 mL/h IV ± fur osemide 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). Malig nancies may also respond to giving steroids (predni sone 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
INDICATIONS FOR PARATHYROIDECTOMY IN PATIENTS WITH ASYMPTOMATIC HYPERPARATHYROIDISM

- age < 50, Ca^2+ > 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.

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, ↑ PTH. Family history can be helpful. Important to differentiate from primary hyperparathyroidism as 15-20% of FHH will have elevated PTH, and FHH does not require treatment.

MILK ALKALI SYNDROME

- PATHOPHYSIOLOGY: ingestion of significant amounts of calcium and absorbable alkali (e.g., CaCO3) used as antacids and treatment of osteoporosis. The combination of increased alkali intake, decreased renal function, and hypercalcinemia contributes to metabolic alkalosis, which decreases calcium excretion and in turn contributes to hypercalcinemia.
- 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 PO4.

Osteoporosis

CANADIAN OSTEOPOOROSIS 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/m², 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).

<table>
<thead>
<tr>
<th>Status</th>
<th>T score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>+ 2.5 to 1.0 (inclusive)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Between 1.0 and 2.5</td>
</tr>
</tbody>
</table>

PATHOPHYSIOLOGY (CONT'D)

<table>
<thead>
<tr>
<th>Status</th>
<th>T score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>≤ 2.5</td>
</tr>
<tr>
<td>Severe</td>
<td>≤ 2.5 and fragility fracture</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>History</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self reported humped back</td>
<td>3.0</td>
<td>0.85</td>
</tr>
<tr>
<td>Physical</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight &lt;51 kg</td>
<td>7.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Kyphosis</td>
<td>3.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Tooth count &lt;20</td>
<td>3.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Rib/pelvis distance ≤2 finger breadths</td>
<td>3.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Wall occiput distance &gt;0 cm</td>
<td>4.6</td>
<td>0.5</td>
</tr>
</tbody>
</table>

(indicative of spine fracture)
CLINICAL FEATURES (CONT’D)

Decision Rules

<table>
<thead>
<tr>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Simple calculated osteoporosis risk estimation (score ≥6)

Osteoporosis risk assessment instrument (score ≥9)

National osteoporosis foundation (score ≥1)

Age/body size/no estrogen (score ≥2)

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]), in ability 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, PO₄, 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) lifestyle Δ + medications

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) lifestyle Δ + medications

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

WHO SHOULD BE TREATED?

- **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)

WHO SHOULD BE TREATED?

- **5-YEAR FRACTURE RISK** for vertebral, non vertebral and hip fractures, score 1 2=12, 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

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
**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.

**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)

**PATHOPHYSIOLOGY (CONT’D)**

Most commonly familial or caused by systemic disorders (hypothyroidism, anorexia nervosa, malnutrition, porphyria, and dermatomyositis) or medications (phenytoin, penicillamine, diazoxide, minoxidil, or cyclosporine)

**CLINICAL FEATURES**

**HISTORY** time course of symptoms, hirsutism and virilization symptoms, menstrual history, weight history, medications, family history

**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

**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)

**INVESTIGATIONS (CONT’D)**

**SPECIAL**
- **LAPAROSCOPY**
- **HYSTEROSALPINGOGRAPH** 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

**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, 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)
<table>
<thead>
<tr>
<th>DISTINGUISHING FEATURES</th>
<th>PCOS</th>
<th>CAH</th>
<th>Idio pathic</th>
<th>Ovary tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Puberty</td>
<td>Puberty</td>
<td>Puberty</td>
<td>30 s</td>
</tr>
<tr>
<td>Menstruation</td>
<td>Altered</td>
<td>May be altered</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++ virilization</td>
</tr>
<tr>
<td>Course</td>
<td>Slow</td>
<td>Slow</td>
<td>Slow</td>
<td>Acute</td>
</tr>
<tr>
<td>Testosterone/DHEAS</td>
<td>+</td>
<td>+</td>
<td>Normal</td>
<td>++</td>
</tr>
<tr>
<td>17 OH prog.</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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, 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

**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 hydroxy progesterone (the substrate for 21 hydroxylation 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)
**Eczema**

**DIFFERENTIAL DIAGNOSIS OF PRURITUS**

**INFLAMMATORY**
- **DERMATITIS** atopic dermatitis, seborrheic dermatitis, stasis dermatitis, irritant contact dermatitis, allergic contact dermatitis
- **PSORIASIS**
- **URTICARIA**
- **DERMATITIS HERPETIFORMIS**

**INFECTIONS**
- **TINEA**, **SCABIES**
- **LYMPHOMA** (mycosis fungoides), myeloma, solid tumors

**NEOPLASTIC**
- **DRUG ERUPTION** antibiotics, anti seizure
- **DRUG-INDUCED PRURITUS** opiates, steroids, aspirin, antimalarials

**IATROGENIC**
- **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, Sjögren'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 extremity 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, scaldier, and may even form stasis ulcers

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, seborrhoeic dermatitis

MALIGNANCY mycosis fungoides, basal 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
- PALMOPRANTAL PSORIASIS mild to severe forms. Well demarcated erythematous plaque with silver scales. Cracking, fissures, or bleeding may be seen. Pustular variant also found

CLINICAL FEATURES (CONT’D)

- 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 silvery 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

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
SEBORRHEIC DERMATITIS

LICHEN PLANUS

PATHOPHYSIOLOGY

TREATMENTS

CLINICAL FEATURES

ASSOCIATIONS

PATHOPHYSIOLOGY

TREATMENTS

CLINICAL FEATURES

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 autoimmunie disease with lymphocytic infiltration in epidermis

ASSOCIATIONS drugs (β-blockers, methyl dopa, penicillamine, NSAIDs, ACE inhibitors, carbamazepine, gold, lithium), HCV infection

- **CLINICAL FEATURES** **5 P’s** Purple, Pruritic, Polygonal, Planar (flat topped) Papules. May also see fine white lines on the surface (Wickham’s striae). Commonly seen in flexor wrists, forearms, and buccal mucosal (lacey white reticular lesions). Lesions may last for a year
- **TREATMENTS** no treatment needed usually. Topical steroids, antihistamines, and antiinflammatory 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 1.25% 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

Acne Vulgaris

363

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

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** 20–250 mg/kg/day for 6–8 weeks, terbinafine, itraconazole), tinea pedis or cruris (terbinafine 1% cream daily BID, clotrimazole/Lotrimin 1% cream BID, itraconazole), 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, itraconazole), systemic (ketoconazole, terbinafine, itraconazole)

GROIN SKIN LESIONS common causes include tinea cruris, candidiasis, erythrasma (*Corynebacterium minutissimum*), and inverse psoriasis

PATHOPHYSIOLOGY

PATHOGENESIS condition affecting pilosebaceous units, commonly seen during puberty. Pathogenesis involves androgens, follicular keratinization, and the Gram positive bacteria *Propionibacterium acnes*. Lesions may present as non inflammatory comedones or inflammatory papules. Inflammatory cysts...
may leave behind hyperpigmentation and sometimes scarring

**RISK FACTORS** drugs (steroids, phenytoin, lithium), androgen excess (PCOS, Cushings’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). Wide spread 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**

**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

**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

**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)

**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 syn drome, 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
**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.

- **CLINICAL FEATURES** young person with fever, malaise, generalized macular erythematous rash including mucous membranes, palms and soles, evolves into petechiae, vesicles, and bullae. Ulcers 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 x1 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), circumsoral 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, Cowpox virus.

**NEOPLASTIC** paraneoplastic pemphigus.

**IATROGENIC** Stevens Johnson syndrome*, toxic epidermal necrolysis*.

*bullous lesions may be seen with or without vesicles.

**PATHOPHYSIOLOGY**

**HYPERSENSITIVITY REACTION** Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) lie on a spectrum of serious, life threatening illness characterized by extensive epidermal necrosis. By definition, SJS involves less than 10% of the body surface area (BSA) and TEN involves greater than 30% of the BSA. Involvement of 10-30% BSA is an overlap between the two. Drugs are the most common offending agents, but *Mycoplasma pneumoniae*, viruses, various chemicals and immunizations have also been associated with SJS/TEN.

**COMMONLY ASSOCIATED DRUGS ★4A’S★**

- Allopurinol
- Antibiotics sulfamethoxazole, cephalosporins, penicillins, quinolones, macrolides
- Antiinflammatory drugs NSAIDs, salicylates
- Anticonvulsants 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 process 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.
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

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  intraepidermal 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

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 niacimamide. 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 multinucleated cells
- TREATMENTS  acyclovir, valacyclovir, famciclovir

VARICELLA ZOSTER VIRUS (VZV)
- CLINICAL FEATURES  crops of vesicles over entire body (varicella) or specific dermatone with reaction (zoster, also known as shingles)
- TREATMENTS  acyclovir, valacyclovir, famciclovir.

Amitriptyline, gabapentin, and opioids may be useful for post herptic neuralgia
Ulcers

DIFFERENTIAL DIAGNOSIS OF ULCERS

VENOUS HYPERTENSION
- STASIS immobility, CHF, incompetent valves, pregnancy
- DVT

ATHEROSCLEROTIC
NEUROPATHIC diabetes, leprosy, syphilis, syringomyelia, peripheral neuropathy
VASCUITIC 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 CBC/D, 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 GANGRENSUM
- COLONOSCOPY if suspect IBD
- MALIGNANCY WORKUP serum protein electrophoresis, CXR
- INFLAMMATORY WORKUP ESR, antiphospholipid antibody, antineutrophil cytoplasmic anti bodies, 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 (CONT’D)

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). Antibiotics if super infected. Superficial vein surgery may prevent recurrence in some patients

ATHEROSCLEROTIC ULCERS
- PATHOPHYSIOLOGY result from peripheral artery disease or vasculitis that prevents adequate blood flow to the lower extremity. Inadequate oxygen and nutrient delivery results in tissue breakdown and 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. Avoid ane 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

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
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 × 3 day), cyclosporine, and TNFα blockade and IVIG 400 mg/kg IV daily × 5 day or 1 g/kg IV daily × 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

DIFFERENTIAL DIAGNOSIS OF PIGMENTED LESIONS

- **BENIGN nevus** (congenital, acquired), freckle, seborrheic keratosis, cafe au Lait
- **PRE MALIGNANT** dysplastic nevus 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, gyneco mastia, Cushing’s, hypercalcemia, neurological

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A MOLE OR A MELANOMA?

