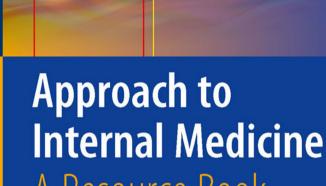
David Hui



A Resource Book for Clinical Practice

Third Edition





# Approach to Internal Medicine

Approach to Internal Medicine

A Resource Book for Clinical Practice

Third Edition

*бу* 

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To Ella and Rupert

David Hui

# Disclaimer

Approach to Internal Medicine is meant to be a practical field guide. Dosages of medications are provided for quick reference only. Readers should consult other resources before applying information in this manual for direct patient care. The author, editors, and publisher of Approach to Internal Medicine cannot be held responsible for any harm, direct or indirect, caused as a result of application of information con tained 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  $\bigstar$ ). In addition to everyday practice, *Approach to Internal Medicine* can be effectively used as an examination study quide 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

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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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<b>Index</b>
Selected Internal Medicine Topics

# PULMONARY MEDICINE

# Section Editor: Dr. Mohit Bhutani

# **Asthma Exacerbation**

# DIFFERENTIAL DIAGNOSIS OF WHEEZING

#### **EXTRATHORACIC AIRWAY OBSTRUCTION**

- OROPHARYNX enlarged tonsils, retropharyngeal abscess, obesity, post nasal drip
- LARYNX laryngeal edema, laryngostenosis, lar yngocele, epiglottitis, anaphylaxis, severe laryn gopharyngeal reflux, and laryngospasm
- VOCAL CORDS vocal cord dysfunction, paralysis, hematoma, tumor, cricoarytenoid arthritis

# INTRATHORACIC AIRWAY OBSTRUCTION

- TRACHEAL OBSTRUCTION tracheal stenosis, tra cheomalacia, tracheobronchitis (herpetic), malig nancy, beniqn tumor, aspiration
- TRACHEAL COMPRESSION goiter, right sided aor tic arch
- LOWER AIRWAY OBSTRUCTION asthma, COPD, bronchiolitis, bronchiectasis, carcinoid tumor, aspiration, malignancy
- PARENCHYMA pulmonary edema
- VASCULAR pulmonary embolism

# PATHOPHYSIOLOGY

# **EXACERBATORS OF ASTHMA**

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

# CLINICAL FEATURES

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

# CLINICAL FEATURES (CONT'D)

**PHYSICAL** HR ↑, RR ↑, pulsus paradoxus, O<sub>2</sub> requirement, moderate severe dyspnea, barrel chest, cyanosis, hyperresonance, decreased breath sounds, wheezing, forced expiratory time

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

# INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, troponin/CK
- MICROBIOLOGY sputum Gram stain/AFB/C&S
- IMAGING CXR

#### **SPECIAL**

- ABG if acute respiratory distress
- PEAK FLOW METER need to compare bedside reading to patient's baseline
- **SPIROMETRY/PFT** (non acute setting) ↑ FEV1 >12% and an absolute ↑ by 200 mL post bronchodilators suggest asthma
- METHACHOLINE CHALLENGE (non acute setting) if diagnosis of asthma not confirmed by spirome try alone. A decrease of FEV1 >20% after metha choline challenge suggests asthma. Sens 95%

# **ACUTE MANAGEMENT**

ABC O<sub>2</sub> 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  $\times$ 7 14 days (may be shorter depending on response) or *methylprednisolone* 0.4 0.8 mg/kg IV daily (until conversion to prednisone)

**OTHERS** if refractory case and life threatening, consider IV epinephrine, IV salbutamol, theophylline, inhaled anesthetics, MgSO<sub>4</sub>

MECHANICAL VENTILATION BIPAP, intubation

2 Asthma Exacerbation

# LONG TERM MANAGEMENT

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

**ENVIRONMENTAL CONTROL avoidance** of out door/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  $2\times$ /week or  $1\times$ /day for exercise induced symp toms, symptoms  $>2\times$ /week, any nocturnal symp toms, activity limitation or PEF <80%

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

**THIRD LINE** inhaled corticosteroid plus **long acting**  $\beta 2$  **agonist** (note that long acting  $\beta 2$  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 subcuta neously q2 4weeks, dosed by IgE level and body weight, for add on therapy or inadequately controlled moderate to severe allergic asthma despite use of high doses of inhaled corticosteroid therapy

NEJM 2009 360:10

# TREATMENT ISSUES

#### COMMON INHALED MEDICATIONS

- SHORT-ACTING β AGONISTS salbutamol metered dose inhaler (MDI) 100 μg 1 2 puffs PRN or 2.5 mg NEB PRN, fenoterol MDI 100 μg 1 2 puffs PRN, terbutaline 500 μg INH PRN
- SHORT-ACTING ANTICHOLINERGICS ipratropium MDI 20 μg 2 puffs QID or 500 μg NEB QID
- LONG-ACTING β AGONISTS formoterol 6 24 μg INH BID, salmeterol diskus 50 μg i puff BID
- LONG-ACTING ANTICHOLINERGICS tiotropium 18  $\mu g$  INH daily
- INHALED CORTICOSTEROIDS beclomethasone 50 400 μg INH BID, budesonide turbuhaler 200 400 μg INH BID or 0.5 1 mg NEB BID, fluticasone 125 250 μg INH BID, ciclesonide MDI 100 400 μg INH daily (only indicated for asthma at this time, not COPD)

# **Related Topics**

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

ADMISSION CRITERIA							
	FEV1 (L)	PEF (L/min)	PaO <sub>2</sub>	Action			
Very severe			<90% with O <sub>2</sub>	Admit			
Severe	<1.6 (<40%)	<200 (<40%)	<90%	Admit			
Moderate	1.6 2.1	200 300	>90%	Admit?			
Mild	>2.1 (>60%)	>300 (>60%)	>90%	Send home			
<b>DISCHARGE CRITERIA</b> consider discharging patient if peak flow >70% of usual (or predicted) value for at							
least 1 h after bronchodilator							

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

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

COPD Exacerbation 3

# 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 leuko triene 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  $\rightarrow \downarrow$  prostaglandin  $E_2 \rightarrow \uparrow$  leukotriene synthesis  $\rightarrow$  asthma symptoms. Manage ment include ASA/NSAIDs avoidance and leukotriene antagonists (montelukast)

# SPECIFIC ENTITIES (CONT'D)

CLINICAL FEATURES (CONT'D)

# ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

- PATHOPHYSIOLOGY associated with asthma and cys tic fibrosis. Due to colonization of the airways by Aspergillus fumigatus, leading to an intense, immedi ate hypersensitivity type reaction in the airways
- CLINICAL FEATURES history of asthma, recurrent epi sodes of fever, dyspnea, and productive cough (brownish sputum). Peripheral eosinophilia. CXR find ings of patchy infiltrates and central bronchiectasis
- DIAGNOSIS above clinical features plus Aspergillus extract skin test, serum IgE level, sputum for Asper gillus and/or serologic tests (IgE and IgG against Aspergillus)
- TREATMENTS systemic glucocorticoids, itraconazole

# **COPD Exacerbation**

NEJM 2004 250:26

# DIFFERENTIAL DIAGNOSIS OF ACUTE DYSPNEA

# RESPIRATORY

- AIRWAY COPD exacerbation, asthma exacerbation, acute bronchitis, infectious exacerbation of bronchiectasis, foreign body obstruction
- PARENCHYMA pneumonia, cryptogenic organiz ing pneumonia, ARDS, acute exacerbation of interstitial lung disease
- VASCULAR pulmonary embolism, pulmonary hypertension
- PLEURAL pneumothorax, pleural effusion CARDIAC
- MYOCARDIAL HF exacerbation, myocardial infarction
- VALVULAR aortic stenosis, acute aortic regurgi tation, 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, progres sion of COPD

#### CLINICAL FEATURES

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

Cama Cma ID ID

	Sells	3pc	LNT	LN
History				
Smoking >70 pack year	40%	95%	8	0.63
Smoking ever	92%	49%	1.8	0.16

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

Accessory muscle use 24% 100% 0.70 APPROACH "no single item or combination of items from the clinical examination rules out air flow 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 car diac 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"

Decreased breath sounds 37% 90% 3.7

JAMA 1995 273:4

0.70

4 COPD Exacerbation

# CLINICAL FEATURES (CONT'D)

#### STEREOTYPES (not useful clinically)

- BLUE BLOATER (more chronic bronchitis) cough and sputum, hypoxemia, CO<sub>2</sub> retention, pulmon ary hypertension, right sided heart failure
- PINK PUFFER (more emphysema) cachexia, rela tively 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 AIR-WAY DISEASE LR+ 7.3
- MAXIMUM LARYNGEAL HEIGHT < 4 cm [<1.6 in.]
   distance between the top of thyroid cartilage
   and suprasternal notch at end of expiration. LR+ 2.8
   JAMA 2000 283:14</li>

# INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, troponin/CK, Ca, Mg, PO<sub>4</sub>
- 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 rever sible. 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 EXACERBA
TION OF COPD in hospital mortality 5 10%
GOLD CLASSIFICATION 2007 all have FEV1/FVC

- 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</li>
   <50% predicted + cor pulmonale</li>

#### **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  $0=\ge 350$  m,  $1=250\ 349$  m,  $2=150\ 249$  m,  $3=\le 149$  m
- EXERCISE MMRC DYSPNEA 0=0 1, 1=2, 2=3, 3=4
- **SCORING** hazard ratio for death from any cause per one point increase in BODE score is 1.34

NEJM 2004 350:10

# ACUTE MANAGEMENT

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

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

**STEROIDS** *prednisone* 40 60 mg PO daily ×14 days (tapering dose not necessary in all cases) or *methylprednisolone* 60 125 mg IV daily (inpatient)

ANTIBIOTICS give if any two of the following criteria are met: ↑ sputum purulence, ↑ dyspnea or ↑ sputum volume. Other considerations include the need for non invasive mechanical ventilation and "at risk" for poor outcome (substantial comorbi dities, severe COPD, frequent exacerbations >3/year, recent antibiotics within 3 months); choices depend on clinical circumstance (levoflox awcin 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). Dis ease specific self management program. **Puffer technique** education and review

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

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

FIRST LINE short acting  $\beta 2$  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  $\beta 2$  agonist plus long acting anticholinergic, with short acting  $\beta 2$  agonist PRN

 FOURTH LINE
 long acting anticholinergic plus
 plus

 long acting
 β2 agonist/inhaled corticosteroid
 corticosteroid

 combination
 (e.g. Advair, Symbicort). No role for inhaled corticosteroid alone in COPD

**FIFTH LINE** fourth line plus **theophylline** 400 mg PO daily  $\times$ 3 days, then 400 600 mg PO daily, ther apeutic level 10 20  $\mu$ g/mL

**SIXTH LINE** fifth line plus home O<sub>2</sub>

COPD Exacerbation 5

# 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, mark edly elevated respiratory rate (>35/min), fatigue and labored respiration, use of accessory muscles, wor sening hypercapnia, acidosis (especially lactic), stridor (impending upper airway obstruction), agonal breathing (impending respiratory arrest)

**LIFE PROLONGING MEASURES FOR COPD** smok ing cessation, supplemental O<sub>2</sub>

INDICATIONS FOR SUPPLEMENTAL HOME O2

ABG done in room air.  $PaO_2 < 55$  mmHg alone or  $PaO_2 < 60$  mmHg in the presence of bilateral ankle edema, cor pulmonale, or hematocrit > 56%

#### SPECIFIC ENTITIES

#### α1 ANTITRYPSIN DEFICIENCY

- PATHOPHYSIOLOGY production of an abnormal protease inhibitor (homozygous ZZ) with impaired transport out of the liver. Serum level is only 10 15% of normal → increased protease activity leads to emphysema and cirrhosis (10%)
- **DIAGNOSIS**  $\alpha$ 1 antitrypsin levels
- TREATMENTS similar to COPD,  $\alpha 1$  antitrypsin replacement

#### **BRONCHIOLITIS OBLITERANS**

- causes infection (viral, mycoplasma), inflamma tory (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 respon sive. Constrictive bronchiolitis (late, fibrotic, con centric) is not responsive to glucocorticoids

#### **BRONCHIECTASIS**

• PATHOPHYSIOLOGY airway obstruction, destruction, altered immunity → ↑ cellular and mediator

# SPECIFIC ENTITIES (CONT'D)

inflammatory response  $\rightarrow \uparrow$  elastase, sputum pro duction  $\rightarrow$  recurrent infections  $\rightarrow$  vicious cycle  $\rightarrow$  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 air ways, 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, immunosup pression, sequelae of toxic inhalation or aspiration of foreign body
  - INTERSTITIAL LUNG DISEASE traction bronchiectasis
  - INFLAMMATORY RA, SLE, Sjogren's syn drome, relapsing polychondritis, IBD
  - INHERITED α1 antitrypsin deficiency, cystic fibrosis, primary ciliary dyskinesia (Kartage ner's syndrome, Young's syndrome), tracheo bronchomegaly (Mounier Kuhn syndrome), cartilage deficiency (Williams Campbell syn drome), 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 rever sible, 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) 6 Pneumonia

# **Pneumonia**

# NEJM 2002 345:25: NEJM 2001 344:9

# **TYPES OF PNEUMONIA**

#### COMMUNITY ACQUIRED PNEUMONIA

- BACTERIAL Streptococcus pneumoniae, Staphy lococcus aureus, Haemophilus, Moraxella
- ATYPICAL Mycoplasma, Chlamydia, Legionella, TB, community acquired MRSA
- VIRAL influenza, parainfluenza, metapneumo virus, RSV, adenovirus
- FUNGAL blastomycosis, cryptococcus, histoplasmosis ASPIRATION PNEUMONIA
- POLYBACTERIAL INCLUDING ANAEROBES Bacter oides, Peptostreptococcus, Fuso bacterium spe cies and other Gram positive bacilli
- CHEMICAL PNEUMONITIS

PNEUMONIA IN THE IMMUNOCOMPROMISED (see p. 259)

# **NOSOCOMIAL PNEUMONIA**

- POLYBACTERIAL Staphylococcus aureus, MRSA, Pseudomonas aeruginosa, Enterobacteriaceae (Klebsiella, Escherichia coli, Serratia), Haemophi lus, Acinetobacter
- VIRAL influenza

VENTILATOR ASSOCIATED PNEUMONIA NURSING HOME ACQUIRED PNEUMONIA

# PATHOPHYSIOLOGY

# **COMPLICATIONS OF PNEUMONIA**

- PULMONARY ARDS, lung abscess  $\pm$  cavitary for mation, parapneumonic effusion/empyema, pleur itis  $\pm$  hemorrhage
- EXTRAPULMONARY purulent pericarditis, hypona tremia, sepsis

# CLINICAL FEATURES

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

	LK+	LK
History		
Cough	1.8	0.31
Sputum	1.3	0.55
Dyspnea	1.4	0.67
Fever	1.7 2.1	0.59 0.71
Asthma	0.10	3.8
Dementia	3.4	0.94
Immunosuppression	2.2	0.85
Physical		
RR >25	1.5 3.4	0.78 0.82
Dullness to percussion	2.2 4.3	0.79 0.93
Decreased breath sounds	2.3 2.5	0.64 0.78