CHECKLIST ★ ABCD ★
- **Asymmetry**, Border irregularity, **Color variegation**, **Diameter >6 mm (sens 92–100%, spc 98% depending on how many criteria...**
used. Evolution (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)

<table>
<thead>
<tr>
<th>Level</th>
<th>TNM</th>
<th>5 year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Intraepidermal (in situ)</td>
<td>100%</td>
</tr>
<tr>
<td>II</td>
<td>Invasion into papillary dermis</td>
<td>85%</td>
</tr>
<tr>
<td>III</td>
<td>Extensive invasion of papillary dermis</td>
<td>65%</td>
</tr>
<tr>
<td>IV</td>
<td>Invasion into reticular dermis</td>
<td>50%</td>
</tr>
<tr>
<td>V</td>
<td>Invasion into subcutaneous tissue</td>
<td>15%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Stage</th>
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<th>10 year survival</th>
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<tr>
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<td>$T1aN0M0$</td>
<td>95%</td>
</tr>
<tr>
<td>IB</td>
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</tr>
<tr>
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</tr>
<tr>
<td>IIB</td>
<td>$T3b4aN0M0$</td>
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<tr>
<td>IIC</td>
<td>$T4bN0M0$</td>
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<tr>
<td>III</td>
<td>$T@N13M0$</td>
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<tr>
<td>IIIA</td>
<td>$T1a4aN1aM0$, $T1a4aN2aM0$</td>
<td>70%</td>
</tr>
<tr>
<td>IIIB</td>
<td>$T1b4bN1aM0$, $T1b4bN2aM0$, $T1a4aN1bM0$, $T1a4aN2bM0$, $T14aN2cM0$</td>
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<tr>
<td>IIIC</td>
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<tr>
<td>IV</td>
<td>$T@N@M1$</td>
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Sentinel Lymph Node Biopsy usually done if primary melanomas 1 4 mm thick or ulcerated

Prognosis by Site of Metastasis

<table>
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<tr>
<th>Stage</th>
<th>TNM</th>
<th>1 year survival</th>
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<tbody>
<tr>
<td>M1a</td>
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<td>1 year survival</td>
</tr>
<tr>
<td>M1b</td>
<td>$=53%$</td>
<td>1 year survival</td>
</tr>
<tr>
<td>M1c</td>
<td>$=33%$</td>
<td>1 year survival</td>
</tr>
</tbody>
</table>

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 $<1\: mm\: thick,\: 2\: cm\: for$
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 exision. **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 and immunosuppression, fair complexion, and red hair.

**RISK FACTORS**
- **History of prior sunburns** (especially in childhood), radiation therapy, family history, immunosuppression, fair complexion, and red hair.
- **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 electrodesiccation 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, 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 exision. 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.

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**ACTINIC KERATOSIS**
- **Pathophysiology** form after chronic sun exposure in susceptible individuals usually on the face, scalp,
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

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

DIFFERENTIAL DIAGNOSIS OF PHOTOSENSITIVITY

IATROGENIC (DRUGS)
- AMIODARONE
- DIURETICS hydrochlorothiazide, loop
- ANTIBIOTICS tetracycline
- NSAIDs
- ANTHEPLASTIC methotrexate, vincristine, 5 fluorouracil

INFLAMMATORY SLE, dermatomyositis

IDIOPATHIC polymorphic light eruption, prurigo, actinic dermatitis, solar urticaria, chronic photosensitivity dermatitis

OTHERS phototoxic dermatitis, phytocontact dermatitis (celery, parsley, lime, lemon, yarrow), porphyria, xeroderma pigmentosum

CLINICAL FEATURES (CONT’D)

BULLOUS LESIONS photosensitivity

LIVERO 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 CBCD, ANA, ENA, dsDNA

SPECIAL SKIN BIOPSY

PORPHYRIA WORKUP porphyrin, urine porphyrin

MANAGEMENT


Related Topics Systemic Lupus Erythematosus (p. 279) Porphyria (p. 421)

SPECIFIC ENTITIES

CENTRAL FACIAL TELANGIECTASIA OR ERYTHEMA common causes include rosacea, 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

Cutaneous Lupus Erythematosus
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, estrogen, smoking, hemodialysis
- CLINICAL FEATURES photodistributed blistering or superficial skin erosion
- TREATMENTS avoid exacerbating factors (alcohol, estrogens, iron supplements, drugs). Phlebotomy. Chloroquine, hydroxychloroquine

DIFFERENTIAL DIAGNOSIS

EXANTHEMS
- ANTIBIOTICS penicillins, sulfonamides, erythromycin, gentamicin
- ANTICONVULSANTS
- ALLOPURINOL
- GOLD

URTICARIA, ANGIOEDEMA
- IMMUNE IgE-MEDIATED penicillins, cephalosporins, sulfonamides, local anesthetic agents, radio contrast, 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 penicillins, sulfonamides, cephalosporins
- ANTICONVULSANTS phenytoin, carbamazepine, phenobarbital
- ANTIINFLAMMATORIES NSAIDs

CONTACT DERMATITIS neomycin, benzocaine, paraben, ethylenediamine, formaldehyde, paraaminobenzoic acid

HYPERSENSITIVITY VASCULITIS
- ALLOPURINOL
- DIURETICS furosemide, thiazide
- ANTIBIOTICS penicillins, sulfonamides
- OTHERS cimetidine, hydantoin

PIGINMENTARY 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

DIFFERENTIAL DIAGNOSIS (CONT’D)

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
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.

  - **Non-allergic forms** of urticaria and angioedema occur from drug induced bradykinin release and/or mast cell degranulation. The reaction typically occurs within 20-30 min of drug administration. Common drugs include NSAIDs, opiates, ACE inhibitors, calcium channel blockers, and radiocontrast.

- **TREATMENTS**
  - Cessation of the offending drug.
  - Antihistamines and oral steroids may be used. For acute, life threatening reactions, ABC, O2, 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.

**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.

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**Erythema Nodosum**

**DIFFERENTIAL DIAGNOSIS OF PAINFUL NODULES**

**PANNICULITIS**

- Erythema nodosum, erythema induratum, Weber Christian disease (relapsing nodular panniculitis)

**INFECTIONS**

- Bacteria, fungi

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**DIFFERENTIAL DIAGNOSIS OF PAINFUL NODULES (CONT'D)**

**CUTANEOUS VASCULITIS**

**SUPERFICIAL THROMBOPHLEBITIS**

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**Related Topics**

- Antibiotics (p. 254)
- Penicillin Allergy (p. 257)
CAUSES OF ERYTHEMA NODOSUM

- INFECTIOUS  bacterial (Streptococcal, Yersinia), 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 with out 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

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 ≤176°, simplified to straight line of <180° for clinical use), hyponychial nail fold angle (angle that nail directs toward the nail tip, normal ≤192°, simplified to <190° for clinical use), phalangeal depth ratio (distal phalangeal finger depth/interphalangeal finger depth ratio normal ≤1), Schamroth sign (normal=diamond)

INVESTIGATIONS

BASIC  CBCD, antistreptolysin O titer, ANA
MICROBIOLOGY  wound C&S, throat C&S (for Streptococcus), TB skin test
IMAGING  CXR

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 (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  CBCD, TSH, AST, ALT, ALP, bili
CARDIAC WORKUP  ECG, echocardiogram
OTHER ETIOLOGY WORKUP  CBCD, TSH, AST, ALT, ALP, bili

MANAGEMENT

TREAT UNDERLYING CAUSE

JAMA 2001 286:3
Dupuytren’s Contracture

DIFFERENTIAL DIAGNOSIS

DIABETIC CHEIROARTHROPATHY (usually all four fingers)

INRINSIC JOINT DISEASE

DUPUYTREN’S CONTRACTURE

VOLKMANN’S ISCHEMIC CONTRACTURE

TRAUMATIC SCARS

PALMAR FASCITIS 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

Related Topics

Celiac Disease (p. 124)
Inflammatory Bowel Disease (p. 120)
Lung Cancer (p. 185)
Geriatric-Specific Issues

THE FRAIL ELDERS

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 ≥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 (≥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 coexisting diseases that are either life threatening or function limiting

POLYPHARMACY number of medications, potential medications that can cause delirium and other significant side effects, adherence, assistance with medications, drug interactions (p. 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

<table>
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<tr>
<th>Discipline</th>
<th>Task</th>
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<tr>
<td>Dieticians</td>
<td>Nutrition and diet</td>
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<tr>
<td>Nurses</td>
<td>Education and assistance</td>
</tr>
<tr>
<td>Occupational</td>
<td>Cognitive and functional</td>
</tr>
<tr>
<td>Therapists</td>
<td>assessments, ADL training</td>
</tr>
<tr>
<td>Pharmacists</td>
<td>Medication use</td>
</tr>
<tr>
<td>Physiotherapists</td>
<td>Training to ↑ ROM, strength,</td>
</tr>
<tr>
<td></td>
<td>endurance, coordination,</td>
</tr>
<tr>
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<td>mobility</td>
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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 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, neoplasm, 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

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Healthcare and Financial Proxy (Cont’d)

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: 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

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Comprehensive Geriatric Management (Cont’d)

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Task</th>
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<tbody>
<tr>
<td>Recreational therapists</td>
<td>Maintenance of social roles</td>
</tr>
<tr>
<td>Social workers</td>
<td>Counseling, evaluation, and disposition within community</td>
</tr>
<tr>
<td>Speech language therapists</td>
<td>Training in communication and therapy for swallowing disorders</td>
</tr>
</tbody>
</table>
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.