# CLINICAL FEATURES (CONT'D)

	LR+	LR
Crackles	1.6 2.7	0.62 0.87
Bronchial breath sounds	3.5	0.90
Egophony	2.0 8.6	0.76 0.96

**PREDICTION RULE Diehr** (rhinorrhea 2, sore throat 1, night sweats +1, myalgias +1, sputum all day +1, RR >25+2, temp  $\geq 37.8^{\circ}$ C [ $\geq 100^{\circ}$ F] +2. If cut off = 1 (i.e.  $\geq 1$  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 charac teristics to rule in or rule out the diagnosis of pneumonia. Decision rules that use the presence or absence of several symptoms and signs to mod ify 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"

# SURFACE LUNG MARKINGS

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

# **Related Topics**

Hypoxemia (p. 92)

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

# INVESTIGATIONS

#### BASIC

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

Pneumonia 7

# INVESTIGATIONS (CONT'D)

# SPECIAL

- BRONCHOSCOPY
- NASOPHARYNGEAL SWAB if suspect viral infection, check for influenza A/B, parainfluenza, human metapneumovirus, RSV, adenovirus
- MYCOPLASMA IGM
- URINE FOR LEGIONELLA ANTIGEN

# DIAGNOSTIC AND PROGNOSTIC ISSUES

# PNEUMONIA SEVERITY OF ILLNESS (PSI) SCORE

- SCORING age, female ( 10), nursing home (+10), cancer (+30), liver disease (+20), heart failure (+10), CVA (+10), renal failure (+10), altered men tal 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), PaO<sub>2</sub> <60 mmHg or O<sub>2</sub> saturation <90% on room air (+10), pleural effusion (+10)
- UTILITY originally developed as a prognostic tool.
   Consider admission if PSI score >90. Clinical judg ment more important than PSI in determining admission

NEJM 2002 347:25

# MANAGEMENT

**ACUTE** ABC,  $O_2$ , IV, consider *salbutamol* 2.5 mg NEB q6h + q1h PRN

#### **ANTIBIOTICS**

- COMMUNITY-ACQUIRED PNEUMONIA see treatment issues for an approach to selecting the appropriate regimen (remember to adjust for renal function)
  - TETRACYCLINE  $doxycycline 100 \ \mathrm{mg} \ \mathrm{PO} \ \mathrm{BID} \times \mathrm{10} \ \mathrm{days}$
  - MACROLIDES azithromycin 500 mg PO first day, then 250 mg PO daily ×4 days; clarithromycin 250 500 mg PO BID ×10 days
  - FLUOROQUINOLONES levofloxacin 500 mg PO daily ×10 days (or 750 mg ×5 days), moxifloxacin 400 mg PO daily ×10 days; avoid if exposed to fluoroquinolone within last 3 6 months
  - β-LACTAMS amoxicillin 1 g PO TID, amoxicil lin clavulanate 2 g PO BID, cefuroxime 750 mg IV q8h or 500 mg PO BID, cefotaxime 1 g IV q8h
  - ANAEROBIC COVERAGE if suspect aspiration, add clindamycin 150 450 mg PO q6h or 600 900 mg IV q8h or metronidazole 500 mg PO/IV BID/TID
- NOSOCOMIAL PNEUMONIA see treatment issues for an approach to selecting the appropriate regimen
  - ANTI-PSEUDOMONAL ceftazidime, cefepime, mer openem, ciprofloxacin, aminoglycosides, pipera cillin tazobactam (do not use same class of agent when double covering for pseudomonas)

# MANAGEMENT (CONT'D)

- FURTHER GRAM-NEGATIVE COVERAGE ciprofloxa cin 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 nega tive 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  $\pm$  clavulanate
- COMORBIDITIES (COPD, diabetes, renal failure, HF, malignancy) macrolide or fluoroquinolone
- SUSPECTED ASPIRATION WITH INFECTION amoxi cillin clavulanate or clindamycin
- INFLUENZA WITH BACTERIAL SUPERINFECTION  $\beta$  lactam or fluoroquinolone

**INPATIENT ANTIBIOTIC CHOICE** second third generation  $\beta$  lactam plus macrolide or respiratory fluoroquinolone

#### ICU ANTIBIOTICS CHOICE

- **PSEUDOMONAS UNLIKELY** macrolide plus  $\beta$  lactam or fluoroquinolone plus  $\beta$  lactam
- Pseudomonas unlikely but  $\beta$ -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

8 Pulmonary Embolism

# 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 pneu mococcal pneumonia associated with bacteremia

**IDSA Guidelines 2003** 

Note: consider vancomycin or linezolid if MRSA sus pected; 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 pneu monia, hemorrhage), non bacterial (viral, fungal), immunocompromised host, antibiotic resistance, pneumonia complications (abscess, empyema, ARDS)

# SPECIFIC ENTITIES (CONT'D)

# **CAUSES OF RECURRENT PNEUMONIA**

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

#### **LUNG ABSCESS**

- CAUSES anaerobes (Peptostreptococcus, Prevotella, Bacteroides, Fusobacterium), Gram positive (S. milleri, microaerophilic streptococcus, S. aureus), Gram negative (Klebsiella, Haemophilus, Legionella). Nocar dia and actinomycosis can rarely cause lung abscess
- TREATMENTS clindamycin until radiographic improvement and stabilization (usually several weeks to months, can be completed with oral antibiotics once patient is stable). No need for percutaneous drainage. If complicated abscess, consider lobectomy or pneumonectomy

# **Pulmonary Embolism**

NEJM 2008 359:26

# DIFFERENTIAL DIAGNOSIS OF ACUTE DYSPNEA

# RESPIRATORY

- AIRWAY COPD exacerbation, asthma exacerbation, acute bronchitis, infectious exacerbation of bronchiectasis, foreign body obstruction
- PARENCHYMA pneumonia, cryptogenic organiz ing pneumonia, ARDS, acute exacerbation of interstitial lung disease
- VASCULAR pulmonary embolism, pulmonary hypertension
- PLEURAL pneumothorax, pleural effusion
- MYOCARDIAL HF exacerbation, myocardial infarction
- VALVULAR aortic stenosis, acute aortic regurgi tation, endocarditis
- PERICARDIAL pericardial effusion, tamponade
   SYSTEMIC sepsis, metabolic acidosis, anemia
   OTHERS neuromuscular, psychogenic, anxiety

# PATHOPHYSIOLOGY

**VIRCHOW'S TRIAD** risk factors for venous thrombo embolism

- INJURY fracture of pelvis, femur, or tibia
- HYPERCOAGUABILITY obesity, pregnancy, estrogen, smoking, cancer (high suspicion of occult malig nancy in patients who develop pulmonary embo lism while on anticoagulation), autoimmune dis orders (anticardiolipin antibody syndrome, lupus anticoagulant, IBD), genetics (history of DVT/PE,

# PATHOPHYSIOLOGY (CONT'D)

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 can cer, immobilization or surgery in last 4 weeks, miscar riages), medications (birth control pill, anticoagulation) PHYSICAL vitals (tachycardia, tachypnea, hypoten sion, fever, hypoxemia), respiratory examination (pul monary hypertension if chronic PE), cardiac examina tion (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 9

# INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, PTT, INR, troponin/CK ×3, D dimer (if low probability for PE or outpati ent), 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 abnorm ality), atrial fibrillation, right ventricular strain (T wave inversion in anterior precordial leads), non specific ST T wave changes, right axis deviation, right bundle branch block and/or S<sub>1</sub>Q<sub>3</sub>T<sub>3</sub> (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, antith rombin 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 effu sion, enlarged central pulmonary artery, elevated hemidiaphragm, Westermark's sign (abrupt trun cation 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 subseg mental 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), immo bilization or surgery in last 4 weeks (+1.5), previous DVT/PE (+1.5), hemoptysis (+1), active cancer (+1)

# 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 sus picious, pulmonary angiogram
- HIGH SUSPICION (sum >6, >70% chance) CT or V/Q scan → if negative but suspicious, leg doppler → if negative but still suspicious, pul monary angiogram

NEJM 2003 349:13

# **Related Topics**

Anticoagulation Therapy (p. 160) DVT (p. 158)

Hypercoagulable States (p. 156) Pulmonary Embolism in Pregnancy (p. 410)

# MANAGEMENT

**ACUTE** ABC, O<sub>2</sub> 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 (unfractio nated 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 fondapar inux 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 hemor rhagic 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 10 Pleural Effusion

# 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 inde finite anticoagulation
- PE AND MALIGNANCY treatment with SC LMWH better than oral warfarin. Treatment should be con tinued 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. Com monly caused by closed fractures of long bones, but may also occur with pelvic fractures, orthope dic procedures, bone marrow harvest, bone tumor lysis, osteomyelitis, liposuction, fatty liver, pan creatitis, 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 pathogno monic). Investigations may include CXR, V/Q scan, CT chest, and MRI head
- TREATMENTS supportive care as most patients will fully recover. Mortality is 10%. Primary prophylaxis includes early mobilization and maybe steroids

# **Pleural Effusion**

NEJM 2002 346:25

# DIFFERENTIAL DIAGNOSIS

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

**TRANSUDATIVE** HF, hypoalbuminemia (Gl losing enteropathy, cirrhosis, nephrotic syndrome, malnu trition), SVC obstruction, hepatohydrothorax, uri nothorax, atelectasis, trapped lung, peritoneal dialy sis, hypothyroidism, pulmonary embolism

**Note:** pulmonary embolism, malignancy, and sar coidosis can present as either exudative or transu dative effusions. HF following diuresis may become "pseudo exudative" (check albumin gradient)

# **CLINICAL FEATURES**

**HISTORY** dyspnea, cough, hemoptysis, chest pain, weight loss, fever, trauma, occupational exposures, past medical history (pneumonia, liver disease, kid ney disease, thyroid disease, cancer, HF, thromboem bolic disease, connective tissue disease, smoking), medications

**PHYSICAL** vitals, cyanosis, clubbing, tracheal devia tion 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 percus sion), cardiac examination, leg swelling (HF or DVT)

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

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

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

CLINICAL FEATURES (CONT'D)					
	Sens	Spc	LR+	LR	
Reduced tactile fremitus	82%	86%	5.7	0.21	
Reduced vocal reconance	76%	88%	6.5	0.27	

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

JAMA 2009 301:3

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, LDH, total protein, AST, ALT, ALP, bilirubin, INR, PTT, albumin
- IMAGING CXR (PA, lateral, decubitus), CT chest
- THORACENTESIS send pleural fluid for cell count and differential, Gram stain, C&S, AFB and fungal cultures, LDH, total protein, pH, and cytology. Under special circumstances, also consider amy lase, glucose, cholesterol, adenosine deaminase (for TB), albumin

#### SPECIAL

 BIOPSY closed pleural biopsy, medical thoraco scopy, bronchoscopy, surgical biopsy (video assisted thoracic surgery)

#### DIAGNOSTIC ISSUES

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

# LIGHT'S CRITERIA FOR EXUDATIVE EFFUSION

any one of the following criteria would suggest exu dative effusion: fluid/serum total protein ratio >0.5, fluid/serum LDH ratio >0.6, fluid LDH >2/3 upper limit of normal serum level

# THORACENTESIS PROCEDURE see NEJM 2006 355:e16

#### PLEURAL FLUID ANALYSIS

- FLUID ACIDOSIS (pH <7.2) complicated parapneu monic, TB, paragonimiasis, malignancy, rheuma toid arthritis, SLE, hemothorax, esophageal rupture
- FLUID GLUCOSE (<3.3 mmol/L [<60 mg/dL]) para pneumonic, TB, paragonimiasis, malignancy, rheu matoid arthritis, Churg Strauss, hemothorax

#### DIAGNOSTIC ISSUES (CONT'D)

- FLUID EOSINOPHILIA (>10%) paragonimiasis, malignancy, Churg Strauss, asbestos, drug reac tion, pulmonary embolism, hemothorax, pneu mothorax, idiopathic (20%)
- CYTOLOGY FOR MALIGNANCY
   the yield for diagnosis with single attempt is 60%, two attempts is 85%, three attempts is 90 95%; obtain as much fluid as possible to increase diagnostic yield
- FLUID FOR AFB obtain as much fluid as possible and ask laboratory to centrifuge collection and to culture sediment to increase diagnostic yield

#### MANAGEMENT

**SYMPTOM CONTROL O**<sub>2</sub>, 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 disap pears with antibiotics alone
- COMPLICATED persistent bacterial invasion and fluid collection. Characterized by pleural fluid acidosis but sterile fluid. Pleural loculation may occur as fibrin gets deposited from inflammation. Treated the same as empyema
- EMPYEMA presence of bacteria in Gram stain or pus in drainage (culture not necessary). pH often <7.2. For unloculated fluid, chest tube/small bore catheter drainage usually adequate. For locu lated effusions, thrombolytics such as streptoki nase or TPA could be considered. Thoracoscopy represents an alternative to fibrinolytics. Open decortication is the last resort

**TRAPPED LUNG** stable chronic effusion, especially with history of pneumonia, pneumothorax, thoracic surgery or hemothorax. Diagnosis is established by measuring negative change in intrapleural pressure

12 Hemoptysis

# 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

# SPECIFIC ENTITIES (CONT'D)

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, bronchiec tasis, neoplasm, foreign body, post viral
- PARENCHYMA occult infection, occult aspira tion, interstitial lung disease, lung abscess
- VASCULAR early pulmonary hypertension

#### PATHOPHYSIOLOGY

**DEFINITION OF CHRONIC COUGH** >3 weeks **COMPLICATIONS OF CHRONIC COUGH** exhaus tion, insomnia, anxiety, headaches, dizziness, hoarse ness, 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, esopha gus, diaphragm, and stomach → afferent nerves (vagus, glossopharyngeal, trigeminal, and phrenic) → cough center in the medulla
- EFFERENT cough center with cortical input → effer ent 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 endobron chial lesion suspected)
- SPIROMETRY/PFT

#### **SPECIAL**

- SINUS IMAGING
- METHACHOLINE CHALLENGE
- ESOPHAGEAL PH MONITORING

#### MANAGEMENT

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

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

# SPECIFIC ENTITIES

#### **POST NASAL DRIP**

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

# **Hemoptysis**

# **DIFFERENTIAL DIAGNOSIS**

**NON CARDIOPULMONARY** epistaxis, upper Gl bleed, coagulopathy

CARDIAC HF, mitral stenosis

#### PULMONARY

- AIRWAY bronchitis (acute, chronic), bronchiec tasis, malignancy, foreign body, trauma
- PARENCHYMA
  - MALIGNANCY lung cancer, metastasis

# DIFFERENTIAL DIAGNOSIS (CONT'D)

- INFECTIONS necrotizing pneumonia (Staphy lococcus, Pseudomonas), abscess, septic emboli, TB, fungal
- ALVEOLAR HEMORRHAGE Wegener's granuloma tosis, Churg Strauss, Goodpasture disease, pul monary capillaritis, connective tissue disease
- VASCULAR pulmonary embolism, pulmonary hypertension, AVM, iatrogenic