DISTINGUISHING FEATURES BETWEEN VARIOUS TYPES OF DEMENTIA

<table>
<thead>
<tr>
<th>Physical findings</th>
<th>Alzheimer’s</th>
<th>Vascular</th>
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</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>Relatively normal</td>
<td>Focal neurological deficits</td>
<td>Disinhibited or passive Primitive reflexes</td>
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<tr>
<td>CT</td>
<td>Globally low</td>
<td>Patchy changes Early executive loss</td>
<td>White matter changes Frontal temporal atrophy</td>
</tr>
</tbody>
</table>

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).

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

<table>
<thead>
<tr>
<th>Test</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>6.3</td>
<td>0.19</td>
</tr>
<tr>
<td>Reports from an informant that the patient has memory loss</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>Memory impairment screen</td>
<td>33</td>
<td>0.08</td>
</tr>
<tr>
<td>Clock drawings</td>
<td>1.2</td>
<td>7.7</td>
</tr>
</tbody>
</table>

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

Special

FURTHER DEMENTIA WORKUP
AST, ALT, ALP, bilir ubin, 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 dys function (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 symp toms or presentation (e.g. progressive aphasia)

CMAJ 1999 160:12; Canadian Consensus Conference on Dementia

MANAGEMENT

**RISK REDUCTION** anti hypertensive (see HYPER TENSION 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 Gl 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 beha viors 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 pneu monia, reduction of pressure sores or infections, functional improvement)

**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. subarach noid 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 (ventriculo peritoneal, 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 test ing quantifies risk, severity, and age of onset

- **CORTICONUCLEAR DEGENERATION** marked visual spatial impairment, substantial apraxia, but mem ory impairment less noticeable

**DIFFERENTIAL DIAGNOSIS**

- **DIMES**
- **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, sulfona mides, isoniazid, rifampin, streptomycin, chloroquine, acyclovir
- **ANTI-HISTAMINES** cimetidine, famotidine, ranitidine

Delirium

NEJM 2006 354:11
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: hepatic, azotemia, hypothyroidism, hypoxia, hypercapnia, hypothermia, hypertensive
- Electrolyte Imbalance: ketoacidosis, glucose (hypo, hyper), hyponatremia, hypernatremia, hypomagnesemia, hypercalcemia
- Structural: subarachnoid, epidural, subdural, intracerebral

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% in 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.

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 (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: CBC, 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, NH₄ if suspect liver disease, Mg, PO₄
- Cardiac Workup: ECG, CK, troponin if suspect ACS
- Seizures Workup: EEG

DELIRIUM SUBTYPES: 1. Acute Onset and Fluctuating Confusion: abnormal behaviors come and go, ↑↓ severity
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 O2, 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)

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 verteobasilar insufficiency
POSTURAL HYPOTENSION 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★ Symptoms associated with fall (circumstances, onset, frequency), Previous falls, Past medical history, Location, Activity preceding fall, Toxin (meds), and Trauma

**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

<table>
<thead>
<tr>
<th>RATIONAL CLINICAL EXAMINATION SERIES: WILL MY PATIENT FALL?</th>
<th>RISK FACTORS FOR FALLS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fallen in the past year</td>
<td>LR+ 2.3 2.8</td>
</tr>
<tr>
<td>Clinically detected abnormalities of gait or balance</td>
<td>1.7 2.4</td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

**INVESTIGATIONS**

**BASIC**
- LABS CBC, 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)

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**Osteoporosis**

See OSTEOPOROSIS (p. 354)

**Urinary Incontinence**

**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

---

**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

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**DIFFERENTIAL DIAGNOSIS OF CHRONIC URINARY INCONTINENCE**

**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 the 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?

<table>
<thead>
<tr>
<th>Type of Incontinence</th>
<th>LR+</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress Incontinence</td>
<td>2.2</td>
<td>0.39</td>
</tr>
<tr>
<td>Simple question: “Do you lose urine during sudden physical exertion, lifting, coughing or sneezing?”</td>
<td>9.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Filled bladder stress test (fill bladder with 200 cc of saline, supine, and observe while cough)</td>
<td>3.7</td>
<td>0.20</td>
</tr>
<tr>
<td>Systematic assessment</td>
<td>4.2</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Urge Incontinence

“Do you experience such a strong and sudden urge to void that you leak before reaching the toilet?”

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.”

Investigations

Basic

- Labs: electrolytes, 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

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 coexisting 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 \( \uparrow \), phase II reactions unaffected), decreased lean body mass (\( \downarrow \) fat), decreased total body water, and increased total body fat

COMPLICATIONS falls, delirium, incontinence, renal impairment, heart failure, gastrointestinal hemorrhage, hypoglycemia, drug–drug interactions

PRESCRIBING PRINCIPLES initiate most medications at half usual starting dose, increase dose slowly. Carry out regular medication reviews and stop any unnecessary medications. Avoid medications with known significant side effects in the elderly. Avoid treating adverse drug reactions with further drugs

UNDER PRESCRIBING IN THE ELDERLY

REASONS FOR UNDER PRESCRIBING under recognition of medication benefit in older patients, affordability, and dose availability (i.e. requiring a dose of medication that is smaller than supplied by the manufacturer, resulting in more complicated dosing strategies such as once every other day 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 \( \rightarrow \) extrapyramidal effects \( \rightarrow \) 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

<table>
<thead>
<tr>
<th>CHARACTERISTIC SIDE EFFECTS OF DRUGS FREQUENTLY USED IN THE ELDERLY</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )1 blockers (doxazosin)</td>
<td>Falls, orthostatic hypotension, dry mouth</td>
</tr>
<tr>
<td>Anticholinergics (diphenhydramine)</td>
<td>Delirium, urinary retention, constipation, dry mouth, blurred vision, postural hypotension</td>
</tr>
<tr>
<td>Benzodiazepines (lorazepam)</td>
<td>Falls, confusion</td>
</tr>
<tr>
<td>NSAIDs (indomethacin)</td>
<td>Gastrointestinal irritation and hemorrhage, renal impairment, hypertension, heart failure</td>
</tr>
<tr>
<td>Sulfonylureas (chlorpropamide)</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Tricyclic antidepressants (amitriptyline)</td>
<td>Falls, orthostatic hypotension, sedation, delirium, arrhythmias</td>
</tr>
</tbody>
</table>
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.

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.
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 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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Cancer</th>
<th>AIDS</th>
<th>Heart Failure</th>
<th>COPD</th>
<th>CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>35 96%</td>
<td>63 80%</td>
<td>41 77%</td>
<td>34 77%</td>
<td>47 50%</td>
</tr>
<tr>
<td>Depression</td>
<td>3 77%</td>
<td>10 82%</td>
<td>9 36%</td>
<td>37 71%</td>
<td>5 61%</td>
</tr>
<tr>
<td>Delirium</td>
<td>6 93%</td>
<td>30 65%</td>
<td>30 65%</td>
<td>18 32%</td>
<td>18 33%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 90%</td>
<td>54 85%</td>
<td>69 82%</td>
<td>68 80%</td>
<td>73 87%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10 70%</td>
<td>11 62%</td>
<td>60 88%</td>
<td>90 95%</td>
<td>11 62%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>30 92%</td>
<td>57%</td>
<td>21 41%</td>
<td>35 67%</td>
<td>25 64%</td>
</tr>
</tbody>
</table>

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

SYMPTOM COMPLEX AND ASSESSMENT (CONT’D)

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


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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, hyperalcalemia, 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 psychiatric symptoms themselves and may require support. 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 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 bath room 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★

- Spiritual belief system
- Personal spirituality
- Integration with a spiritual community
- Ritualized practices/restrictions
- Implications for medical care
- Terminal 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, clergy, 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 the 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 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 interprofessional 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

PREDISPOSING FACTORS TO 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

DISTINGUISHING FEATURES OF PAIN

<table>
<thead>
<tr>
<th>Somatic</th>
<th>Visceral</th>
<th>Neuropathic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Localized</td>
<td>Poorly localized, referred</td>
</tr>
<tr>
<td>Nature</td>
<td>Aches</td>
<td>Squeezing, cramping</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Opioids, NSAIDs</td>
<td>Opioids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiation, dermatome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Shooting, burning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opioids, TCAs, antiepileptics, venlafaxine</td>
</tr>
</tbody>
</table>
PATHOPHYSIOLOGY (CONT’D)

CAUSES OF INTRACTABLE CANCER PAIN  disease progression, neuropathic pain, bone pain, break through 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 gas tritis, 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/hydrocodone 325 mg/ 5 10 mg PO q4h, tramadol 50 100 mg PO q4 6h

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/ splanchic 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)  nor triptyline 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)  chemother apy, radiation (external beam radiation for focal tumor infiltration, Strontium89, or Samarium153 for multifocal osteoblastic bone metastases), hormonal agents

• BISPHOSPHONATES (bone metastases, hypercalca mia)  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 pres sure, 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 2h (see table below). Need to increase scheduled dose if ≥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)

OPPIOID 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

<table>
<thead>
<tr>
<th></th>
<th>Ratio</th>
<th>Starting</th>
<th>q1h PRN</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>0.1</td>
<td>30 60 mg</td>
<td>2.5 5 mg</td>
<td>PO/PR</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>0.5</td>
<td>1 10 mg</td>
<td>0.5 1 mg</td>
<td>PO/PR/SC/IV</td>
</tr>
<tr>
<td>Morphine</td>
<td>1</td>
<td>5 mg</td>
<td>2.5 5 mg</td>
<td>PO/PR/IV</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>5</td>
<td>1 2 mg</td>
<td>0.5 1 mg</td>
<td>PO/PR/SC/IV</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>1.5</td>
<td>5 mg</td>
<td>2.5 mg</td>
<td>PO/PR/SC</td>
</tr>
<tr>
<td>Fentanyl drip</td>
<td>100</td>
<td>10 50 μg/hr</td>
<td>25 μg</td>
<td>IV</td>
</tr>
<tr>
<td>Methadone</td>
<td>2</td>
<td>5 mg</td>
<td>25 μg</td>
<td>IV</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Fentanyl TD (μg/h)</th>
<th>Morphine PO (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>45 134</td>
</tr>
<tr>
<td>50</td>
<td>135 224</td>
</tr>
<tr>
<td>75</td>
<td>225 314</td>
</tr>
<tr>
<td>100</td>
<td>315 404</td>
</tr>
<tr>
<td>125</td>
<td>405 494</td>
</tr>
<tr>
<td>150</td>
<td>495 584</td>
</tr>
</tbody>
</table>

• 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 25x3.6=90 mg of oral morphine/day

• CONVERSION BETWEEN INTRAVENOUS FENTANYL AND INTRAVENOUS MORPHINE 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

<table>
<thead>
<tr>
<th>Oral morphine equivalent daily dose (mg/day)</th>
<th>Initial dose ratio (morphine:methadone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 mg/day</td>
<td>2:1</td>
</tr>
<tr>
<td>30–99 mg/day</td>
<td>4:1</td>
</tr>
<tr>
<td>100–299 mg/day</td>
<td>8:1</td>
</tr>
<tr>
<td>300–499 mg/day</td>
<td>12:1</td>
</tr>
<tr>
<td>500–999 mg/day</td>
<td>15:1</td>
</tr>
<tr>
<td>&gt;1000 mg/day</td>
<td>20:1 or greater</td>
</tr>
</tbody>
</table>

2. DETERMINE THE SCHEDULE

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (MS)</td>
<td>66%</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>TDD</td>
<td>TDD</td>
<td>TDD</td>
<td>TDD</td>
</tr>
<tr>
<td>Methadone (ME)</td>
<td>33%</td>
<td>66%</td>
<td>100%</td>
</tr>
<tr>
<td>TDD</td>
<td>TDD</td>
<td>TDD</td>
<td>TDD</td>
</tr>
<tr>
<td>Break through</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>w/morphine</td>
<td>w/morphine</td>
<td>w/morphine</td>
<td>w/morphine</td>
</tr>
</tbody>
</table>

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 (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 under diagnosed and under treated

**CLINICAL FEATURES**

**SCREENING** “How would you rate your fatigue on a scale of 0-10 over the past 7 days?”

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Absence of fatigue</td>
</tr>
<tr>
<td>1-3</td>
<td>Mild fatigue</td>
</tr>
<tr>
<td>4-6</td>
<td>Moderate fatigue</td>
</tr>
<tr>
<td>7-10</td>
<td>Severe fatigue</td>
</tr>
</tbody>
</table>

**INVESTIGATIONS**

**BASIC**

- **LABS** CBC, 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 (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, loraze pam), neuroleptics (e.g. haloperidol, chlorpromazine, methotrimeprazine). Good for delirium and may be combined with midazolam), propofol (intra venous 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 methotrimeprazone 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)
  - STEROIDS dexamethasone 4-10 mg PO/SC/IV BID
  - NEUROLEPTICS methotrimeprazone 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

**CONSTIPATION IN THE PALLIATIVE SETTING**

DIFFERENTIAL DIAGNOSIS

★DUODENUM★

- Diet low fiber, dehydration

SYNDROME depression, somatization, obses
tive compulsive disorder

OBSTRUCTION cancer, strictures, adhesions

DRUGS opioids, TCAs, neuroleptics, antihista
mes, calcium channel blockers, iron, antacids

ENDOCRINE diabetes, hypothyroidism, hyper
calcemia, hypokalemia, hypomagnesemia, uremia

NEUROLOGIC spinal cord compression/injury, Parkinson's, multiple sclerosis, stroke, autonomic neuropathy (cachexia anorexia syndrome)

UNKNOWN

MISCELLANEOUS immobility, irritable bowel syn
drome (IBS), amyloidosis, scleroderma

PATHOPHYSIOLOGY

CONSTITUTION IN THE PALLIATIVE CARE SET

ING the most common causes are opioids, other medications, dehydration, and immobility. Even if there is no food intake, a small amount of stool is produced everyday due to shedding of intestinal epithelium. It is important to rule out bowel obstruction

RISK FACTORS FOR CONSTIPATION old age, female sex, intraabdominal malignancies, opioids use

COMPLICATIONS OF CONSTIPATION abdominal pain, distension, nausea and vomiting, overflow diar

hea, hemorrhoids, anal fissures, confusion/delirium, fear of opioid use

INVESTIGATIONS

BASIC

- IMAGING AXR

SPECIAL

- WORKUP lytes, urea, Cr, glucose, Mg, Ca, albu

min, 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

**SYMPTOM CONTROL (CONT’D)**

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 4L 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 DISIMPACITION** 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 constipating medications if possible. Methadone and fentanyl may be less constipating than other opioids (controversial)

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**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

- **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 CBC, lytes, urea, Cr, Ca, PO4, 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 (CONT’D)

MANAGEMENT

NUTRITIONAL COUNSELING patients with advanced disease should be encouraged to eat things they enjoy in small and frequent portions, without 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 viscous 2% or lidocaine spray, taste changes with zinc sulfate 220 mg PO BID, early satiety with metoclopramide, pain with analgesics, constipation with laxatives, and depressive mood with antidepressants

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 resilience 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 are you 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 every thing 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. How ever, 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 ratios nale. 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?”
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 < 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× 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)

PALLIATIVE PROGNOSTIC INDEX (PPI)

ORAL INTAKE  normal=0, moderately reduced=1, severely reduced=2.5

EDEMA  absent=0, present=1

DYSPNEA AT REST  absent=0, present=3.5

DELIRIUM  absent=0, present=4

UTILITY  with total score of 4 as cutoff, PPV for 6 week survival is 83%, NPV is 71%

PALLIATIVE PROGNOSTIC TOOLS (PaP)

CLINICIAN PREDICTION OF SURVIVAL  >12 weeks=0, 11 12 weeks=2, 7 10 weeks=2.5, 5 6 weeks=4.5, 3 4 weeks=6, 1 2 weeks=8.5

KARNOFSKY PERFORMANCE STATUS  ≥50%=0, 10 40%=2.5

ANOREXIA  absent=0, present=1.5

DYSPNEA  absent=0, present=1

TOTAL WBC  4.8 8.5=0, 8.5 11=0.5, >11=1.5

LYMPHOCYTE PERCENTAGE  20 40%=0, 12 19.9%=1, 0 11.9%=2.5

UTILITY  30 day survival for total score 0 5.5 = 97%, 5.6 11 = 59%, 11.1 17.5 = 25%

Related Topics
Death and Dying (p. 391)
Discussing Prognosis (p. 400)
<table>
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<tr>
<th>PPS</th>
<th>Mobility</th>
<th>Activity and evidence of disease</th>
<th>Self care</th>
<th>Intake</th>
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<td>100%</td>
<td>Full</td>
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<td>60%</td>
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<td>Occasional assist</td>
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<td>Full or confusion</td>
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<td></td>
<td>Significant disease</td>
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<td>50%</td>
<td>Mainly sit or lie</td>
<td>Unable to do any work</td>
<td>Considerable assist</td>
<td>Normal or reduced</td>
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<td>Extensive disease</td>
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<td>40%</td>
<td>Mainly in bed</td>
<td>Unable to do most activity</td>
<td>Mainly assist</td>
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<td>30%</td>
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<td>Unable to do any activity</td>
<td>Total care</td>
<td>Minimal to sips</td>
<td>Full or drowsy ± confusion</td>
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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

REPRODUCTIVE
- irregular menses, anovulatory cycles, infertility
- IRREGULAR CYCLES hyperinsulinemia, prediabetes, type 2 diabetes

ENDOCRINE/C15 INSULIN RESISTANCE (hyperinsulinemia, prediabetes, type 2 diabetes)

REPRODUCTIVE/G15 IRREGULAR CYCLES (irregular menses, anovulatory cycles, infertility)

CARDIOVASCULAR/C15 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 (PaCO2 ≥ 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
- GYNECOLOGIC 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/height²) under weight < 18.5 kg/m², normal 18.5 - 24.9 kg/m², over weight 25 - 29.9 kg/m², obesity ≥ 30 39.9 kg/m², severe or morbid obesity ≥ 40 kg/m²

PATHOPHYSIOLOGY (CONT’D)

WAIST CIRCUMFERENCE

<table>
<thead>
<tr>
<th>Ethnic group</th>
<th>Men</th>
<th>Women</th>
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<tr>
<td>Europid</td>
<td>≥ 94 cm</td>
<td>≥ 80 cm</td>
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<td>[≥ 37 in.]</td>
<td>[≥ 31.5 in.]</td>
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<tr>
<td>South Asian, Chinese,</td>
<td>≥ 90 cm</td>
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<tr>
<td>Japanese</td>
<td>[≥ 35.4 in.]</td>
<td>[≥ 31.5 in.]</td>
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</table>

Use Europid cutoff points for South and Central American, sub Saharan African, Eastern Mediterranean, and Middle Eastern populations until more specific data are available

BASELINE ENERGY EXPENDITURE approximately 22 kcal/kg/day [10 kcal/lb/day] is required for weight maintenance (e.g. 1540 kcal is the basic energy need for a 70 kg [154 lb] adult)

INVESTIGATIONS

BASIC
- LABS CBC, 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
MANAGEMENT (CONT’D)

(depression, abuse, binge eating) are major barriers to weight loss success.