# PATHOPHYSIOLOGY

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

#### CLINICAL FEATURES

HISTORY characterize hemoptysis (amount, fre quency, 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), medi cations (warfarin, ASA, NSAIDs, natural supplements)

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

# INVESTIGATIONS

#### BASIC

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

# INVESTIGATIONS (CONT'D)

#### SPECIAL

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

### MANAGEMENT

**ACUTE** ABC, **O**<sub>2</sub>, **IV**, **intubation** to protect airway if significant hemoptysis

**SYMPTOM CONTROL** cough suppressants, seda tives, stool softeners. **Transfusions**. Urgent interven tional **bronchoscopy** (topical epinephrine, cold sal ine, cautery). **Angiographic arterial embolization**. **Lung resection** 

TREAT UNDERLYING CAUSE correct coagulopa thy (vitamin K 10 mg SC  $\times$ 1 dose or FFP); antibiotics; radiation for tumors; diuresis for HF; immunosup pression 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

# **Solitary Pulmonary Nodule**

# NEJM 2003 348:25

#### DIFFERENTIAL DIAGNOSIS

**MALIGNANT** bronchogenic, carcinoid, meta static cancer

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

# **CLINICAL FEATURES**

**HISTORY** dyspnea, cough, hemoptysis, wheezing, chest pain, weight loss, fever, night sweats, rheuma tologic screen, past travel history, occupational expo sures, medical history (smoking, lung cancer or other malignancies, TB, infections, rheumatoid arthritis), medications

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

# INVESTIGATIONS

# BASIC

- LABS CBCD, lytes, urea, Cr, LDH, AST, ALT, ALP, bilirubin, INR, PTT
- IMAGING old films (2 years ago), CXR, CT chest SPECIAL
- ABG
- SCREENING FOR INFLAMMATORY DISORDERS ESR, CRP, ANA, ANCA
- BIOPSY bronchoscopy or CT guided
- PET/CT SCAN if moderate to high suspicion of lung cancer

#### DIAGNOSTIC ISSUES

# FINDINGS SUGGESTIVE OF MALIGNANCY ★ABCD★

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

# 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/uncalcified calcification
- TUBERCULOSIS OR HISTOPLASMOSIS central/com plete 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 thora coscopy (for patients who cannot tolerate thoracot omy medically and physiologically)

# SPECIFIC ENTITIES

#### PANCOAST TUMOR

- PATHOPHYSIOLOGY superior sulcus tumors (mostly squamous cell carcinoma) invading and compres sing the paravertebral sympathetic chain and bra chial 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 4<sup>th</sup> and 5<sup>th</sup> digit). Other asso ciated findings include clubbing, lymphadenopa thy, phrenic or recurrent laryngeal nerve palsy, and superior vena cava syndrome
- **DIAGNOSIS** CXR, CT chest, percutaneous core biopsy
- TREATMENTS concurrent chemoradiotherapy

# SPECIFIC ENTITIES (CONT'D)

#### THORACIC OUTLET OBSTRUCTION

- PATHOPHYSIOLOGY obstruction of the neurovascu lar bundle supplying the arm at the superior aper ture 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, particu larly 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 infraclavi 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 back ward and downward), hyperabduction maneuver (raise hands above head with elbows flexed and extending out laterally from the body), and Tinel's maneuver (light percussion of brachial plexus in supraclavicular fossa reproduces symptoms)
- DIAGNOSIS cervical spine films, CXR, MRI
  - **TREATMENTS** conservative (keep arms down at night, avoiding hyperabduction), surgery

#### Related Topics

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

# **Pulmonary Hypertension**

# NEJM 2004 351:15; NEJM 2004 351:16

# WHO CLASSIFICATION OF PULMONARY HYPERTENSION

# GROUP I. PULMONARY ARTERIAL HYPERTENSION

- IDIOPATHIC primary
- FAMILIAL AND RELATED DISORDERS collagen vascular disease, congenital systemic to pulmonary shunts, portal hypertension, HIV, drugs and toxins, thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary

# WHO CLASSIFICATION OF PULMONARY HYPERTENSION (CONT'D)

hemorrhagic telangiectasia, hemoglobinopa thies, myeloproliferative disorders, splenectomy

- ASSOCIATED WITH SIGNIFICANT VENOUS OR CAPILLARY INVOLVEMENT pulmonary veno occlusive dis ease, pulmonary capillary hemangiomatosis
- PERSISTENT PULMONARY HYPERTENSION OF NEWBORN GROUP II. PULMONARY VENOUS HYPERTEN SION left sided atrial or ventricular heart disease, left sided valvular heart disease

Interstitial Lung Disease 15

# WHO CLASSIFICATION OF PULMONARY HYPERTENSION (CONT'D)

GROUP III. PULMONARY HYPERTENSION ASSO CIATED 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, pulmon ary 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 mea sured 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 ventri cular heave, palpable P2, narrowly split or paradoxi cally split S2, right sided S4, tricuspid requiritation

# CLINICAL FEATURES (CONT'D)

murmur, Graham Steell murmur (high pitched, decrescendo diastolic rumble over LUSB), crackles, congestive liver, ascites, ankle edema

### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, INR, albumin, ANA, RF, anti CCP, anti SCL 70, anticentromere antibody, ESR, HIV serology, TSH
- IMAGING CXR, CT chest, V/Q scan or CT chest PE protocol, echocardiogram
- FCG
- OVERNIGHT POLYSOMNOGRAPHY if suspect OSA
- ABG
- PFT

#### SPECIAL

RIGHT HEART CATHETERIZATION

# MANAGEMENT

**SYMPTOM CONTROL 0<sub>2</sub>, 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 HYPER

**TENSION** pulmonary artery hypertension and iso lated 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 pneumo nia (UIP), respiratory bronchiolitis associated inter stitial 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, peni cillin, sulfonylurea, gold, penicillamine, pheny toin, amiodarone, nitrofurantoin

# DIFFERENTIAL DIAGNOSIS (CONT'D)

- INFILTRATIVE lymphangitic carcinomatosis, sarcoidosis
- INFECTIONS TB, histoplasmosis, coccidioidomycosis
- **INFLAMMATORY** rheumatoid arthritis, SLE, sclero derma, ankylosing spondylitis, myositis
- CONGESTIVE HEART FAILURE
- ENVIRONMENT organic dust (hypersensitivity pneumonitis), inorganic dust (asbestos, silica, ber yllium, coal worker's pneumoconiosis)
- EOSINOPHILIA-ASSOCIATED PULMONARY INFIL-TRATES allergic bronchopulmonary aspergillo sis (ABPA), parasitic, drugs

16 Interstitial Lung Disease

## DIFFERENTIAL DIAGNOSIS (CONT'D)

 ETC pulmonary histiocytosis X, idiopathic pul monary hemosiderosis, lymphangioleiomyoma tosis, 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 med ical history (smoking), medications, family history

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

## **Related Topics**

Allergic Bronchopulmonary Aspergillosis (p. 3) Restrictive Lung Disease (p. 21) Rheumatoid Arthritis (p. 277) Sarcoidosis (p. 420) Tuberculosis (p. 250)

## INVESTIGATIONS

#### BASIC

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

#### SPECIAL

 BIOPSY bronchoscopy (transbronchial biopsy), open lung biopsy

## DIAGNOSTIC ISSUES

## CHARACTERISTIC CXR PATTERNS FOR INTERSTITIAL LUNG DISEASE

- UPPER LOBE PREDOMINANCE sarcoidosis, hyper sensitivity pneumonitis, pneumoconiosis, silico sis, histiocytosis X, PJP, ankylosing spondylitis, ABPA, TB
- LOWER LOBE PREDOMINANCE idiopathic pulmonary fibrosis, asbestosis, rheumatoid arthritis, sclero derma, drugs

## DIAGNOSTIC ISSUES (CONT'D)

- BILATERAL HILAR/MEDIASTINAL ADENOPATHY WITH INTERSTITIAL INFILTRATES sarcoidosis, berylliosis, lymphangitic carcinomatosis, TB, fungal, lymphoma
- EGGSHELL CALCIFICATION OF HILAR/MEDIASTINAL LYMPH NODES silicosis (other pneumoconiosis), TB, fungal
- CALCIFIED PLEURAL PLAQUES asbestos
- PLEURAL EFFUSIONS WITH INTERSTITIAL INFILTRATES
   HF, lymphangitic carcinomatosis, rheumatoid arthritis, SLE

## MANAGEMENT

TREAT UNDERLYING CAUSE steroids in most cases. Idiopathic pulmonary fibrosis (steroids plus either azathioprine or cyclophosphamide). Sarcoido sis (if ≥stage II or symptomatic, give steroids for at least 6 months, even with improvement of symptoms. See p. 420 for details)

#### LUNG TRANSPLANT

#### SPECIFIC ENTITIES

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

- KNOWN AS USUAL INTERSTITIAL PNEUMONIA (UIP)
   PATHOPHYSIOLOGY unknown. Fibrotic rather than inflammatory process
- DIAGNOSIS CT chest (honeycombing, interlobular septal thickening, traction bronchiectasis, periph eral, sub pleural, lack of ground glass pattern), bronchoscopy (to rule out other causes, mostly infectious); consider open lung biopsy if CT is not consistent with above
- TREATMENTS steroid monotherapy usually inef fective. For patients <50 with early disease and minimal fibrosis, consider steroids plus either azathioprine or cyclophosphamide. Lung trans plant 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 symp toms, antigen exposure, imaging findings, lavage lymphocytosis, histologic findings (poorly formed granulomas), reexposure triggers symptoms); minor criteria (bilateral crackles, ↓ DLCO, hypox emia). Combination of major and minor criteria will help raise suspicion of hypersensitivity pneumoni tis. Serology may be helpful
- TREATMENTS cessation of exposure, steroids CRYPTOGENIC ORGANIZING PNEUMONIA (COP) previously known as bronchiolitis obliterans organiz ing pneumonia (BOOP)
- CAUSES idiopathic (80%), post infectious (CMV, influenza, adenovirus, Chlamydia), drugs

Obstructive Sleep Apnea 17

## SPECIFIC ENTITIES (CONT'D)

(amiodarone, bleomycin, gold, sulfasalazine, cephalosporin, cocaine), connective tissue dis ease (RA, SLE, scleroderma, Sjogren's, dermato myositis), immunologic (essential mixed cryoglo bulinemia), transplantation (bone marrow, lung, kidney), malignancy (MDS, lymphoproliferative diseases, radiation)

 CLINICAL FEATURES about 50% of cases preceded by viral like respiratory infection. Symptoms

## SPECIFIC ENTITIES (CONT'D)

include dyspnea on exertion, persistent non pro ductive cough, and weight loss

- DIAGNOSIS characteristic findings on CXR and CT chest include bilateral, diffuse, ill defined alveolar opacities distributed peripherally. PFT shows mainly restrictive lung disease pattern
- TREATMENTS prednisone 1 mg/kg PO daily

## **Obstructive Sleep Apnea**

NEJM 2007 356:17

## DIFFERENTIAL DIAGNOSIS OF SLEEP DISORDERS

#### HYPERSOMNOLENCE

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

#### INSOMNIA

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

**PARASOMNIA** sleep walking, sleep terrors, noctur nal seizures, rapid eye movement behavior disorder

## PATHOPHYSIOLOGY

**ABNORMAL PHARYNX ANATOMY** decreased upper airway muscle tone and reduced reflexes pro tecting 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 hypersom nolence. Severe chronic hypoxemia leads to pulmon ary hypertension

**ASSOCIATIONS** obesity, hypothyroidism, acrome galy, amyloidosis, neuromuscular disease, vocal cord paralysis, nasopharyngeal carcinoma, Down syn drome (macroglossia)

**COMPLICATIONS** hypertension, pulmonary hyper tension, CAD, CVA, increased motor vehicle accidents

## **Related Topics**

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

## CLINICAL FEATURES

HISTORY daytime sleepiness, habitual snoring, wit nessed 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,  $\uparrow$  neck circumference (>42 cm [>16.5 in.] for  $\sigma$ , >39 cm [>15.4 in.] for  $\sigma$ , and acanthosis nigricans. Perform respiratory and cardiac examination (hypertension and pulmonary hypertension, restrictive lung disease). Inspect for potential causes such as nasopharyngeal carcinoma, hypothyroidism (goiter), acromegaly (course facial structures), and amyloidosis (periorbital infiltrate, shoulder pad sign)

## INVESTIGATIONS

POLYSOMNOGRAPHY ABG PFT

#### MANAGEMENT

**LIFESTYLE CHANGES** sleep hygiene (avoid day time 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, uvulopalatopharyngo plasty; 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, ↓ hypox emia, ↑ sleep quality, and ↑ cardiac function (↓ LV transmural pressure and improves cardiac output)

#### SPECIFIC ENTITIES

## **OBESITY HYPOVENTILATION SYNDROME (OHS)**

also known as Pickwickian syndrome. Defined by hypoventilation (awake  $PaCO_2 > 45$  mmHg) in the absence of other causes of hypoventilation. OHS patients have sleep disordered breathing, and most have OSA. BMI is usually  $>35~kg/m^2$ . Treatment options include respiratory stimulants, ventilatory support, oxygen therapy, and weight loss

## SPECIFIC ENTITIES (CONT'D)

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

#### RESTLESS LEG SYNDROME

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

NEJM 2003 348:21

## **Respiratory Acidosis: Hypoventilation**

#### DIFFERENTIAL DIAGNOSIS

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

#### RESPIRATORY

- **UPPER AIRWAY OBSTRUCTION** epiglottitis, laryngospasm
- LOWER AIRWAY OBSTRUCTION COPD, asthma, sleep apnea
- DEAD SPACE VENTILATION infection, pleural effusion
- MUSCULAR myasthenia gravis, Guillain Barre syndrome, myopathy, ALS, hypophosphatemia, hypokalemia
- CHEST WALL RESTRICTION kyphosis, scoliosis, ankylosing spondylitis

**PHYSIOLOGIC COMPENSATION** secondary to metabolic alkalosis

## PATHOPHYSIOLOGY

**DEFINITION OF RESPIRATORY ACIDOSIS** PaCO<sub>2</sub> >40 mmHg (or upper limit of normal), which is synonymous with hypoventilation

## INVESTIGATIONS

## BASIC

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

## MANAGEMENT

**ACUTE** ABC, O<sub>2</sub>, 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 embo lism, mechanical ventilation

**NON CARDIOPULMONARY** fever, sepsis, CNS, anxi ety, hyperthyroidism, drugs, pregnancy, liver failure

**PHYSIOLOGIC COMPENSATION** secondary to metabolic acidosis

## PATHOPHYSIOLOGY

**DEFINITION OF RESPIRATORY ALKALOSIS** PaCO<sub>2</sub> <40 mmHg (or lower limit of normal), which is synonymous with hyperventilation

## INVESTIGATIONS

#### **BASIC**

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, TSH, urinalysis, βhCG in women of reproductive age
- IMAGING CXR, CT chest
- ABG