DRUG THERAPY consider for patients with BMI > 30 kg/m² or BMI > 27 kg/m² 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/m² or BMI > 35 kg/m² 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 (CONT’D)

OVERALL APPROACH

1. Identify overweight or obese adults
2. If BMI > 25 kg/m², 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/m² plus risk factors or BMI ≥ 30 kg/m². Consider if patient has not lost 0.5 kg/week [1.1 lb/week] by 3 6 months of lifestyle changes
  • BARIATRIC SURGERY if BMI ≥ 35 kg/m² plus risk factors or BMI ≥ 40 kg/m². Consider if other weight loss attempts have failed. Requires lifelong monitoring.

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, N₂O

**PATHOPHYSIOLOGY**

**DEFINITION OF VITAMIN B12 DEFICIENCY** vitamin B12 <148 pmol/L [<200 pg/mL]. Borderline is 148–222 pmol/L [200–300 pg/mL]. Normal values vary in different regions; check local laboratory ranges. Note that vitamin B12 is also called cobalamin (cbl).

**VITAMIN B12 LEVELS** daily requirement 6–9 μg. Body store 2–5 mg. It takes years to deplete stores.

**VITAMIN B12 ABSORPTION PATHWAY**

- **DIET** vitamin B12 protein complex
- **IN STOMACH** vitamin B12 in food is bound to protein. This is catalyzed by acid/pepsin (in stomach). Once released, vitamin B12 quickly binds to R factors produced in the saliva and gastric juice. This complex is not absorbable.
- **IN DUODENUM** pancreatic proteases break down B12 R factor bond. Vitamin B12 then binds to intrinsic factor (from stomach).
- **IN ILEUM** absorption of vitamin B12 intrinsic factor complex

**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

**Related Topics**
- Macrocytic Anemia (p. 146)
- Malabsorption (p. 125)
- Vitamin Deficiencies (p. 126)

**CLINICAL FEATURES (CONT’D)**

**SUBACUTE COMBINED DEGENERATION** lateral (corticospinal tract) and dorsal (vibration and proprioception) columns affected. Spinthalamic 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** sensitivity 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 cyano Cbl 1–2 μg PO, then Cbl 1000 μg IM 1 h later to saturate tissue binding sites and flush out any orally absorbed radiolabeled Cbl into the urine. A 24 h urine is collected. Normally 10–35% of radiolabeled oral dose is eliminated in the urine. If Cbl malabsorption, <8% is eliminated. Diagnostic 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 achlorhydria 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...
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.

**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 malnutrition (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 $\times 1.1 + 48.2$ kg or in lbs = (height in inches $\times 6 + 106$ lbs)
- **♀ IBW (kg)** = (height in cm $\times 0.9 + 45.5$ kg or in lbs = (height in inches $\times 60$ in.) $\times 5 + 100$ lbs

**DAILY ENERGY REQUIREMENTS**
- **14 KCAL/KG** [6.4 KCAL/LB] **BODY WEIGHT** BMI $> 40 \text{ kg/m}^2$
- **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 $> 30 \text{ kg/m}^2$ 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**

**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 $> 1 \text{ L/24 h}$, uncontrollable nausea, vomiting and/or diarrhea, short gut, radiation enteritis

**ROUTES FOR ENTERAL FEEDS**
- **NASOGASTRIC/KAOFEEDE/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 promotility therapies, and recheck 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/mLarginine 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 CO₂ production. For patients with COPD or CO₂ 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 (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 pre vent 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), P (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, ↓PO₄, ↓K.
- TIMEFRAME usually occurs within 3 days of initiation of feed (parenteral, enteral feed, oral intake, IV glucose).
- MANAGEMENT start carbohydrate/feeds low and increase slowly. Monitor electrolytes (lytes, Mg, PO₄ daily ×3 days sand replete PRN), monitor glycemic control.
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 Hemolysis (i.e. microangiopathic hemolytic anemia), Elevated Liver enzymes (i.e. RUQ or epigastric pain), and Low Platelets

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

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

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  CBC, 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, O2 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, clenodine, hydralazine are alternatives

Related Topics
Hypertension (p. 57)
Proteinuria (p. 74)
Seizures (p. 309)
SEIZURE PREVENTION AND TREATMENT  MgSO4
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

RECURRENT  recurrence rate of preeclampsia is 18-66% in subsequent pregnancies. Rule out anti phospholipid syndrome if preeclampsia or placental insufficiency <34 weeks. ASA 81 mg/day before and during next pregnancy is recommended

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 (with out 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)

Imaging  Estimated fetal radiation exposure (rad)
CT chest (PE protocol) 0.0003 0.002 (T1)
CT head 0.0008 0.0077 (T2)
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

FETAL RADIATION EXPOSURE FOR COMMON IMAGING MODALITIES

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Estimated fetal radiation exposure (rad)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>None</td>
</tr>
<tr>
<td>CXR</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CT head</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>V/Q scan</td>
<td>0.01 0.02 ventilation (V)</td>
</tr>
<tr>
<td></td>
<td>0.01 0.03 perfusion (Q)</td>
</tr>
</tbody>
</table>

TREATMENTS  LMWH (monitor anti Xa level). LMWH is contraindicated for 12-24 h prior to neuraxial anesthesia, 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

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 immunosupression, 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, con tinue 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 consid ered during 2nd and 3rd trimesters for more thrombo genic valves until 36th week, and then switch back to unfractionated heparin in preparation for delivery. Preconception counseling should be emphasized

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 com mon 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 diag nosed 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)

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)

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 low-density 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.

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. Contraindicated 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, MgSO4, 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 BACTERIURIAs occur in 2–7% of pregnancies, associated with preterm 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.

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 antibiotic (nitrofurantoin 50–100 mg PO qhs [risk of hemolytic anemia] or cephalaxin 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/mm³. Baseline testing includes CBC, LTES, 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 nonpregnant 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.

TORCHES INFECTIONS

INFECTIONS ASSOCIATED WITH BIRTH DEFECTS
★ TORCHES ★ Toxoplasma, Rubella, CMV, Herpes, and Syphilis 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 amino glycosides (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 still birth, 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 < 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)

• 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 (IGT)
  • 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.

NEJM 2002 346:24

DIABETES IN PREGNANCY (CONT’D)
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 post partum 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

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

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 vita mins, which decrease its absorption

COMPLICATIONS untreated hypothyroidism can lead to neurodevelopmental abnormalities in the child
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. Plaque nil, 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 anti SSA and anti SSB are at increased risk for severe exacerbations with acute renal failure, preeclampsia, and maternal death. Children of patients with antiphospholipid antibodies are at increased risk for congenital heart block and neonatal lupus.

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 x 10^9/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 x 10^9/L. Cesarean delivery safe if platelet >50 x 10^9/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, anti cardiolipin 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 antcardiolipin pin 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)
Approach to Diagnostic Tests and Clinical Trials

## Diagnostic Tests

### 2 x 2 Table

<table>
<thead>
<tr>
<th></th>
<th>Disease present</th>
<th>Disease absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>a (true positive)</td>
<td>b (false positive)</td>
<td>a+b</td>
</tr>
<tr>
<td>Test negative</td>
<td>c (false negative)</td>
<td>d (true negative)</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>a+b+c+d</td>
</tr>
</tbody>
</table>

### Sensitivity (SnOut)

\[ \text{Sensitivity} = \frac{a}{a+c} \]

- out of 100 patients with disease, how many have a positive test result? Independent of prevalence and helps to rule out disease

### Specificity (SpIn)

\[ \text{Specificity} = \frac{d}{b+d} \]

- 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)

\[ \text{PPV} = \frac{a}{a+b} \]

- out of 100 patients with a positive test result, how many actually have disease? Dependent on prevalence of disease

### Negative Predictive Value (NPV)

\[ \text{NPV} = \frac{d}{c+d} \]

- 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:

- \( \text{LR}+ > 1.0 \) increases the probability the disorder is present. A test with \( \text{LR}+ > 10 \) is particularly useful
- \( \text{LR}+ < 1.0 \) decreases the probability the disorder is present. A test with \( \text{LR}+ < 0.1 \) is particularly useful

### Positive Likelihood Ratio (LR+)

\[ \text{LR}+ = \frac{\text{sensitivity}}{\text{1 - specificity}} \]

### Negative Likelihood Ratio (LR-)

\[ \text{LR}^- = \frac{\text{1 - sensitivity}}{\text{specificity}} \]

### Accuracy

\[ \text{Accuracy} = \frac{a+d}{a+b+c+d} \]

- 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**
  - disease prevalence (if no other diagnostic test previously performed) or post test probability (after other initial investigations)
- **Pre-Test Odds** = pre test probability/(1 - pre test probability)
- **Post-Test Odds** = pre test odds \times likelihod 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)

**DIAGNOSTIC TESTS (CONT’D)**

**2×2 TABLE**

<table>
<thead>
<tr>
<th></th>
<th>Outcome positive</th>
<th>Outcome negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure positive</td>
<td>a</td>
<td>b</td>
<td>a+b</td>
</tr>
<tr>
<td>Exposure negative</td>
<td>c</td>
<td>d</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
<td>a+b+c+d</td>
</tr>
</tbody>
</table>

**ODDS RATIO (OR)** case control study

\[ \text{OR} = \frac{ad}{bc} \]

Odds ratio approximates RR if the disease is relatively rare

**RELATIVE RISK (RR)** cohort study

\[ \text{RR} = \frac{a/(a+b)}{c/(c+d)} \]

**RELATIVE RISK REDUCTION (RRR)**

\[ \text{RRR} = \frac{a/(a+b) - c/(c+d)}{c/(c+d)} \]

**ABSOLUTE RISK REDUCTION (ARR)**

\[ \text{ARR} = a/(a+b) - c/(c+d) \]

**NUMBER NEEDED TO TREAT (NNT)**

\[ \text{NNT} = \frac{1}{\text{ARR}} \]

Smoking Cessation

**COMPLICATIONS AND SMOKING ASSOCIATED DISORDERS**

**CANCER** lung, head and neck (larynx, pharynx, oral cavity), esophagus, pancreas, bladder, kidney, stomach, cervix, AML

**CARDIOVASCULAR DISEASES** CAD, CVD, PVD, Buerger’s disease

**RESPIRATORY DISEASES** COPD, pneumonia

**METABOLIC** diabetes mellitus, infertility, premenopause, 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 unpleasurable effects of nicotine withdrawal such as dysphoria, anxiety, irritability, insomnia, decreased concentration, increased appetite and over the long term increased weight

**LUNG CANCER** cigarette smoke contains numerous carcinogenic substances. In particular, N nitrosamines and polycyclic aromatic hydrocarbons are metabolized to nitrosamine ketone and N’ nitroso normononitro nicotine 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.