## SPECIAL

- SEPTIC WORKUP blood C&S, urine C&S
- D DIMER if suspect PE but low probability

## MANAGEMENT

**ACUTE** ABC, O<sub>2</sub>, IV, sedation (use with great cau tion as patients may experience respiratory decompensation)

TREAT UNDERLYING CAUSE

## Hypoxemia

See HYPOXEMIA (p. 92)

## **Ventilation Issues**

See VENTILATION ISSUES (p. 94)

## **Approach to Chest Imaging**

## APPROACH TO CHEST X RAY INTEPRETATION

- 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

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

notch), NG tube, ECG leads, pacer wires, O<sub>2</sub> tubing, nipple markers (used to differentiate nipple shadows from pulmonary nodules)

## 4. MSK

- **soft tissues** fat, muscle, breast shadow
- BONES rib or clavicle #, osteoporosis
- MEDIASTINUM WIDENING right paratracheal stripe >4 mm, azygous region >4 mm, hilar involve ment, AP window, tracheal deviation, carina angle widening
- HEART
  - **CARDIOTHORACIC RATIO** heart to thorax ratio of >30% on PA film or >50% on AP suggests cardiomegaly
  - CHAMBER ENLARGEMENT see table below

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

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

#### 7. LUNGS

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

## LUNG CAVITIES

INFECTIONS bacterial (Staphylococcus,  $\beta$  hemoly tic Streptococcus, Klebsiella, Enterobacteriaceae, Nocardia [multiple cavities], anaerobes), mycobac teria (TB, non TB), fungal (histoplasmosis, coccidioi domycosis), 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, eso phagus, or cervix; adenocarcinomas such as lung, breast, and GI tract tumors; melanoma)

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

## FOCAL INFILTRATE

LOBAR PNEUMONIA LUNG INFARCTION OR HEMORRHAGE

## FOCAL INFILTRATE (CONT'D)

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

#### DIFFUSE AIRSPACE DISEASE

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

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

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

**INFLAMMATORY** cryptogenic organizing pneu monia, eosinophilic pneumonia, pulmonary alveolar proteinosis

MALIGNANCY bronchoalveolar carcinoma, lymphoma

#### RETICULAR PATTERN

#### **PULMONARY EDEMA**

INFECTIONS bacterial, viral, PJP

**INTERSTITIAL LUNG DISEASE** idiopathic pul monary fibrosis, drug induced fibrosis, pneumoco niosis, hypersensitivity pneumonitis, connective tissue disease related fibrosis, asbestosis, ankylos ing spondylitis, sarcoidosis, ABPA, opportunistic infections

**TUMOR** lymphangitic carcinomatosis (subacute)

## NODULAR OR RETICULONODULAR PATTERN

**INFECTIONS** TB (miliary), viral, fungal

INFLAMMATORY GRANULOMAS sarcoidosis, sili cosis, histiocytosis X, hypersensitivity pneumonitis

METASTASES melanoma, lung cancer, breast can cer, 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 (lym phoma, 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 sternomanubrial joint and T4 vertebra) thyr oid goiters, cystic hygromas, adenopathy, aneurysm

ANTERIOR MEDIASTINUM (in front of heart border)
★5T's★

- Thymoma
- · Thyroid retrosternal
- Teratoma
- Terrible lymphoma
- Tumor bronchogenic carcinoma

MIDDLE MEDIASTINUM (between anterior heart border and vertebral bodies) infections (TB, fun gal), neoplastic (bronchogenic, lymphoma, metas tases, neurogenic, mesothelioma), sarcoidosis, aneurysm, cysts (bronchogenic, pericardial, esopha geal), Castleman's disease (giant LN hyperplasia) POSTERIOR MEDIASTINUM neural tumors (sheath tumors [schwannomas, neurofibromas], ganglion cell tumors [neuroblastoma, ganglioneur

## MEDIASTINAL MASSES (CONT'D)

oma]), **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 inter stitial markings (upper lobes progressing to the lower lobes), bronchiectasis (peribronchial cuffing, "tram tracks," ring shadows), cysts, scarring (retraction of hilar regions), pulmonary arterial hyperten sion (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

- ID AND DEMOGRAPHICS name, date/time, age, height, weight, BMI, smoking history
- ANALYZE FLOW VOLUME LOOP AND SPIROMETRY identify obstructive or restrictive pattern
- ANALYZE SPIROMETRY identify obstructive defect, rever sibility, and severity. Note that restrictive defect cannot be diagnosed without knowledge of lung volumes
- ANALYZE LUNG VOLUMES identify restrictive defect, severity
- 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, cys tic fibrosis, bronchiolitis obliterans

#### RESTRICTIVE

- PARENCHYMAL sarcoidosis, idiopathic pulmonary fibro sis, pneumoconiosis, other interstitial lung diseases
- EXTRAPARENCHYMAL neuromuscular (diaphrag matic 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 mid dle of a FVC maneuver, represents flow of small airways

## TERMINOLOGIES (CONT'D)

**FEV1** forced expiratory volume during the first sec ond of a FVC maneuver

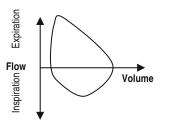
**FVC** forced vital capacity, maximum volume exhaled after maximum inhalation

MEP maximum expiratory pressureMIP maximum inspiratory pressure

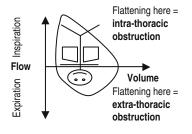
TLC total lung capacity at maximal inhalation

## FLOW VOLUME LOOP PATTERNS

## **NORMAL**

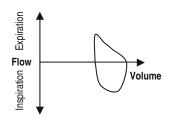


**OBSTRUCTIVE DISEASE** scooped appearance of expiratory curve seen in COPD. Variable extrathoracic obstruction (e.g. paralyzed vocal cords) appears as flattening of inspiratory curve. Variable intrathoracic obstruction (e.g. tracheal tumor) appears as flattening of expiratory curve. As illustrated by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



## FLOW VOLUME LOOP PATTERNS (CONT'D)

**RESTRICTIVE DISEASE** expiratory portion of curve appears relatively tall (preserved flow rates), but nar row (\( \) lung volumes)



## SPIROMETRY AND LUNG VOLUME PATTERNS

**OBSTRUCTIVE DISEASE** ↓ FEV1/FVC ratio (↓ FEV1 out of proportion to ↓ FVC); definitions vary but GOLD criteria define ↓ FEV1/FVC as <70%. If improvement >12% and 200 mL post bronchodilator, consider diagnosis of asthma (reversibility). Note that mild obstructive (small airways) disease may have normal FEV1/FVC with ↓ FEF 25 75%

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

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

OVERALL APPROACH				
	TLC	<u>FEV1</u> FVC	MIP	MEP
Obstructive	N/↑		N	N
Restrictive	1.77	*		
<ul> <li>Parenchymal</li> </ul>	1	N/↑	N	N
<ul> <li>Extraparenchymal (inspiratory)</li> </ul>	1	N	N/↓	N
<ul> <li>Extraparenchymal (in+expiratory)</li> </ul>	1	↓/N/↑	N/↓	N/↓

% predicted
>140%
81 140%
76 80%
61 75%
41 60%
<40%

**OBSTRUCTIVE DISEASE PRESENT** DLCO usually normal in asthma and chronic bronchitis but  $\downarrow$  in emphysema

## ANALYZING DLCO (CONT'D)

**RESTRICTIVE DISEASE PRESENT** DLCO adjusted for alveolar volume usually ↓ in interstitial lung dis eases and atelectasis and normal in neuromuscular diseases, chest wall abnormalities, and obesity **ISOLATED DLCO ABNORMALITY (WITHOUT** 

ISOLATED DLCO ABNORMALITY (WITHOUT OBVIOUS OBSTRUCTIVE OR RESTRICTIVE DIS EASE) ↓ DLCO may result from anemia, increased carboxyhemoglobinemia, PE, and pulmonary hyper tension; ↑ DLCO may result from pulmonary hemor rhage, obesity, left to right shunts, and polycythemia

24 Notes

## Notes

## **2** Cardiology

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

## **Aortic Dissection**

## DIFFERENTIAL DIAGNOSIS

#### CARDIAC

- · MYOCARDIAL myocardial infarction, angina
- VALVULAR aortic stenosis, aortic regurgitation
- PERICARDIAL pericarditis
- VASCULAR aortic dissection

#### RESPIRATORY

- · PARENCHYMAL pneumonia, cancer
- PLEURAL pneumothorax, pneumomediasti num, pleural effusion, pleuritis
- VASCULAR pulmonary embolism, pulmonary hypertension

**GI** esophagitis, esophageal cancer, GERD, peptic ulcer disease, Boerhaave's, cholecystitis, pancreatitis **OTHERS** musculoskeletal, shingles, anxiety

#### PATHOPHYSIOLOGY

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

AORTIC TEAR AND EXTENSION aortic tear may produce a tearing, ripping sudden chest pain radiating to the back. Aortic regurgitation can produce diastolic murmur. Pericardial tamponade may occur, leading to hypotension or syncope. Initial aortic tear and subsequent extension of a false lumen along the aorta may also occlude blood flow into any of the following vascular structures:

- CORONARY acute myocardial infarction (usually RCA)
- BRACHIOCEPHALIC, LEFT SUBCLAVIAN, DISTAL AORTA absent or asymmetric peripheral pulse, limb ischemia
- · RENAL anuria, renal failure
- CAROTID syncope/hemiplegia/death
- ANTERIOR SPINAL paraplegia/quadriplegia, ante rior 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 coarcta tion, Turner syndrome, aortic valve replacement
- OTHERS cocaine, trauma

#### **CLINICAL FEATURES**

## RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN ACUTE THORACIC AORTIC DISSECTION?

9
37
2

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

JAMA 2002 287:17

## INVESTIGATIONS

#### BASIC

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

## SPECIAL

AORTOGRAPHY

## DIAGNOSTIC AND PROGNOSTIC ISSUES

**CXR FINDINGS** wide mediastinum (>6 cm [2.4 in.]), indistinct aortic knuckle, pleural cap, differ ence in diameter between ascending and descending aorta, blurring of aortic margin secondary to local extravasation of blood, pleural effusion or massive hemothorax, displaced calcification (separation of the intimal aortic calcification from the edge of the aortic shadow >1 cm [0.4. in.])

#### **PROGNOSIS**

 TYPE A with surgery, 1 month survival 75 80%, 10 year survival 55%

## DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

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

## MANAGEMENT

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

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

#### **Related Topics**

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

## **Acute Coronary Syndrome**

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

## DIFFERENTIAL DIAGNOSIS OF CHEST PAIN

#### CARDIAC

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

## RESPIRATORY

STEMI

• PARENCHYMAL pneumonia, cancer

## DIFFERENTIAL DIAGNOSIS OF CHEST PAIN (CONT'D)

- **PLEURAL** pneumothorax, pneumomediasti num, pleural effusion, pleuritis
- VASCULAR pulmonary embolism

**GI** esophagitis, esophageal cancer, GERD, peptic ulcer disease, Boerhaave's, cholecystitis, pancreatitis **OTHERS** musculoskeletal (costochondritis), shin gles, anxiety

## PATHOPHYSIOLOGY

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

ST elevation MI

## PATHOPHYSIOLOGY (CONT'D)

## UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION (MI)

 TYPE 1 spontaneous MI due to a primary coron ary event (atherosclerotic plaque rupture or ero sion with acute thromboembolism)

Complete occlusion

• TYPE 2 MI due to supply demand mismatch

## PATHOPHYSIOLOGY (CONT'D)

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

## PATHOPHYSIOLOGY (CONT'D)

#### **RISK FACTORS**

- MAJOR diabetes, hypertension, dyslipidemia, smoking, family history of premature CAD, advanced age, male gender
- ASSOCIATED obesity, metabolic syndrome, seden tary lifestyle, high fat diet
- **EMERGING** lipoprotein abnormalities, inflamma tion (↑ CRP), chronic infections, renal failure

**POST MI COMPLICATIONS** arrhythmia (VT/VF, bra dycardia), sudden death, papillary muscle rupture/dys function, myocardial rupture (ventricular wall, interven tricular septum), ventricular aneurysm, valvular disease (especially acute mitral regurgitation), heart failure/car diogenic shock. pericarditis (Dressler's syndrome)

#### CLINICAL FEATURES

**CHEST PAIN EQUIVALENTS** dyspnea, syncope, fatigue, particularly in patients with diabetic neuro pathy 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, symp toms improved but angina with minimal provocation
  - IVc = unstable angina persists, not manageable on oral treatment or hemodynamically unstable

#### KILLIP CLASS CLASSIFICATION

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

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

	LR+
History	
Radiation to right shoulder	2.9
Radiation to left arm	2.3

CLINICAL FEATURES (CONT'D)	
	LR+
Radiation to both arms	7.1
Nausea or vomiting	1.9
Diaphoresis	2.0
Pleuritic chest pain	0.2
Sharp or stabbing chest pain	0.3
Positional chest pain	0.3
Chest pain reproducible by palpation	0.2 0.4
Physical	
Hypotension	3.1
<b>S3</b>	3.2
Pulmonary crackles	2.1
ECG	
New ST elevation $\geq$ 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 $\geq$ 1 mm	3.1
New T wave inversion	2.4 2.8
Any conduction defect	2.7

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

JAMA 1998 280:14

## INVESTIGATIONS

## **BASIC**

- LABS CBCD, lytes, urea, Cr, glucose, troponin/ CK ×3 q8h, AST, ALT, ALP, bilirubin, INR/PTT, Mg, Ca, PO<sub>4</sub>, 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

28 Acute Coronary Syndrome

## DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

arrhythmia, acute pericarditis, aortic dissection, PE, severe symptomatic aortic stenosis

- GOAL keep on treadmill until subject reaches 85 90% of age predicted heart rate (220 age)
- ISCHEMIA CRITERIA ≥1 mm horizontal or down sloping ST ↓ over multiple leads, or ST ↑ → myocardial ischemia (sens 68%, spc 77%) → proceed to angiogram
- INCONCLUSIVE premature termination due to chest pain/poor exercise tolerance → proceed to pharmacological stress test
- DUKE TREADMILL SCORE (exercise time in min utes) 5×(maximum ST ↓ in mm) 4×(tread mill angina index [0=none, 1=non limiting, 2=exercise limiting]). Low risk ≥5 (4 year sur vival 98 99%), moderate risk 10 to +4, high risk < 11 (4 year survival 71 79%)</li>
- DIPYRIDAMOLE/ADENOSINE MIBI dipyridamole (Per santine) causes vasodilation. In CAD, the coronary artery is already maximally dilated to compensate, so addition of dipyridamole will not change perfusion to diseased vessel(s) further. This results in a relative perfusion mismatch compared to areas with normal dilatory reaction. Contraindicated in asthma/COPD. Antidote is aminophylline or caffeine
- DOBUTAMINE ECHOCARDIOGRAPHY assesses wall motion abnormalities. Compared to MIBI, echo cardiogram is more specific and less sensitive. Contraindicated in severe hypertension and arrhythmias