Smoking Cessation

**NEJM 2002 346:7; NEJM 2008 359:19**

**NEJM 2008**

**PATHOPHYSIOLOGY OF SMOKING (CONT’D)**

Smoking Cessation
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
APPRAISAL 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.

OBSTACLES TO CESSATION
- WEIGHT GAIN AFTER QUITTING 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)
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, hemochromatosisis, amyloidosis, sarcoïdosis, porphyria

ENDOCRINE diabetes, hyperthyroidism

HEMOCROMATOSIS

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 (nor mally 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, cho langiocarcinoma 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 (CONT’D)

chronological, cardiac (arrhythmia especially con duction 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, hypersplen ism), 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, PO4, 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 con figuration → deposition in different organs

CLINICAL FEATURES constitutional (fatigue, weight loss), renal (nephrotic range proteinuria, dis tal RTA, nephrogenic diabetes insipidus), cardiac (HF, cardiomyopathy, arrhythmia, heart block, MI),
AMYLOIDOSIS (CONT'D)
neurologic (peripheral neuropathy, autonomic neuropathy), GI tract (GI bleed, malabsorption, pseudo obstruction), 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 k light chain, whereas light chain deposition disease involves lambda 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 connective tissue diseases) → cryoglobulin precipitates with complexes at temperature <37°C [<98.6°F] → deposition in different organs/vesels → 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), spleenomegaly, lymphadenopathy
DIAGNOSIS laboratory (↑ cryoglobulin level >800 μg/L or cryocrit >1% over 3-6 months, hypo complementemia, ↑ 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, hypotenremia), 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 acute 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, hypotenremia), 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 HEREDITARY COPROPHORPHYRIA acutephase symptoms related to the nature of precursors. There are seven types of porphyria representing defects at each of the seven steps of the pathway

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 sulfa*methoxazole 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)

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**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 ARHYTHMIAS** high grade AV block, Mobitz II AV block, 3rd degree AV block, supraventricular 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 cm², 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%) intraoperative necal 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

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**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 day s=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 CBC, 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, radio nuclide 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 under going 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/know lung pathologies
- **PULMONARY FUNCTION TESTS** patients under going thoracic or upper abdominal surgery with unexplained dyspnea and for those with COPD or asthma where clinical evaluation can not determine if airflow obstruction has been optimally reduced
- **LUNG RESECTION WORKUP** patients with pre operative FEV1 >2 L can probably tolerate pneumonectomy. Patients with FEV1 <2 L but pre dicted postoperative FEV1 >800 mL can probably tolerate lung resection. DLCO <40% suggests high postoperative risk. Patients with VO2max >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). Angio plasty (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 mg PO daily or bisoprolol 5 mg 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

3. **BACTERIAL ENDOCARDITIS PROPHYLAXIS**
   - **HIGH-RISK CARDiac CONDITIONS**
     - PROSTHETIC prosthetic cardiac valve, prosthetic material used for cardiac valve repair
     - CYANOTIC CONGENITAL HEART DISEASE unre paired, 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 teeth, perforation of oral mucosa
     - RESPIRATORY TRACT tonsillectomy, adenoidectomy, bronchoscopy with a rigid broncho scope, 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 4h 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, propranolol, metoprolol, or esmolol). α Agonists (continue up to and including day of surgery. If prolonged NPO, substitute with TD clonidine or IV methyl dopa). 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 5-10X, 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 ×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 ×24 h, then 25 mg q8h ×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)

- DVT PROPHYLAXIS early ambulation, intermittent pneumatic compression, low dose heparin, LMWH, coumadin

- BLEEDING RISK ASSESSMENT inquire about any recurrent bleeding tendencies and bleeding complications from past surgeries. Review Hb, platelets, INR, and PTT

- ANESTHETIC RISK ASSESSMENT inquire about past surgeries and family history of malignant hyperthermia

- DELIRIUM RISK ASSESSMENT inquire about alcohol and illicit drug use, and diagnosis of dementia to assess the risk of postoperative 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★

- Wound infection
- Wind pulmonary (pneumonia, atelectasis, PE)
- Weins DVT/PE
POSTOPERATIVE COMPLICATIONS (CONT’D)

- Water UTI
- Wonder drugs
- What the heck sepsis
- What else thyroid storm

POSTOPERATIVE DELIRIUM ★DIMS★ (see p. 380 for more details)

- Drugs alcohol withdrawal, benzodiazepines, pain (i.e. lack of appropriate drugs)
- Infections pneumonia, UTI, sepsis
- Metabolic myocardial infarction, hypoxia (pulmonary embolism), electrolyte abnormalities
- Structural stroke, intracranial hemorrhage

POSTOPERATIVE HYPERTENSION (see p. 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
- 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

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Private driver</th>
<th>Professional driver</th>
</tr>
</thead>
<tbody>
<tr>
<td>First seizure</td>
<td>3 months</td>
<td>12 months</td>
</tr>
<tr>
<td>EtOH withdrawal</td>
<td>6 months (EtOH and seizure free and completed rehabilitation)</td>
<td></td>
</tr>
<tr>
<td>Epilepsy</td>
<td>6 months (seizure free on meds)</td>
<td>5 years (seizure free on/off meds)</td>
</tr>
<tr>
<td>MI</td>
<td>1 month</td>
<td>3 months</td>
</tr>
<tr>
<td>PTCA</td>
<td>48 h</td>
<td>7 days</td>
</tr>
<tr>
<td>CABG</td>
<td>1 month</td>
<td>3 months</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>If no symptoms</td>
<td>If no symptoms</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>1 week</td>
<td>1 month</td>
</tr>
<tr>
<td>Heart failure</td>
<td>No if NYHA ≥IV</td>
<td>No if NYHA ≥II, EF &lt;35% or &gt;3 VT on Holter</td>
</tr>
<tr>
<td>AAA</td>
<td>No if &gt;5 cm [≥2 in.]</td>
<td>No if &gt;5 cm [≥2 in.]</td>
</tr>
<tr>
<td>TIA</td>
<td>If no symptoms</td>
<td>If no symptoms</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 month</td>
<td>1 month</td>
</tr>
</tbody>
</table>
**GENERAL PRINCIPLES (CONT’D)**

<table>
<thead>
<tr>
<th>Vision</th>
<th>Private driver</th>
<th>Professional driver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vision</td>
<td>No if poor vision &lt;20/50, hemianopsia, or diplopia</td>
<td>No if poor vision &lt;20/40, hemianopsia, or diplopia</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No if hypoglycemia ≤6 months</td>
<td>No if unstable insulin regimen, hypoglycemia, ≤6 months, neuropathy, retinopathy</td>
</tr>
<tr>
<td>COPD</td>
<td>No if on home O₂ (need road test)</td>
<td>No if on home O₂</td>
</tr>
</tbody>
</table>

**NOTE**: regulations for specific jurisdiction may vary

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**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**
- **ACTUAL PROCEDURE**

**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
- 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**

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**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 sel dom 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 representatives 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
**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

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**Asystole/PEA**

- VF/pulseless VT
- Tachycardia 12 lead ECG
- Bradydysrhythmias

**VF/pulseless VT**

- **Asystole/PEA**
- **VF/pulseless VT**
- **Tachycardia 12 lead ECG**
- **Bradydysrhythmias**

**Important Principles**

- **CPR**—ensure good compressions by allowing chest to recoil vs. trying to minimize interrupting compressions. Aim for 100 compressions per min for 2 m in each cycle. Continue until regain pulse.

  - For initial resuscitation should be done on one or more high-quality CPR. Frequent pulse check, initiation, and central line insertion, and medical care often separating from this important task.

  - **Airway**—avoid hyperinflation as this could increase intrathoracic pressure. Initial use of oropharyngeal airway with bag-valve-mask is reasonable, 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 5 s.