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

## DIFFERENTIAL DIAGNOSIS OF TROPONIN ELEVATION

- CARDIAC myocardial infarction, myocarditis, con gestive heart failure, pericarditis, vasospasm, tachycardia with hemodynamic compromise, cocaine ingestion
- PULMONARY pulmonary embolism
- HEPATIC liver failure

**SERUM MARKERS** 

- RENAL chronic kidney disease
- NEUROLOGIC stroke, intracranial hemorrhage
- **SYSTEMIC** sepsis, prolonged strenuous exercise
- TROPONIN I/T rises within 4 6 h, peaks at 18 24 h, remains elevated 7 10 days (sens 40% at presen tation, 40 70% after 6 9 h of symptoms)

## DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- CK/CKMB rises within 4 6 h, peaks at 18 24 h, remains elevated 3 4 days (sens 35 50% at pre sentation, 90% after 3 h in ER)
- MYOGLOBIN rises within 1 2 h, peaks in few hours

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

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

## TIMI SCORE FOR PATIENTS WITH UNSTABLE ANGINA/NSTEMI

- SCORING (out of 7) age ≥65, ≥3 CAD risk factors, known CAD (stenosis >50%), ASA use within 7 days, ≥2 angina episodes within 24 h, ↑ cardiac marker, ST deviation >0.5 mm
- RISK GROUPS low = 0 2, intermediate = 3 4, high = 5 7. Consider GPIIb/IIIa and early angio graphy with revascularization in intermediate or high risk groups
- RISK OF DEATH, MI OR REVASCULARIZATION IN 14 DAYS 0/1=5%, 2=8%, 3=13%, 4=20%, 5=26%, 6/7=41%

#### TIMI SCORE FOR PATIENTS WITH STEMI

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

IN HOSPITAL OUTCOMES			
	NSTEMI	STEMI	
Death	4%	6%	
Reinfarction	0.9%	1.1%	
Cardiogenic shock	2.8%	6.4%	
Stroke	0.7%	0.8%	
Major bleeding	10%	12%	
	<b>ACTION registry 2008</b>	/2009 data	

## ACUTE MANAGEMENT

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

**PAIN CONTROL nitroglycerin** (*nitro drip* 25 mg in 250 mL D5W, start at 5  $\mu$ g/min IV, then  $\uparrow$  by 5 10  $\mu$ g/min every 3 5 min to 20  $\mu$ g/min, then  $\uparrow$  by 10  $\mu$ g/min every 3 5 min up to 200  $\mu$ g/min, or until relief of pain, stop titration if SBP is <100 mmHg. *Nitro patch* 0.4 mg/h daily. *Nitro spray* 0.4 mg SL q5min  $\times$ 3.

## ACUTE MANAGEMENT (CONT'D)

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

#### CLOT CONTROL

- ANTIPLATELET ASA 162 325 mg PO chew ×1 dose, then 75 162 mg PO daily (for medically treated unstable angina/NSTEMI), or 162 325 mg PO daily (post PCI minimum  $\times 1$  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/ Illa inhibitor (tirofiban 0.4 μg/kg/min ×30 min IV, then continue 0.1  $\mu$ g/kg/min  $\times$ 18 24 h after angioplasty/atherectomy. Eptifibatide 180 μg/kg IV bolus, then 2  $\mu$ g/kg/min  $\times$ 72 96 h)
- ANTICOAGULATION options include LMWH (enox aparin 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

## ACUTE MANAGEMENT (CONT'D)

- 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. Fibrino lytics (TPA 15 mg IV over 2 min, then 0.75 mg/kg over 30 min [maximum 50 mg], then 0.5 mg/kg over 60 min [overall maximum 100 mg]. Streptokinase 1.5 million units IV over 30 60 min. Tenectepalse IV bolus over 10 15 s, weight based: 30 mg for weight <60 kg, 35 mg for 60 69 kg, 40 mg for 70 79 kg, 45 mg for 80 89 kg, 50 mg for >90 kg)

**RATE CONTROL** IV metoprolol is mostly 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  $\beta$  blocker contraindicated, consider non dihydropyridine calcium chan nel blockers *diltiazem* 30 120 mg PO QID or *verapa mil* 80 120 mg PO TID (contraindicated if LV dysfunction)

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

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

OVERALL APPROACH			
	Stable angina	Unstable angina or NSTEMI	STEMI
ASA	✓	✓	✓
Nitrates	✓	✓	✓
Morphine	±	$\checkmark$	✓
β blockers	✓	$\checkmark$	✓
ACE inhibitors	✓	$\checkmark$	✓
HMG CoA inhibitors	✓	$\checkmark$	✓
Heparin or antithrombin	NO	$\checkmark$	✓
Clopidogrel	NO	$\checkmark$	✓
GPIIb/IIIa inhibitors	NO	$\checkmark$ (if TIMI $\ge$ 3)	NO
Fibrinolytics or PCI <sup>a</sup>	NO	NO	✓
Cardiology consult	Outpatient <sup>b</sup>	CCU <sup>c</sup>	CCU <sup>c</sup>

 $<sup>^{</sup>a}$ for fibrinolytics, the ideal door to needle time is <30 min; for PCI, the ideal door to balloon time is <90 min; urgent CABG is also an option post catheterization

## ACUTE MANAGEMENT (CONT'D)

**CAUTIONS IN TREATMENT OF ACUTE MYOCAR DIAL INFARCTION** avoid negative inotropic agents such as  $\beta$  blockers and non dihydropyridine calcium channel blockers if clinical heart failure. Avoid

## ACUTE MANAGEMENT (CONT'D)

administration of nitroglycerin, morphine, and diure tics to patients with right ventricular infarction as these medications can cause venodilation and decrease preload, leading to hypotension

<sup>&</sup>lt;sup>b</sup>Outpatient cardiology for stress test

<sup>&</sup>lt;sup>c</sup>CCU consult for risk stratification, monitoring, PCI, and/or CABG

## LONG TERM MANAGEMENT OF CORONARY ARTERY DISEASE

**ANTIANGINAL nitroglycerin** (*nitro* patch 0.4 0.8 mg/h daily; nitro spray 0.4 mg SL q5min ×3; isosorbide mononitrate 30 mg PO daily, maximum 240 mg), **β blocker** (*metoprolol* 25 100 mg PO BID, atenolol 50 100 mg PO daily, bisoprolol 5 10 mg PO daily), **calcium channel blocker** (*amlodipine* 5 10 mg PO daily)

**ACE INHIBITOR** ramipril 2.5 10 mg PO daily **ANTIPLATELET ECASA** 81 mg PO daily and/or **clo** 

pidogrel 75 mg PO daily

ANTICOAGULATION controversial especially in combination with ASA and/or clopidogrel. May be considered for patients post STEMI or NSTEMI with

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 possi bility 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 circum flex 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

## TREATMENT ISSUES (CONT'D)

- 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 echocardio gram, 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 pre sents within 12 h (ideal door to needle time <30 min), ECG criteria (>1 mm ST ↑ in ≥2 con tiguous leads, or new LBBB with suggestive his tory, 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 contraindi cation 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 treplase (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, ventri cular aneurysm, hyperkalemia, LBBB, and early repolarization abnormality

#### **Related Topics**

Aortic Dissection (p. 25)

Asystole (p. 431)

Diabetes Mellitus (p. 337)

ECG (p. 62)

Hyperlipidemia (p. 61)

Hypertension (p. 57)

Pericarditis (p. 32)

Shock (p. 97)

Smoking Cessation (p. 418)

#### TREATMENT ISSUES (CONT'D)

## PERCUTANEOUS CORONARY INTERVENTION (PCI, PTCA)

- INDICATIONS FOR ACUTE STEMI patient presents within 12 h of chest pain (ideal time from initial medical contact to treatment or "door to balloon time' <90 min), ECG criteria (>1 mm ST ↑ in ≥2 contiguous leads, new or presumed new left bun dle 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, hemato mas, 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 pacli taxel) are designed to inhibit cell proliferation and decrease the risk of in stent restenosis. There has been some controversy regarding higher observed mortality rate in patients with drug eluting stents. The most recent outcomes research analysis suggests that drug eluting stents are associated with decreased rate of repeat revascularization (19% vs. 23%, HR 0.82) at 2 years and no significant difference in mortal ity (8.4% vs. 8.4%)
- BENEFITS primary PCI is generally preferred given the superior outcomes compared to fibri nolysis, particularly if (1) fibrinolysis contraindi cated, (2) previous history of CABG, or (3) cardio genic shock. However, patients who were able to seek medical attention within 1 h of chest pain onset, allergic to contrast dye, or do not have access to PCI in a timely fashion should consider fibrinolytics

## TREATMENT ISSUES (CONT'D)

## OUTCOMES FOR FIBRINOLYTICS VS. PRIMARY PCI Fibrinolytics Primary

reinfarction and

stroke

NEJM 2007 356:1; NEJM 2007 356:10; NEJM 357:16

#### CORONARY ARTERY BYPASS GRAFT SURGERY

- CORONARY ANATOMY
  - RIGHT CORONARY (RCA) gives rise to right mar ginal (RMA), right posterior descending (RPDA), and right posterolateral branches (RPL 1, 2, 3)
  - LEFT MAIN (LM) gives rise to left anterior des cending (LAD) → diagonal (D1, 2 3) and septals; ramus intermediate (Ram Int); and left circum flex (LCX) → obtuse marginal (OM 1, 2, 3)
  - DOMINANT ARTERY defined as the artery that sup plies 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. Dia betic 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% symp tom free at 5 years. Recurrent disease more com mon 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 sto mach (GA). A total of 90% of arterial graft and 50% of vein graft remain patent by 10 years
- COMPLICATIONS
  - CARDIAC MI 2 4%, arrhythmia (AF 40%, sustained VT/VF 2 3%), AV block requiring pacemaker 0.8 4%, pericarditis/tamponade, aortic dissection
  - NEUROLOGICAL stroke, postoperative delirium, cognitive impairment, depression, phrenic nerve damage, intercostal nerve damage
  - OTHERS renal failure, bleeding, infection, pleural effusions
- MEDICATIONS hold clopidogrel 5 7 days prior to CABG. Continue ASA before and after surgery

## **Pericardial Diseases: Pericarditis and Tamponade**

## DIFFERENTIAL DIAGNOSIS

#### **★MINT**★

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

**INFARCTION** MI (early, late)

INFECTIOUS HIV, Coxsackie, echovirus, adenovirus, TB INFLAMMATORY psoriatic arthritis, enteric arthritis, rheumatoid arthritis, SLE, mixed connec tive tissue disease

## DIFFERENTIAL DIAGNOSIS (CONT'D)

## **IDIOPATHIC**

**NEOPLASTIC** primary (mesothelioma), metasta sis (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 TAMPONADE?

	Sens	Spc
History		
Dyspnea	87 89%	
Fever	25%	
Chest pain	20%	
Cough	7 10%	
Physical		
Tachycardia	77%	
Pulsus paradoxus >10 mmHg <sup>a</sup>	82%	70%
Elevated JVP	76%	
↓ heart sounds	28%	
Hypotension	26%	
Hypertension	33%	
Tachypnea	80%	
Peripheral edema	21 28%	
Pericardial rub	19 29%	
Hepatomegaly	28 55%	
Kussmaul sign	26%	
ECG		
Low voltage	42%	
Atrial arrhythmia	6%	
Electrical alternans	16 21%	
ST elevation	18 30%	
PR depression	18%	
aPulsus paradovus IR+ 3.3 IR 0.03		

<sup>&</sup>lt;sup>a</sup>Pulsus paradoxus LR+ 3.3, LR 0.03

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

JAMA 2007 297:16

DISTINGUISHING FEATURES OF ACUTE TAMPONADE AND CHRONIC CONSTRICTIVE PERICARDITIS  Acute tamponade  Constrictive pericarditis			
Va. 1	•	•	
Vitals	Tachycardia, Hypotension +++, Pulsus paradoxus	Hypotension, Pulsus paradoxus (rare)	
JVP	Elevated, Kussmaul (rare)	Elevated, Kussmaul	
	Prominent x' descent but blunted y descent	Prominent x' and y descent (Friedrich's sign)	
Apex beat	Impalpable	Impalpable	
Heart sounds	Distant	Distant, early S3/knock	
Other features	Dullness and bronchial breath sounds over left base (Ewart sign)	Hepatosplenomegaly, edema	

## INVESTIGATIONS

#### BASIC

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

#### SPECIAL

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

## MANAGEMENT

**ACUTE PERICARDITIS ASA** (650 mg PO TID  $\times$ 3 4 weeks), **NSAIDs** (indomethacin 25 50 mg PO TID  $\times$ 2 4 weeks). Add **colchicine** 0.6 mg PO BID  $\times$ 3 months for adjuvant treatment and long term pro phylaxis. **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  $\times 4$  8 weeks) or **NSAIDs** (*indomethacin* 25 50 mg PO TID  $\times 4$  8 weeks). Add **colchicine** (0.6 mg PO BID $\times 2$  months) for adjuvant treatment and long term prophylaxis. Avoid anticoagulation as risk of hemopericardium. **Prednisone** 0.25 0.5 mg/kg PO daily may also be useful, although symptoms may recur upon withdrawal

## MANAGEMENT (CONT'D)

**TAMPONADE** ABC, **O**<sub>2</sub>, *IV*'s, bolus IV fluids, **pericar diocentesis** (subxyphoid blind approach, echocardio gram guided parasternal or apical approach), **pericar diectomy**, **pericardial window** if recurrent/malignant effusion. Avoid nitroglycerin and morphine if tampo nade as they may decrease preload, leading to worsen ing of cardiac output

**CONSTRICTIVE PERICARDITIS** complete pericar diectomy

#### 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 inflam matory signs or tamponade suggests chronic idio pathic 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 ele vated JVP. Tamponade causes restriction in left or right ventricular diastolic filling. Tamponade with inflamma tory signs suggests malignant effusion (LR+ 2.9)

constrictive pericarditis contraction of peri cardium due to chronic inflammation, leading to left and/or right heart failure. May follow pericarditis or radiation. May be difficult to distinguish from restric tive cardiomyopathy clinically

## **Heart Failure**

## NEJM 2003 348:20 Canadian Heart Failure Guidelines 2006

## DIFFERENTIAL DIAGNOSIS OF HF EXACERBATION/ DYSPNEA

#### CARDIAC

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

#### RESPIRATORY

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

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

- VASCULAR pulmonary embolism, pulmonary hypertension
- PLEURAL pneumothorax, pleural effusion
   SYSTEMIC sepsis, ARDS, metabolic acidosis, ane mia, neuromuscular, psychogenic, anxiety

#### PATHOPHYSIOLOGY

## ANATOMIC/PHYSIOLOGIC CLASSIFICATION OF CARDIOMYOPATHY

 DILATED (dilatation and impaired contraction of one or both ventricles) idiopathic, ischemic, valvular, viral, genetic, late manifestation of hypertrophic heart disease, tachycardia induced, alcohol induced, peripartum

## PATHOPHYSIOLOGY (CONT'D)

- HYPERTROPHIC (disorder with disproportionate hypertrophy of the left ventricle and occasionally right ventricle) idiopathic (autosomal dominant inheritance with incomplete penetrance), storage disease (Fabry's disease, Pompe disease, Hurler's syndrome, Noonan's syndrome), athlete's heart, obesity, amyloid
- RESTRICTIVE (non dilated ventricles with impaired ventricular filling) idiopathic familial, infiltrative (amyloidosis, hemochromatosis, sarcoidosis), drugs, radiation, endomyocardial fibrosis
- ARRHYTHMOGENIC RIGHT VENTRICULAR (replacement of right ventricular free wall with fatty tissue) arrhythmogenic RV dysplasia
- UNCLASSIFIABLE endocardial fibroelastosis, left ventricular non compaction

## ETIOLOGIC CLASSIFICATION OF CARDIOMYOPATHY

- ISCHEMIC CARDIOMYOPATHY (mostly dilated) vary ing 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, restric tive) left ventricular hypertrophy and dysfunction
- **DIABETIC CARDIOMYOPATHY** (dilated) left ventricu lar dysfunction in the absence of atherosclerosis or hypertension
- INFLAMMATORY CARDIOMYOPATHY (mostly dilated)
   infectious (diphtheria, rheumatic fever, scarlet
   fever, typhoid fever, meningococcal, TB, Lyme dis
   ease, Leptospirosis, RMSF, poliomyelitis, influenza,
   mumps, rubella, rubeola, variola, varicella, EBV,
   Coxsackie virus, echovirus, CMV, hepatitis, rabies,
   mycoplasma, psittacosis, arboviruses, histoplasmo
   sis, cryptococcosis, Chagas disease), autoimmune,
   idiopathic myocardial inflammatory diseases
- METABOLIC CARDIOMYOPATHY (dilated, restrictive, and/or hypertrophic) endocrine (thyrotoxicosis, hypothyroidism, acromegaly, pheochromocy toma), storage diseases (glycogen storage disease, Fabry's disease, Gaucher's disease, Nie mann Pick disease), nutritional deficiencies (Beriberi, Kwashiorkor, pellagra), deposition (amyloidosis, hemochromatosis, sarcoidosis)

## PATHOPHYSIOLOGY (CONT'D)

- MUSCULAR DYSTROPHIES (mostly dilated) Duch enne, Becker's, myotonic dystrophy
- NEUROMUSCULAR Friedreich's ataxia (hyper trophic), Noonan's syndrome, lentiginosis
- GENERAL SYSTEMIC DISEASE (mostly dilated) con nective tissue diseases (rheumatoid heart dis ease, ankylosing spondylitis, SLE, scleroderma, der matomyositis), granulomatous (sarcoidosis, Wegener's granulomatorsis, granulomatous myo carditis), other inflammatory (giant cell myocar ditis, hypersensitivity myocarditis), neoplasm (pri mary, 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, cardio myopathy (dilated, infiltrative), valvular (aortic regurgitation, mitral regurgitation, burn out aor tic stenosis), burn out hypertension and myocarditis
- DIASTOLIC DYSFUNCTION (normal LVEF) S4 (stiff ventricle), LVH, \( \preceq\) ventricular relaxation, normal LVEF, \( \preceq\) chamber pressures. Mechanisms include decreased active relaxation and passive relaxation (stiff ventricle). Causes include ischemia, hypertension, valvular (aortic stenosis), cardio myopathy (restrictive, hypertrophic), and pericar dial disease
- MIXED DYSFUNCTION in many cases, diastolic dys function is present with systolic heart failure

## PRECIPITANTS OF HF ★FAILURE★

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

## CLINICAL FEATURES

## DISTINGUISHING FEATURES BETWEEN COPD AND HEART FAILURE

COPD Heart Failure
History Previous COPD Previous HF
Medications Medications

Inspect Nicotine stain, barrel chest

Laryngeal height <4 cm

Cardiac exam Subxyphoid cardiac pulse Elevated JVP, S3, S4

## CLINICAL FEATURES (CONT'D)

COPD Hyperresonance

Resp. exam Hyperresonance Prolonged expiratory time

Investigations CXR shows hypeinflation

ABG shows hypercapnia and hypoxemia

**Heart Failure** 

Bilateral crackles

CXR shows redistribution and cardiomegaly

ABG shows hypoxemia

Elevated BNP

## CLINICAL FEATURES (CONT'D)

**LEFT HEART FAILURE** left sided S3, rales, wheezes, tachypnea. Causes include previous MI, aor tic 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

## CLINICAL FEATURES (CONT'D)

in 1 2 min, **4** = stretched skin, fluid leaking, very deep edema present after 5 min

## NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

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

# RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS DYSPNEIC PATIENT IN THE EMERGENCY DEPARTMENT HAVE CONGESTIVE HEART FAILURE? Sens Spc LR+ LR

History	50.15	SPC		
Initial clinical judgment	61%	80%	4.4	0.45
Hx heart failure	60%	90%	5.8	0.45
Myocardial infarction disease	40%	87%	3.1	0.69
Coronary artery	52%	70%	1.8	0.68
Dyslipidemia	23%	87%	1.7	0.89
Diabetes	28%	83%	1.7	0.86
Hypertension	60%	56%	1.4	0.71
Smoker	62%	27%	0.84	1.4
COPD	34%	57%	0.81	1.1
PND	41%	83%	2.6	0.70
Orthopnea	50%	77%	2.2	0.65
Edema	51%	76%	2.1	0.64
Dyspnea on exertion	84%	34%	1.3	0.48
Fatigue and weight gain	31%	70%	1.0	0.99
Cough	36%	61%	0.93	1.0
Physical				
S3	13%	99%	11	0.88
AJR	24%	96%	6.4	0.79
JVD	39%	92%	5.1	0.66
Rales	60%	78%	2.8	0.51
Any murmur	27%	90%	2.6	0.81
Lower extremity edema	50%	78%	2.3	0.64
Valsalva maneuver	73%	65%	2.1	0.41
SBP <100 mmHg	6%	97%	2.0	0.97
S4	5%	97%	1.6	0.98
SBP ≥150 mmHg	28%	73%	1.0	0.99
Wheezing	22%	58%	0.52	1.3
Ascites	1%	97%	0.33	1.0
CXR				
Pulmonary venous congestion	54%	96%	12	0.48

CLINICAL FEATURES (CONT'D)				
	Sens	Spc	LR+	LR
Interstitial edema	34%	97%	12	0.68
Alveolar edema	6%	99%	6.0	0.95
Cardiomegaly	74%	78%	3.3	0.33
Pleural effusions	26%	92%	3.2	0.81
Any edema	70%	77%	3.1	0.38
Pneumonia	4%	92%	0.50	1.0
Hyperinflation	3%	92%	0.38	1.1
ECG				
Atrial fibrillation	26%	93%	3.8	0.79
New Twave changes	24%	92%	3.0	0.83
Any abnormal finding	50%	78%	2.2	0.64
ST elevation	5%	97%	1.8	0.98
ST depression	11%	94%	1.7	0.95
BNP				
BNP ≥100 pg/mL			4.1	0.09
For potionts with an actionated	CED -f 15 CO   / !-	. /1 722 - 41	L-1-1-6 201 /	

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 abdominojugular reflux (AJR). To perform the AJR, the blood pressure cuff is pumped  $6\times$  and then pressed against the abdomen at 20 35 mmHg for 15 30 s. Normal = no change in JVP, or transient increase of >4 cm that returns to baseline before 10 s, or sustained increase <3 cm throughout. Positive AJR occurs when abdominal compression causes a sustained increase in JVP >4 cm (sens 24%, spc 96%, LR+6.4)

**APPROACH** "once the JVP is identified, measure the vertical height. A distance  $\geq$ 4 cm above the sternal angle is considered abnormal (i.e. CVP  $\geq$ 9cmH $_2$ O). An assessment of low JVP has an LR+ for low CVP of 3.4, while an assessment of high JVP has an LR+ for high CVP of 4.1"

JAMA 1996 275:8

## CLINICAL FEATURES (CONT'D)

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

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

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

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

## CLINICAL FEATURES (CONT'D)

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

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

JAMA 1997 277:21

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, troponin/CK ×3, BNP, D dimer, TSH, albumin
- **IMAGING** CXR, echocardiogram (check E/A ratio if diastolic dysfunction)
- ECG
   SPECIAL
- FURTHER IMAGING MIBI, MUGA
- STRESS TEST to assess ischemic heart disease
- CARDIAC CATHETERIZATION
- · ABG if severe dyspnea

## DIAGNOSTIC AND PROGNOSTIC ISSUES

## **B TYPE NATRIURETIC PEPTIDE**

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

#### **BNP**

<100 pg/mL 100 250 pg/mL 250 500 pg/mL

500 1000 pg/mL >1000 pg/mL

## Heart Failure diagnosis

Unlikely
Compensated LV dysfunction
HF with both diastolic and
systolic dysfunction
Decompensated HF
High risk of substantial HF

PROGNOSIS BNP >80<sup>th</sup> percentile is associated with a >50% increase in long term mortality
 HF PROGNOSIS 33% 1 year mortality, 75% 6 year mortality

## ACUTE MANAGEMENT

**ABC**  $O_2$  to keep sat >95%, IV's

SYMPTOM CONTROL ★LMNOP★ Lasix/furose mide 20 100 mg IV PRN, Morphine 2 5 mg IV PRN, Nitroglycerin 0.4 mg SL PRN, O<sub>2</sub>, Position (upright)

## LONG TERM MANAGEMENT

## **★DDDD**★

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

DIURETICS furosemide 20 100 IV/PO daily BID with daily adjustments (try to use smallest dose possible to allow ACE inhibitor) ± metolazone 2.5 5 mg PO 30 min before furosemide, spironolactone 12.5 50 mg PO daily or eplerenone 25 50 mg PO daily VASODILATORS ACE inhibitor (captopril 6.25 50 mg PO TID, enalapril 2.5 20 mg PO BID, ramipril 2.5 10 mg PO daily, lisinopril 2.5 20 mg PO daily, perindopril 2.8 mg PO daily). ARB (valsartan 40 160 mg PO BID, candesar tan 8 32 mg PO daily). Hydralazine 10 mg PO QID and nitropatch 0.4 mg PO daily). β blockers (metoprolol 50 100 mg PO BID, carvedilol 3.125 25 mg PO BID, bisoprolol 2.5 10 mg PO daily).

**DIGITALIS** digoxin 0.125 0.25 mg PO daily

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

**DEVICES** if ejection fraction <30 35%, consider cardiac resynchronization therapy (CRT/biventri cular pacing)  $\pm$  implantable cardioerter defibrilla tors (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) con sider substitution with ARB if ACE inhibitor *not toler ated* (e.g. cough). May also be used as adjunct to ACE inhibitor if  $\beta$  blocker not tolerated. Contraindications similar to ACE inhibitor

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

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

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

38 Digoxin Intoxication

## 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 mortal ity 0.99 and mortality/hospitalization 0.92. Particu larly useful for patients with both HF and atrial fibril lation, or symptomatic HF despite maximum treatment

**OVERALL APPROACH** treat underlying cause if possible. Non pharmacological treatments (diet, exercise, smoking cessation)  $\rightarrow$  add ACE inhibitor for all (or hydralazine/nitrates if renal failure, ARB if cough secondary to ACE inhibitor)  $\rightarrow$  add  $\beta$  blocker when euvolemic  $\rightarrow$  add spironolactone/eplerenone if NYHA III/IV  $\rightarrow$  add digoxin  $\pm$  ARB if still sympto matic. If ejection fraction is <30 35% despite optimal medical therapy, consider revascularization, implan table cardioverter defibrillator, cardiac resynchroniza tion (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/obstruc tion, 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

## SPECIFIC ENTITIES (CONT'D)

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 ventri cular wall thickness >30 mm, and family history of sudden death. Minor risk factors include left ventri cular 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, bifitid carotid pulse, double apical impulse, systolic ejection murmur (LLSB, louder with stand ing and Valsalva) ± mitral requrgitation 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 stren uous exercise), medical (β blockers and non dihy dropyridine calcium channel blockers as first line, disopyramide as second line), interventional/sur gical (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)

NEJM 2004 350:13

## **Digoxin Intoxication**

## Circulation 2004 109:24

#### 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, cardiomyopa thy, 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 col lected 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 mem brane 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 \(\gamma\) 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, hypokale mia, 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, par oxysmal atrial tachycardia, unifocal or multifocal PVCs, bidirectional ventricular tachycardia, accel erated 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, flat tened T waves, U waves, and shortened QT. Not to be confused with digoxin toxicity

## DIAGNOSTIC ISSUES (CONT'D)

 TOXIC LEVELS first degree heart block, paroxysmal atrial tachycardia, regularized atrial fibrillation, uni focal or multifocal PVCs, ventricular bigeminy, bidirectional VT

## MANAGEMENT

ACUTE ABC, O<sub>2</sub>, 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/puri fied antidigoxin FAB fragments (if ingested 10 mg of more in adults, or digoxin level >13 nmol/L [10 ng/mL], K >5 mM and life threatening arrhythmia, hemodynamic instability or severe bradycardia. May see response in 20 min and complete response up to 4 h. Monitor potassium levels after treatment with Digibind)

#### TREATMENT ISSUES

#### AVOID

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

**HALF LIVES** plasma  $t_{y_2}$  for digoxin 1.6 days, digitoxin 5 days

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

## **Atrial Fibrillation**

## NEJM 2001 344:14; NEJM 2004 351:23

#### DIFFERENTIAL DIAGNOSIS OF PALPITATIONS

## \*PPP\*

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

#### PATHOLOGIC ★CDE★

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

## DIFFERENTIAL DIAGNOSIS OF PALPITATIONS (CONT'D)

- DRUGS sympathomimetic agents, vasodilators, anticholinergic agents, β blocker withdrawal, illicit (cocaine, amphetamines)
- ENDOCRINE hypoglycemia, hyperthyroidism, pheochromocytoma

**PSYCHIATRIC** panic attack/disorder, generalized anxiety disorder, somatization

## DIFFERENTIAL DIAGNOSIS OF NARROW COMPLEX TACHYCARDIA

#### REGULAR NARROW COMPLEX TACHYCARDIA

sinus tachycardia, atrial flutter with fixed block (rate 300, 150, 100, 75, 60), supraventricular tachycardia (atrial tachycardia, AV nodal reentry, AV reentrant/WPW), accelerated junctional tachycardia

IRREGULAR NARROW COMPLEX TACHYCAR

DIA 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), wander ing pacemaker (rate 60 100), premature atrial rhythm/beat, multifocal atrial tachycardia (rate >100), ectopic atrial tachyarrhythmia with variable block, atrial flutter with variable block, atrial fibrillation

**VENTRICULAR** premature ventricular contrac tion, polymorphic ventricular tachycardia, ventricu lar fibrillation

## PATHOPHYSIOLOGY

#### **CAUSES OF ATRIAL FIBRILLATION**

- CARDIOVASCULAR myocardial (hypertension, CAD, HF, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, infiltration [amyloido sis, sarcoidosis, hemochromatosis], ASD), valvular (rheumatic, acquired, endocarditis), arrhythmia (WPW, SSS), pericardial (pericarditis), cardiac surgery
- PULMONARY COPD, pulmonary embolism, pleural effusion