  - **Access**—the preferred route is through a peripheral intravenous (IV) line, which can be easily established early. The intravenous (IV) route represents a second choice, and central line and endotracheal tube should be the last resort for medication access.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>% sat</td>
<td>Percentage saturation</td>
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<td>AAA</td>
<td>Abdominal aortic aneurysm</td>
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<td>ABC</td>
<td>Airway, breathing, circulation</td>
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<td>Arterial blood gas</td>
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<td>Left lower quadrant</td>
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<td>Lower motor neuron</td>
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<td>Level of consciousness</td>
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<td>MCV</td>
<td>Mean corpuscular volume</td>
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<td>PTCL</td>
<td>Peripheral T-cell lymphoma</td>
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<tr>
<td>PTH</td>
<td>Parathyroid hormone</td>
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<td>PTLD</td>
<td>Post-transplant lymphoproliferative disease</td>
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<tr>
<td>PTP</td>
<td>Post transfusion purpura</td>
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<tr>
<td>PTT</td>
<td>Partial thromboplastin time</td>
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<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td>PTU</td>
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<td>PUD</td>
<td>Peptic ulcer disease</td>
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<td>PVC</td>
<td>Paroxysmal ventricular contraction</td>
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<tr>
<td>PVD</td>
<td>Peripheral vascular disease</td>
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<tr>
<td>QID</td>
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<tr>
<td>RA</td>
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<tr>
<td>RAA</td>
<td>Right atrial abnormality</td>
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<tr>
<td>RAE</td>
<td>Right atrial enlargement</td>
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<tr>
<td>RAS</td>
<td>Renal artery stenosis</td>
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<tr>
<td>RBBB</td>
<td>Right bundle branch block</td>
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<td>RBC</td>
<td>Red blood cell</td>
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<tr>
<td>RCA</td>
<td>Right coronary artery</td>
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<tr>
<td>RDW</td>
<td>Red blood cell distribution width</td>
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<tr>
<td>RF</td>
<td>Rheumatoid factor</td>
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<td>RLL</td>
<td>Right lower lobe</td>
</tr>
<tr>
<td>RLQ</td>
<td>Right lower quadrant</td>
</tr>
<tr>
<td>RPGN</td>
<td>Rapidly progressive glomerulonephritis</td>
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<tr>
<td>RR</td>
<td>Respiratory rate, relative risk</td>
</tr>
<tr>
<td>RRR</td>
<td>Relative risk reduction</td>
</tr>
<tr>
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<td>Respiratory syncytial virus</td>
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<tr>
<td>RSVp</td>
<td>Right ventricular systolic pressure</td>
</tr>
<tr>
<td>RTA</td>
<td>Renal tubular acidosis</td>
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<tr>
<td>RT-PCR</td>
<td>Reverse transcriptase polymerase chain reaction</td>
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<td>RUL</td>
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<tr>
<td>RUQ</td>
<td>Right upper quadrant</td>
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<tr>
<td>RSAH</td>
<td>Subarachnoid hemorrhage</td>
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<td>SCLC</td>
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<td>SCT</td>
<td>Stem cell transplant</td>
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<td>Sensitivity</td>
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<td>SLL</td>
<td>Chronic lymphocytic lymphoma</td>
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<td>Spc</td>
<td>Specificity</td>
</tr>
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<td>SPN</td>
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<tr>
<td>SR</td>
<td>Slow release</td>
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<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
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<td>Sick sinus syndrome</td>
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<td>SSSS</td>
<td>Staphylococcal scalded skin syndrome</td>
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<td>STE</td>
<td>ST elevation</td>
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<td>SVC</td>
<td>Superior vena cava</td>
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<tr>
<td>SVR</td>
<td>Systemic vascular resistance</td>
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<td>SVT</td>
<td>Supraventricular tachycardia</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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<tr>
<td>TBI</td>
<td>Total body irradiation</td>
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<td>TCA</td>
<td>Tricyclic antidepressants</td>
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<tr>
<td>TD</td>
<td>Transdermal</td>
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<tr>
<td>TEE</td>
<td>Transesophageal echocardiogram</td>
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<tr>
<td>TGL</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
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<tr>
<td>TIBC</td>
<td>Total iron-binding capacity</td>
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<tr>
<td>TD</td>
<td>Three times per day</td>
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<td>TMI</td>
<td>Thrombolysis in myocardial infarction</td>
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<td>TIPS</td>
<td>Transjugular intrahepatic portosystemic shunt</td>
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<td>TNF</td>
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<td>TP-EIA</td>
<td>Treponema pallidum enzyme immunoassay</td>
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<td>Total parenteral nutrition</td>
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<td>TPO</td>
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<td>Thyroid stimulating hormone</td>
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<td>TST</td>
<td>Tuberculin skin test</td>
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<td>TTE</td>
<td>Transthoracic echocardiogram</td>
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<tr>
<td>TTP</td>
<td>Thrombotic thrombocytopenic purpura</td>
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<tr>
<td>TUR</td>
<td>Transurethral resection</td>
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<tr>
<td>TURP</td>
<td>Transurethral resection of prostate</td>
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<tr>
<td>U/A</td>
<td>Urinalysis</td>
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<td>UGI</td>
<td>Upper gastrointestinal</td>
</tr>
<tr>
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<td>Usual interstitial pneumonia</td>
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<tr>
<td>UMN</td>
<td>Upper motor neuron</td>
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<td>UNC</td>
<td>Urine net charge</td>
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<td>Ultrasound</td>
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<td>Urinary tract infection</td>
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<td>Ultraviolet</td>
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<td>V/Q</td>
<td>Ventilation/perfusion</td>
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<tr>
<td>VAP</td>
<td>Ventilator-associated pneumonia</td>
</tr>
<tr>
<td>VC</td>
<td>Vital capacity</td>
</tr>
<tr>
<td>VDRL</td>
<td>Venereal Disease Research Laboratory</td>
</tr>
<tr>
<td>VF</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>VHL</td>
<td>Von Hippel–Lindau syndrome</td>
</tr>
<tr>
<td>VLDP</td>
<td>Very low density lipoprotein</td>
</tr>
<tr>
<td>VRE</td>
<td>Vancomycin-resistant enterococci</td>
</tr>
<tr>
<td>VSD</td>
<td>Ventricular septal defect</td>
</tr>
<tr>
<td>VT</td>
<td>Ventricular tachycardia</td>
</tr>
<tr>
<td>VWD</td>
<td>Von Willebrand disease</td>
</tr>
<tr>
<td>VZV</td>
<td>Varicella zoster virus</td>
</tr>
<tr>
<td>WBC</td>
<td>White blood cell</td>
</tr>
<tr>
<td>WPW</td>
<td>Wolff–Parkinson–White</td>
</tr>
</tbody>
</table>
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**

<table>
<thead>
<tr>
<th></th>
<th>SI units</th>
<th>US units</th>
<th>SI—US ratio</th>
<th>US—SI ratio</th>
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<tbody>
<tr>
<td><strong>Hematocrit</strong></td>
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<tr>
<td>Male</td>
<td>0.41—0.50</td>
<td>41—50%</td>
<td>100</td>
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<tr>
<td>Female</td>
<td>0.35—0.45</td>
<td>35—45%</td>
<td>100</td>
<td>0.01</td>
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<tr>
<td><strong>Hemoglobin</strong></td>
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<tr>
<td>Male</td>
<td>140—175 g/L</td>
<td>14—17.5 g/dL</td>
<td>0.1</td>
<td>10</td>
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<tr>
<td>Female</td>
<td>120—160 g/L</td>
<td>12—16 g/dL</td>
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<tr>
<td><strong>RBC count</strong></td>
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<td></td>
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<tr>
<td>Male</td>
<td>4.5—5.9 × 10^12/L</td>
<td>4.5—5.9 × 10^9/μL</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Female</td>
<td>4.0—5.2 × 10^12/L</td>
<td>4.0—5.2 × 10^9/μL</td>
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<td>1</td>
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<tr>
<td><strong>Platelet count</strong></td>
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<td></td>
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<tr>
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<td>140—440 × 10^3/L</td>
<td>140—440 × 10^9/μL</td>
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<td>1</td>
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<tr>
<td><strong>WBC count</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil</td>
<td>1.7—7.3 × 10^9/L</td>
<td>1.7—7.3 × 10^6/μL</td>
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<td>1</td>
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<tr>
<td>Lymphocyte</td>
<td>1.0—4.8 × 10^9/L</td>
<td>1.0—4.8 × 10^6/μL</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Monocyte</td>
<td>0.08—0.70 × 10^9/L</td>
<td>0.08—0.70 × 10^6/μL</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Eosinophil</td>
<td>0.04—0.40 × 10^9/L</td>
<td>0.04—0.40 × 10^6/μL</td>
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<td>1</td>
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<tr>
<td>Basophil</td>
<td>0—0.10 × 10^9/L</td>
<td>0—0.10 × 10^6/μL</td>
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<tr>
<td>CD4 count</td>
<td>0.64—1.18 × 10^9/L</td>
<td>640—1175/mm³</td>
<td>1000</td>
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<tr>
<td>CD8 count</td>
<td>0.34—0.88 × 10^9/L</td>
<td>335—875/mm³</td>
<td>1000</td>
<td>0.001</td>
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<td>CD4:CD8 ratio</td>
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<td>1.0—4.0</td>
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<tr>
<td><strong>Reticulocyte count</strong></td>
<td>0.005—0.025</td>
<td>0.5—2.5%</td>
<td>100</td>
<td>0.01</td>
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**COAGULATION STUDIES**

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<th>US—SI ratio</th>
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<tbody>
<tr>
<td>aPTT</td>
<td>22.1—35.1 s</td>
<td>22.1—35.1 s</td>
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<td>1</td>
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<tr>
<td>Bleeding time</td>
<td>2—9.5 min</td>
<td>2—9.5 min</td>
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<td>1</td>
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<tr>
<td>D-dimer</td>
<td>&lt;0.5 mg/L</td>
<td>&lt;0.5 μg/mL</td>
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<tr>
<td>INR</td>
<td>0.8—1.2</td>
<td>0.8—1.2</td>
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<td>1</td>
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<tr>
<td>PT</td>
<td>10—13 s</td>
<td>10—13 s</td>
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<td>1</td>
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<tr>
<td>Thrombin time</td>
<td>16—24 s</td>
<td>16—24 s</td>
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**TUMOR MARKERS**

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<td>AFP</td>
<td>&lt;15 μg/L</td>
<td>&lt;15 ng/mL</td>
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<td>1</td>
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<tr>
<td>β2 microglobulin</td>
<td>0—2 mg/L</td>
<td>0—2 mg/mL</td>
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<td>1</td>
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<tr>
<td>CA 19–9</td>
<td>&lt;37 kU/L</td>
<td>&lt;37 U/mL</td>
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<td>1</td>
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<tr>
<td>CA 27.29</td>
<td>&lt;32 kU/L</td>
<td>&lt;32 U/mL</td>
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<td>CA 125</td>
<td>&lt;35 kU/L</td>
<td>&lt;35 U/mL</td>
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<tr>
<td>CEA</td>
<td>&lt;4 μg/L</td>
<td>&lt;4 ng/mL</td>
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<tr>
<td>HCG</td>
<td>&lt;5 IU/L</td>
<td>&lt;5 mIU/mL</td>
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<tr>
<td>PSA</td>
<td>&lt;4 μg/L</td>
<td>&lt;4 ng/mL</td>
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### Serum protein electrophoresis