## PATHOPHYSIOLOGY (CONT'D)

- METABOLIC thyrotoxicosis, obesity
- **DRUGS** theophylline, adenosine, digitalis,  $\beta$  ago nists, alcohol
- IDIOPATHIC (10%)

## **CLASSIFICATION OF ATRIAL FIBRILLATION**

- PAROXYSMAL ATRIAL FIBRILLATION episodes of AF last <7 days (usually <24 h). Self terminating</li>
- 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, dizzi ness, syncope, past medical history (AF, SVT, WPW, CAD, HF, hypertension, diabetes, stroke, TIA, thyroid dysfunction), medications (antihypertensives, antiar rhythmics), DVT/PE risk factors

**PHYSICAL** vitals (pulse rate and rhythm, blood pressure), cardiac and pulmonary examination for heart failure

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

## **CLINICAL FEATURES**

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

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

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

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

JAMA 2009 302:19

#### INVESTIGATIONS

#### **BASIC**

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

#### **SPECIAL**

• ELECTROPHYSIOLOGY STUDIES

## ACUTE MANAGEMENT

**ABC**  $O_2$  to keep sat >95%, IV

**SYNCHRONIZED CARDIOVERSION** premedicate if possible with *midazolam* 1 2 mg IV q2 3min, *fenta nyl* 50 150  $\mu$ g IV  $\times$ 1, shock 50, 100, 200, 300, 360 J, prepare to intubate and give IV anti arrhythmics PRN

#### ACUTE MANAGEMENT (CONT'D)

## AV NODAL BLOCKING AGENTS ★ABCD★

- AMIODARONE amiodarone 150 mg IV bolus over 10 min, q10 15 min. Alternatively, infusion 60 mg/h over 6 hours, then 30 mg/h over 18 h. Maximum 2.2 q/day
- β-BLOCKERS esmolol 500 μg/kg IV over 1 min, maintenance dose 50 200 μg/kg/min IV, metopro lol 5 mg IV over 1 min g5min ×3 PRN
- CALCIUM CHANNEL BLOCKERS diltiazem 15 20 mg IV over 2 min, repeat in 15min at 20 25 mg PRN, maintenance dose 5 20 mg/h IV; verapamil 2.5 5.0 mg IV over 1 2 minutes, followed by 5 10 mg in 15 30 minutes PRN with maximum of 30 mg, maintenance dose 0.05 0.2 mg/min IV
- DIGITALIS digoxin 0.25 0.5 mg IV q6h to a total dose of 1 mg, maintenance dose 0.125 0.25 mg PO/IV daily

## ACUTE MANAGEMENT (CONT'D)

#### OVERALL APPROACH

- UNSTABLE ATRIAL FIBRILLATION perform cardiover sion immediately
- STABLE ATRIAL FIBRILLATION < 48 HOUR rate con trol ( $\beta$  blockers, calcium channel blockers, digoxin) and consider rhythm control (DC cardi oversion, amiodarone, propafenone, flecainide). Need to be anticoagulated for 4 weeks post cardioversion
- STABLE ATRIAL FIBRILLATION >48 HOUR OR UNKNOWN DURATION rate control ( $\beta$  blockers, calcium chan nel blockers, digoxin) and consider **rhythm control** (IV heparin  $\rightarrow$  TEE to exclude atrial thrombus  $\rightarrow$  cardioversion within 24 h  $\rightarrow$  anticoagulate  $\times$ 4 weeks; ALTERNATIVELY anticoagulate  $\times$ 3 weeks  $\rightarrow$  cardioversion  $\rightarrow$  anticoagulate  $\times$ 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.  $\beta$  **blocker** (propranolol 10 30 mg PO TID QID, metoprolol 50 100 mg PO BID). **Calcium channel blockers** (diltiazem CD 120 480 mg PO daily). **Digitalis** (digoxin 0.5 mg PO  $\times$ 1 dose, then 0.25 mg  $\times$ 2 doses q6 12h, then 0.125 0.25 mg daily)

RHYTHM CONTROL elective cardioversion (only after a 3 week course of therapeutic anticoagulation or atrial thrombus excluded by TEE. Cardioversion should be followed by 4 weeks of anticoagulation). Antiarrhythmics (amiodarone 200 400 mg PO daily, sotalol 80 160 mg PO BID, especially if CAD; flecainide 50 mg PO q12h, especially if no structural heart disease; propafenone 150 mg PO q8h, especially if no structural heart disease)

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

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

## TREATMENT ISSUES

## STROKE RISK FACTORS IN PATIENTS WITH ATRIAL FIBRILLATION ★CHADS2★

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

## TREATMENT ISSUES (CONT'D)

- DIABETES (1 point)
- STROKE OR TIA (2 points)
- RISK OF STROKE 0 points=0.49%/year (lone AF), 1=1.5%, 2=2.5%, 3=5.3%, 4=6.0%, 5 6=6.9%
- OTHER RISK FACTORS CAD, echocardiography abnormalities (atrial size >5 cm, LV dysfunction), rheumatic valve disease (RR 17). All mitral stenosis and HOCM patients with AF should have chronic anticoagulation
- RISK REDUCTION anticoagulation decreases risk of stroke by  ${\sim}60\%$  (consider warfarin if CHADS2 score  ${>}1$ ). ASA decreases risk by  ${\sim}30\%$
- RISK OF BLEEDING ON ANTICOAGULATION 1.9% per year of major bleed. Thus, only recommend antic oagulation 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 sig nificant 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 amiodar one may not develop classic symptoms of hyperthyroidism; however, recurrence of AF should prompt investigations. Hypothyroidism is more common (20%)
- PULMONARY (<3%) chronic interstitial pneumo nitis (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 ster oids 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

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## 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

NEJM 2007 356:9

#### Related Topics

ACLS (p. 431) Digoxin (p. 38) ECG (p. 62)

Wolff Parkinson White Syndrome (p. 65)

## Syncope

See SYNCOPE (p. 312)

## **Cardiac Examination**

#### PULSE

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

**BRISK PULSE** (rapid carotid upstroke) hypertrophic cardiomyopathy

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

**PULSUS BISFERIENS** (double peaked) combina tion aortic stenosis and regurgitation

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

**IRREGULARLY IRREGULAR PULSE** atrial fibrilla tion, premature atrial or ventricular contractions

## BLOOD PRESSURE

**CORRECT CUFF SIZE** width of bladder  $\geq$ 40% of arm circumference or length of bladder  $\geq$ 80% of arm circumference

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

WIDE PULSE PRESSURE isolated systolic hyper tension, 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

## BLOOD PRESSURE (CONT'D)

maneuver may be useful for determining the pre sence of pseudohypertension

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

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

## JUGULAR VENOUS PRESSURE

A WAVE atrial contraction

- PROMINENT A WAVE tricuspid stenosis, pulmonary stenosis, pulmonary hypertension, hypertrophic cardiomyopathy, and Ebstein'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 dur ing systole

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## JUGULAR VENOUS PRESSURE (CONT'D)

V WAVE atrial filling. S2 just before peak of v
 DOMINANT V WAVE tricuspid regurgitation (cv

- wave), right heart failure, atrial septal defect
- **Y DESCENT** opening of tricuspid valve/atrial emptying
- RAPID STEEP Y DESCENT constrictive pericarditis (square root sign), severe right heart failure
- DECREASED Y DESCENT tricuspid stenosis
- **BLUNTED/ABSENT Y DESCENT** tamponade

**ABDOMINOJUGULAR REFLUX (AJR)** blood pres sure 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 peri carditis, SVC obstruction, and pulmonary embolism

#### PRECORDIAL EXAMINATION

INSPECTION apex, right ventricular heave
PALPATION apex, heaves, thrills, palpable heart
sounds

- **DISPLACED APICAL BEAT** (lateral to mid clavicular line) left ventricular dilatation, LR+ 8.0
- ENLARGED APICAL BEAT (≥2.5 cm) left ventricular dilatation, LR+ 4.7
- SUSTAINED APICAL BEAT (outward impulse extends to, or past, S2) left ventricular pressure overload (aortic stenosis), volume overload (aortic regurgi tation, VSD), severe cardiomyopathy, or ventricular aneurysm
- RETRACTING APICAL BEAT (retraction during systole; inward motion begins at \$1, outward impuse after \$2) constrictive pericarditis (up to 90%), tricus pid requrgitation

## PRECORDIAL EXAMINATION (CONT'D)

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

## **HEART SOUNDS**

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

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

#### **INTENSITY OF S1 AND S2**

- LOUD P2 > A2 AT PULMONIC AREA increased pul monary pressure (left ventricular failure, mitral stenosis, pulmonary hypertension), increased pul monary 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

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

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## HEART SOUNDS (CONT'D)

High pitch sounds are best heard with the dia phragm, 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
- P2 separates from A2 on inspiration, while open ing snap tends to move closer to S2 on inspiration

## **DISTINGUISHING FEATURES BETWEEN S4 AND S1**

- S4 is usually best heart at apex with the bell while S1 is best heard at base
- 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
- Left ventricular S3 is louder at the apex while right ventricular S3 or S4 is usually best heart at left sternal border or at the base

## MURMURS

#### TIMING

- MID-SYSTOLIC aortic stenosis, aortic sclerosis, pul monary stenosis, hypertrophic obstructive cardio myopathy, atrial septal defect, flow murmurs (fever, pregnancy, hyperthyroidism, anemia, aortic regurgitation due to high flow)
- PANSYSTOLIC mitral regurgitation, tricuspid regurgitation, ventricular septal defect, aortopul monary shunts
- LATE SYSTOLIC mitral valve prolapse, papillary muscle dysfunction
- EARLY DIASTOLIC aortic regurgitation, pulmonary regurgitation
- MID-DIASTOLIC mitral stenosis, tricuspid stenosis, atrial myxoma, Austin Flint murmur of aortic regur gitation, 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 ↑ sys temic 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 sys tolic 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 \(\gamma\) venous return and \(\gamma\) systemic arterial resistance) produces opposite effect
- ISOMETRIC EXERCISE (↑ systemic arterial resis tance) murmurs caused by blood flow across normal or obstructed valves (e.g. mitral or pul monic 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 regur gitation, and ventricular septal defect, but not murmurs due to other causes

## MURMURS (CONT'D)

DISTINGUISHING FEATURES AMONG COMMON SYSTOLIC AND DIASTOLIC MURMURS										
	Systolic murmurs  Systolic murmurs  Mitral valve Mitral Aortic Aortic Hyper-				Diastolic murmurs					
Findings <sup>a</sup>	Tricuspid regurgita- tion	Mitral valve prolapse	Mitral regurgita- tion	sclerosis	Aortic stenosis	Hyper- trophic cardio- myopathy	Tricuspid stenosis	Pulmonary regurgita- tion	Mitral stenosis	Aortic regurgita- tion
Inspection	Dyspnea Cyanosis Cachexia Jaundice	Pectus excavatum Marfan's coliosis	Dyspnea	Normal	Dyspnea Sustained apex	Dyspnea Double apex	Normal	Dyspnea	Mitral facies Cyanosis Dyspnea	Argyll Robertson Marfan's Ank. spond
Radial pulse	Irregular (AF)	Normal	Irregular (AF)	Normal	Brachio- radial delay	Brisk	Irregular (AF)	Normal	Irregular (AF)	Water- hammer
BP Carotid	Normal Normal	Normal Normal	Normal Bounding Irregular (AF)	Normal Normal	Narrow PP Pulsus parvus et tardus	Normal Brisk bifid	Normal Irregular (AF)	Normal Normal	Narrow PP Irregular (AF)	Wide PP Bounding/ collapsing pulse
JVP	V wave Prominent a wave (pul. HTN), no a wave (AF)	Normal	Absent a wave (AF)	Normal	Normal	Prominent a wave	Prominent a wave, slow y descent, absent a wave (AF)	Prominent a wave (pul. HTN)	Absent a wave (AF) Prominent a wave (pul. HTN), cv wave (TR)	Normal
Palpation	Palpable P2 (pul. HTN), thrill RV heave	Normal	Enlarged, displaced apex, thrill RV heave	Normal	Sustained apex, thr II LV heave	Double api- cal impulse Thri I LV heave	Normal	Palpable P2 (pul. HTN), thr II RV heave	RV heave Palpable P2 (pul. HTN)	Sustained, displaced apex, thrill LV heave
S1 <sup>b</sup>	Soft	Normal	Soft	Normal	Normal	Normal	Wide sp it- ting S1	Normal	Loud S1	Split (chronic) Absent (acute)
S2 <sup>b</sup>	Loud (pul. HTN)	Normal	Normal	Normal	Paradoxical split, soft	Paradoxical split	Normal	Loud (pul. HTN)	Palpable P2 (pul. HTN)	Soft
S3	R sided	Normal	L sided	Normal	Normal	L sided	Normal	R sided	Absent	L sided
S4	None	Normal	Normal	Normal	L sided	L sided	Normal	R sided	Normal	L sided
Clicks or snaps	None	Mid-sys- tolic click	None	None	Early systol- ic click	None	Opening snap (LLSB)	None	Opening snap (apex)	None
Murmur <sup>c</sup>	LLSB	Apex	Apex	RUSB	RUSB	LLSB, apex	LLSB	LUSB	Apex	RUSB
	High pitch Holosystolic	High pitch Latesystolic	High pitch Holosystolic	High pitch Mid-systolic	High p tch Mid-systolic	High pitch Mid-systo ic	Low pitch Mid-diastolic	High pitch Early dias- tolic	Low pitch Mid- diastolic <sup>e</sup>	High pitch Early dias- tolic
Radiation	Xyphoid	None	Axilla	None	Clavicle Carotids	Base of heart	None	None	None	Apex Sternum
Maneuvers	† inspiration, sustained abdominal pressure	↑ standing, Valsalva <sup>d</sup> ↓ squatting	↑ isometric, transient art. occlusion	None	↑ squatting, leg raise ↓ standing, Valsalva, isometric	↑ standing, Valsalva ↓ squatting	↑ inspiration	↑ inspiration	↑ isometric ↓ standing, Valsalva	↑ isometric, transient art. occlusion, Best heard sitting up in end expira- tion
Other associated murmurs/ clinical features	Graham Steell murmur (pul. HTN) Ascites, pulsat le liver, edema	Mitral regurgitation (holosyst olic at apex)	Pulmonary edema	None	Gallavardin phenome- non (mid- systolic murmur at apex)	Mitral regur- gitation (mid- systolic at apex)	Mitral ste- nosis may also be present	PR murmur called <b>Gra-</b> <b>ham Steell</b> <b>m.</b> f sec- ondary to pul. HTN	Pulmonary and tricus- pid regurg. murmurs (pul. HTN)	Austin Flint murmur (mid-dia- stolic over apex) Mid-systolic flow m. Other signs

a Not all findings listed for each condition may be present on examination

b Loud heart sounds are usually due to mild-moderate stenotic lesions, while ight heart sounds are usually due to regurgitant or severe stenotic lesions

c Regurgitant murmurs usually start early, while stenotic murmurs tend to start mid-way

d For mitral valve prolapse, maneuvers that increase murmur intens ty also move both the click and murmur closer to S1