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<tr>
<td>Total protein</td>
<td>60—80 g/L</td>
<td>6—8 g/dL</td>
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<tr>
<td>Globulins</td>
<td>25—35 g/L</td>
<td>2.5—3.5 g/dL</td>
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<tr>
<td>Alpha1</td>
<td>2—4 g/L</td>
<td>0.2—0.4 g/dL</td>
<td>0.1</td>
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<tr>
<td>Alpha2</td>
<td>5—9 g/L</td>
<td>0.5—0.9 g/dL</td>
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<tr>
<td>Beta</td>
<td>6—11 g/L</td>
<td>0.6—1.1 g/dL</td>
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<tr>
<td>Gamma</td>
<td>7—17 g/L</td>
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### CHEMISTRY

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<td>Albumin</td>
<td>35—50 g/L</td>
<td>3.5—5 g/dL</td>
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<td>Calcium</td>
<td>2.05—2.55 mmol/L</td>
<td>8.2—10.2 mg/dL</td>
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<td>0.25</td>
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<td>Creatinine</td>
<td>53—106 µmol/L</td>
<td>0.6—1.2 mg/dL</td>
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<td>Cr clearance</td>
<td>1.24—2.08 mL/s</td>
<td>75—125 mL/min</td>
<td>59.9</td>
<td>0.017</td>
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<td>Glucose</td>
<td>4.2—6.4 mmol/L</td>
<td>75—115 mg/dL</td>
<td>18.02</td>
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<tr>
<td>Glucose</td>
<td>&lt;6.7 mmol/L</td>
<td>&lt;120 mg/dL</td>
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<td>0.0555</td>
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<tr>
<td>Na</td>
<td>136—142 mmol/L</td>
<td>136—142 mEq/L</td>
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<td>K</td>
<td>3.5—5.0 mmol/L</td>
<td>3.5—5.0 mEq/L</td>
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<tr>
<td>Cl</td>
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<td>96—106 mEq/L</td>
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<tr>
<td>Cr</td>
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<td>8—23 mg/dL</td>
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<tr>
<td>Fasting</td>
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<td>0.0555</td>
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<tr>
<td>Postprandial 2 h</td>
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<td>&lt;120 mg/dL</td>
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<tr>
<td>HCO₃⁻</td>
<td>22—30 mmol/L</td>
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<td>2.78</td>
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</tr>
<tr>
<td>Glucose</td>
<td>4.2—6.4 mmol/L</td>
<td>75—115 mg/dL</td>
<td>18.02</td>
<td>0.0555</td>
</tr>
<tr>
<td>Glucose</td>
<td>&lt;6.7 mmol/L</td>
<td>&lt;120 mg/dL</td>
<td>18.02</td>
<td>0.0555</td>
</tr>
<tr>
<td>Electrolytes panel</td>
<td>4.2—6.4 mmol/L</td>
<td>75—115 mg/dL</td>
<td>18.02</td>
<td>0.0555</td>
</tr>
<tr>
<td>Glucose</td>
<td>&lt;6.7 mmol/L</td>
<td>&lt;120 mg/dL</td>
<td>18.02</td>
<td>0.0555</td>
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</table>

### Lipid profile

<table>
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<th>SI—US ratio</th>
<th>US—SI ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL</td>
<td>&lt;2.59 mmol/L</td>
<td>&lt;100 mg/dL</td>
<td>38.5</td>
<td>0.026</td>
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<tr>
<td>Near normal</td>
<td>2.59—3.34 mmol/L</td>
<td>100—129 mg/dL</td>
<td>38.5</td>
<td>0.026</td>
</tr>
<tr>
<td>Borderline high</td>
<td>3.36—4.12 mmol/L</td>
<td>130—159 mg/dL</td>
<td>38.5</td>
<td>0.026</td>
</tr>
<tr>
<td>High</td>
<td>4.13—4.99 mmol/L</td>
<td>160—189 mg/dL</td>
<td>38.5</td>
<td>0.026</td>
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<tr>
<td>Very high</td>
<td>≥4.91 mmol/L</td>
<td>≥190 mg/dL</td>
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<td>HDL</td>
<td>38.5</td>
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<td>Low</td>
<td>&lt;1.03 mmol/L</td>
<td>&lt;40 mg/dL</td>
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<td>High</td>
<td>≥1.55 mmol/L</td>
<td>≥60 mg/dL</td>
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<tr>
<td>Total cholesterol</td>
<td>&lt;5.17 mmol/L</td>
<td>&lt;200 mg/dL</td>
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<tr>
<td>Borderline high</td>
<td>5.17—6.17 mmol/L</td>
<td>200—239 mg/dL</td>
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<tr>
<td>High</td>
<td>≥6.18 mmol/L</td>
<td>≥240 mg/dL</td>
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<td>Triglycerides</td>
<td>&lt;1.8 mmol/L</td>
<td>&lt;160 mg/dL</td>
<td>90.9</td>
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### Liver function tests

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<td>ALP</td>
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<td>50—120 U/L</td>
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<td>Bilirubin</td>
<td>5—21 µmol/L</td>
<td>0.3—1.2 mg/dL</td>
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<td>Direct</td>
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<td>&lt;0.2 mg/dL</td>
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### CHEMISTRY (CONT'D)

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<td>Magnesium</td>
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<td>2.4</td>
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<td>Phosphate</td>
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<td>Uric acid</td>
<td>240–510 μmol/L</td>
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<td>Vitamin B12</td>
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<td>Normal</td>
<td>&gt;185 pmol/L</td>
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<td>Lipase</td>
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### ENDOCRINE TESTING

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<td>ACTH</td>
<td>&lt;26 pmol/L</td>
<td>4.54</td>
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<td>Aldosterone</td>
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<td>Supine</td>
<td>55–250 pmol/L</td>
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<td>Standing</td>
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<td>Calcitonin</td>
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<tr>
<td>Male</td>
<td>0.8–7.6 pmol/L</td>
<td>3.42</td>
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<tr>
<td>Female</td>
<td>0.58–5.0 pmol/L</td>
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<tr>
<td>Cortisol</td>
<td>8 am–noon</td>
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<td>Noon–8 pm</td>
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<td>8 pm–8am</td>
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<td>EPO</td>
<td>5–36 U/L</td>
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<td>Glucagon</td>
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<td>Insulin</td>
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<td>Metanephrine</td>
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<td></td>
<td>&lt;0.5 nmol/L</td>
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<tr>
<td></td>
<td>Urine, 24 h</td>
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<td>&lt;5 μmol</td>
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<td>Norepinephrine</td>
<td>89–473 nmol</td>
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<td></td>
<td>Urine, 24 h</td>
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<tr>
<td>Prolactin</td>
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<td>Female</td>
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<td>0–10 ng/mL</td>
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<td>PTH</td>
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<td>Testosterone</td>
<td>Men</td>
<td>270–1070 ng/dL</td>
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<td>Women</td>
<td>6–86 ng/dL</td>
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<td>Thyroglobulin</td>
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<td>TSH</td>
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<td>Free</td>
<td>3.5–6.5 pmol/L</td>
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<td>Total</td>
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<td>Vitamin D</td>
<td>1.25–(OH)2–vit D</td>
<td>60–108 pmol/L</td>
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<td>25–(OH) vit D</td>
<td>35–150 nmol/L</td>
<td>14–60 mg/mL</td>
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### DRUG LEVELS

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<td>Acetaminophen</td>
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<tr>
<td>Therapeutic range</td>
<td>66–199 μmol/L</td>
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<tr>
<td>Toxic range</td>
<td>&gt;1324 μmol/L</td>
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<td>Amitriptyline</td>
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<td>Therapeutic range</td>
<td>433–903 nmol/L</td>
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<tr>
<td>Toxic range</td>
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<td>Carbamazepine</td>
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<td>26–51 μmol/L</td>
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<td>DRUG</td>
<td>Therapeutic range</td>
<td>Toxic range</td>
<td>Therapeutic US</td>
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<tr>
<td>Clonazepam</td>
<td>48–190 nmol/L</td>
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<td>Clozapine</td>
<td>0.6–1.0 µmol/L</td>
<td>200–350 ng/mL</td>
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<td>Cocaine</td>
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<td>Diazepam</td>
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<td>0.35–3.51 µmol/L</td>
<td>100–1000 ng/mL</td>
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<td>Digoxin</td>
<td>Therapeutic range</td>
<td>1.0–2.6 nmol/L</td>
<td>0.8–2.0 ng/mL</td>
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<tr>
<td>Ethanol</td>
<td>Toxic dose</td>
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<td>Gentamicin</td>
<td>Peak</td>
<td>16.7–20.9 µmol/L</td>
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<td>Trough</td>
<td>&lt;4.2–8.4 µmol/L</td>
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<td>Imipramine</td>
<td>Therapeutic range</td>
<td>446–893 nmol/L</td>
<td>125–250 ng/mL</td>
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<td>Lidocaine</td>
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<td>&gt;1784 nmol/L</td>
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<td>Lithium</td>
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<td>Toxic range</td>
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<td>&gt;2 mEq/L</td>
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<td>Methadone</td>
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<td>Morphine</td>
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<td>35–280 nmol/L</td>
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<td>Nortriptyline</td>
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<td>Phenytoin</td>
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<td>44–111 µmol/L</td>
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<td>&gt;110 µmol/L</td>
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<td>Tobramycin</td>
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<td>Valproic acid</td>
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<td>347–1040 µmol/L</td>
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<td>Toxic range</td>
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<td>Vancomycin</td>
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<td>3–7 µmol/L</td>
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<td>Amikacin</td>
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<td>43–60 µmol/L</td>
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<td>Trough</td>
<td>6.8–13.7 µmol/L</td>
<td>4–8 µg/mL</td>
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