■ For mitral stenosis, the murmur is classically described as mid-dissolic with presystolic accentuation
I at the following special signs for aordic regurgitation are related to increased pulse pressure. These include Quincke's pulses (pulsatile fingertips and lips), Becker's sign (pulsatile relinal arterly), deMusset's sign (head bob), Mueller's sign (pulsatile vuls), Mayne's sign (DBP ↓ 15 mmHg), Ger-hard's sign (pulsatile spleen), Rosenbach's sign (pulsatile vulse), Traube's sign (pistol shot pulse in femoral arteries), Duroziez's sign (femoral artery but with compression), Hill's sign (pistol shot pulse in femoral arteries), Duroziez's sign (femoral artery but with compression), Hill's sign (pistol shot pulse in femoral arteries). Duroziez's sign (femoral artery but with compression), Hill's sign (popileal SBP-brachial SBP by 60 mmHg)

## MURMURS (CONT'D)

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

AORTIC STENOSIS 'presence of any of following significantly increases the likelihood of aortic stenosis: effort syncope, slow carotid upstroke, late or mid peaking systolic murmur, decreased or absent S2, apical carotid delay, brachioradial delay. The absence of any systolic murmur or murmur radiation to the right carotid artery reduces the likelihood of aortic stenosis'

**MITRAL REGURGITATION** "for cardiologists, absence of a mitral area murmur or a late systo lic/holosystolic murmur significantly reduces the likelihood of mitral regurgitation, except in the

## MURMURS (CONT'D)

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

TRICUSPID REGURGITATION "cardiologists can accurately detect the murmur of tricuspid regurgi tation. Cardiologists can accurately rule in and rule out tricuspid regurgitation using the quiet inspira tion and sustained abdominal pressure maneuvers" HYPERTROPHIC CARDIOMYOPATHY "cardiologists can rule in or rule out hypertrophic cardiomyo pathy by evaluating for decreased murmur intensity when the patient goes from a squatting to standing position'

Aortic Stenosis 47

## 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,

## MURMURS (CONT'D)

the likelihood of mild or greater aortic regurgita tion is increased significantly. The absence of a typical **diastolic murmur** significantly reduces the likelihood of aortic regurgitation"

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

**PULMONARY REGURGITATION** 'when a cardiolo gist 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, mur mur grade  $\geq$ 3, diastolic murmur, or when other cardiac findings are present

## **Aortic Stenosis**

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

## DIFFERENTIAL DIAGNOSIS

#### VALVULAR

- CONGENITAL MALFORMATIONS unicuspid, bicus pid, tricuspid
- CALCIFICATION degenerative or senile, athero sclerosis, Paget's disease, chronic renal failure
- **INFECTIONS** rheumatic fever, *Chlamydia pneu moniae*
- RHEUMATOID ARTHRITIS

#### **SUBVALVULAR**

- **DISCRETE LESIONS** membranous diaphragm, fibromuscular ring
- OBSTRUCTIVE hypertrophic cardiomyopathy
  SUPRAVALVULAR localized or discrete narrowing
  of the ascending aorta (Williams' syndrome)

**LOW GRADIENT AORTIC STENOSIS** resulting from low cardiac output

## PATHOPHYSIOLOGY

## **COMPLICATIONS** ★BEE★

- 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, hyper dynamic apical beat, systolic thrill at the base of heart, narrowly split or paradoxical splitting of S2 or absent S2, harsh mid systolic ejection murmur (radiation to carotids), Gallavardin phenomenon

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

## DISTINGUISHING FEATURES BETWEEN AORTIC SCLEROSIS AND AORTIC STENOSIS MURMUR Aortic sclerosis Aortic stenosis

Pathophysiology Abnormally thickened valve leaflets but Decreased functional area of valve to minimal outflow obstruction cause decreased outflow

Carotid pulse Normal Pulsus parvus et tardus

S2 Normal Soft single S2 (P2)

Murmur Mid systolic murmur Late peaking of systolic murmur

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## CLINICAL FEATURES (CONT'D)

## DISTINGUISHING FEATURES BETWEEN AORTIC STENOSIS, MITRAL REGURGITATION, AND HYPER TROPHIC CARDIOMYOPATHY

TROPHIC CARDIOM TOPATH							
	Aortic Stenosis	Mitral Regurgitation	HOCM				
Carotid upstroke	Slow, low amplitude	Normal or low amplitude	Brisk				
S1	Normal	Soft	Normal				
S2	Single if severe	Normal	Often reversed				
S3	No	Loud	No				
S4	If severe	No	Yes				
Loudest murmur	RUSB	Apex	LLSB and apex				
Maneuvers							
Standing	<b>↓</b>	<b>↓</b>	<b>↑</b>				
Squatting	<b>↑</b>	<b>↑</b>	<b>↓</b>				
Valsalva	<b>↓</b>	<b>↓</b>	<b>†</b>				

#### INVESTIGATIONS

## **BASIC**

- CXR
- ECHOCARDIOGRAM transthoracic
- **ECG** left ventricular hypertrophy
- EXERCISE TESTING

#### **SPECIAL**

CARDIAC CATHETERIZATION

## DIAGNOSTIC AND PROGNOSTIC ISSUES

## **AORTIC VALVE AREA AND SEVERITY**

- NORMAL =  $3.4 \text{ cm}^2$
- MILD = 1.5 2 cm<sup>2</sup> or mean gradient <25 mmHg
- MODERATE = 1 1.5 cm<sup>2</sup> or mean gradient 25 40 mmHg
- **SEVERE** = <1 cm<sup>2</sup> or mean gradient >40 mmHg
- SYMPTOMS usually do not appear until valve <1 cm². The significance of valve area depends on patient size (larger patient = more severe for same valve area)
- PROGRESSION valve area decreases by ~0.1 cm<sup>2</sup>/ year and the mean gradient increases by 7 mmHg/ year (particularly if cardiac risk factors)

## PROGNOSIS OF AORTIC STENOSIS ★ASH★ (Angina, Syncope, Heart failure)

- SEVERE AORTIC STENOSIS WITH NO SYMPTOMS 1 2% die in short period
- SEVERE AORTIC STENOSIS WITH ANGINA PRESENTA-TION 50% die in 5 years
- SEVERE AORTIC STENOSIS WITH SYNCOPE PRESENTA-TION 50% die in 3 years
- SEVERE AORTIC STENOSIS WITH HEART FAILURE PRESEN-TATION 50% die in 2 years
- SEVERE AORTIC STENOSIS AFTER VALVE REPLACEMENT survival similar to normal individuals

## MANAGEMENT

MILD OR MODERATE AORTIC STENOSIS follow clinically and with echocardiogram (every 3 5 years for mild, every 1 2 years for moderate, every year for

## MANAGEMENT (CONT'D)

severe). Statins may slow progression with early aor tic stenosis

# SEVERE OR SYMPTOMATIC AORTIC STENOSIS aortic valve replacement (see criteria below), bal loop valvuloplasty (offers no survival benefit and is

loon valvuloplasty (offers no survival benefit and is only a temporizing measure)

NASONI ATOPS we with couring in the setting of

**VASODILATORS** use with caution in the setting of hypertension or HF. ACE inhibitors preferred over  $\beta$  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 sympto matic patients
- RISK OF AVR mortality 1 2%, morbidity 1%/year (venous thromboembolic disease, bleeding, dete rioration of prosthetic valve, endocarditis)

MECHANICAL VS. BIOPROSTHETIC VALVE com pared to human tissue valves, mechanical valves have prolonged durability, but higher chance of throm boembolism and bleeding from chronic anticoagula tion. 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**

## ACC/AHA 2008 Guidelines

#### DIFFERENTIAL DIAGNOSIS

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

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

## PATHOPHYSIOLOGY

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

## CLINICAL FEATURES

#### PHYSICAL

- GENERAL APPEARANCE Marfan's syndrome, ankylos ing 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 (tap ping impulse in forearm, especially when arm is

## CLINICAL FEATURES (CONT'D)

raised vertically), **Corrigan's pulse, Mayne's sign** (>15 mmHg decrease in diastolic blood pressure with arm elevation)

- CARDIAC soft S1, left sided S3 (heart failure), dia stolic 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 REGURGITA TION MURMUR

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

## DISTINGUISHING FEATURES BETWEEN AUSTIN FLINT AND MITRAL STENOSIS MURMUR

#### **Austin Flint** Mitral stenosis Gender M > FF > MAlmost never Likely mitral stenosis Hemoptysis Rhythm Sinus Atrial fibrillation M1 Usually faint Usually loud P2 Normal or ↑ Usually loud Ventricular gallop/S3 Always present Absent Diastolic murmur Usually early or mid diastolic Often presystolic accentuation (if in sinus rhythm) Opening snap Present Absent CXR Boot shaped LAF FCG Sinus, LVH, Prolonged PR Atrial fibrillation, P mitrale

50 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 dysfunc tion <3.5%/year; sudden death <0.2%/year</li>

## 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 dilata tion, but not for long term management of asympto matic 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 symp tomatic; asymptomatic with end systolic dimension >55 mm, end diastolic dimension >75 mm, ejection fraction <50%; or asymptomatic severe aortic regur gitation at time of concomitant cardiac surgery. Intra aortic balloon pumps should not be used

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

## **Mitral Stenosis**

## ACC/AHA 2008 Guidelines; Circulation 2009 119:11

## **DIFFERENTIAL DIAGNOSIS**

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

## PATHOPHYSIOLOGY

**STENOTIC MITRAL VALVE** left ventricular inlet obstruction  $\rightarrow$  left atrial overload and left ventricle output failure  $\rightarrow$  atrial fibrillation, pulmonary hyper tension and eventually right heart failure

**VALVE AREA** normal 4 5 cm<sup>2</sup>, mild symptoms 1.5 2 cm<sup>2</sup> (mean gradient <5 mmHg), moderate symptoms 1 1.5 cm<sup>2</sup> (mean gradient 5 10 mmHg), severe symptoms <1 cm<sup>2</sup> (mean gradient >10 mmHg)

## CLINICAL FEATURES

**HISTORY** 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 laryn geal nerve), complications (endocarditis, throm boembolism), past medical history (rheumatic fever), medications

## CLINICAL FEATURES (CONT'D)

## PHYSICAL

- GENERAL APPEARANCE tachypnea, peripheral cya nosis, mitral facies (purple patches on cheeks sec ondary to vasoconstriction)
- VITALS decreased pulse volume
- JVP prominent a wave (pulmonary hyperten sion), 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)  $\pm$  pre systolic accentuation, tricus pid regurgitation
- ABDOMINAL hepatomegaly, ascites, edema

## INVESTIGATIONS

#### BASIC

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

#### **SPECIAL**

CARDIAC CATHETERIZATION

Mitral Regurgitation 51

## DIAGNOSTIC AND PROGNOSTIC ISSUES

## MITRAL VALVE AREA AND SEVERITY

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

**PROGRESSION**  $\sim$  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 dis ability. 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 pro long 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). Pro phylaxis for rheumatic fever (secondary prevention) **FOLLOW UP** any change in symptoms warrant re evaluation 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 valvu loplasty (particularly for patients with non calcified mitral valve, mild mitral regurgitation, and no other cardiac interventions) is equivalent to surgical val vuloplasty in terms of success. Average increase in valve area is 1.0 cm<sup>2</sup>

## SPECIFIC ENTITIES

## ACUTE RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

- PATHOPHYSIOLOGY group A Streptococcus infection → non suppurative inflammation with car diac, 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)
    - Nopules (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 evi dence 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 rheu matic fever (penicillin G 1.2 M U IM q4weeks, peni cillin V 250 mg PO BID, or erythromycin 250 mg PO BID if allergic to penicillin). For patients with valve involvement, therapy should continue for at least 10 years after the last episode of rheumatic fever and to at least age 40. With a history of carditis in the absence of persistent valvular disease, treat for 10 years or until age 21 (whichever is longer)

## **Mitral Regurgitation**

## ACC/AHA 2008 Guidelines

## DIFFERENTIAL DIAGNOSIS

VALVE ABNORMALITY rheumatic heart disease, infective endocarditis, mitral valve prolapse, myx omatous 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  $\rightarrow$  atrial fibrillation and left heart failure

## CLINICAL FEATURES

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

#### INVESTIGATIONS

#### BASIC

- CXR cardiomegaly, LAE
- ECHOCARDIOGRAM
- ECG P mitrale, LVH SPECIAL
- CARDIAC CATHETERIZATION

52 Endocarditis

#### 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 bet ter outcome if technically possible) or replacement if symptomatic, atrial fibrillation, pulmonary hyperten sion, 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 fail ure, pulmonary hypertension, Eisenmenger syn drome, pulmonic stenosis), valve abnormality (rheumatic heart disease, infective endocarditis,

#### SPECIFIC ENTITIES (CONT'D)

Ebstein's anomaly). Rarely is it due to isolated tricuspid valve abnormality

- CLINICAL FEATURES cachexia, jaundice, JVP cv wave, RV heave, S3 (with dilated RV), S4 (with stiff RV), holosystolic murmur (over left lower ster nal border), hepatomegaly, edema
- INVESTIGATIONS ECG (P pulmonale, RVH), CXR (cardiomegaly), echocardiogram, cardiac catheter ization, rule out intracardiac shunts
- TREATMENTS valve repair or replacement if severe symptoms

#### MITRAL VALVE PROLAPSE

- **PATHOPHYSIOLOGY** autosomal dominant inherited connective tissue disorder with morphologic abnormalities of the mitral valve (increased leaflet thickness and redundancy, chordal elongation, and sagging of the leaflets into the left atrium in systole)
- TREATMENTS ASA 75 325 mg PO daily for history of transient ischemic attacks, atrial fibrillation (age <65 years, no MR, no HTN, no HF). Anticoagulation with warfarin for atrial fibrillation (if age >65, MR, HTN, or HF), history of stroke/TIA, or left atrial thrombus

## TWO SUBTYPES OF MITRAL VALUE PROLAPSE

Mild subtype

Demographics Mainly women (age 20 50)
Pathology Mild leaflet abnormalities

Minimal MR

Symptoms Orthostatic hypotension

Palpitations

Physical Mid systolic click with or without a late

findings systolic murmur

Prognosis Few patients have progressive MR

#### Severe subtype

Mainly men (age 40 70) Myxomatous disease

Considerable leaflet thickening and MR

Atrial fibrillation

MR murmur

Chordal rupture may lead to sudden

worsening of MR

Progressive MR requiring surgery Increased risk of sudden death

## **Endocarditis**

NEJM 2001 345:18

#### **DIFFERENTIAL DIAGNOSIS**

#### INFECTIVE ENDOCARDITIS

- COMMON Streptococcus viridans (S. sanguis, S. mutans, S. mitis), Streptococcus pneumoniae, Streptococcus bovis, Enterococcus (E. faecalis, E. faecium), Staphylococcus aureus, Gram nega tive bacilli
- LONG INCUBATION TIME (7–21) DAYS ★HACEK★
  - · Haemophilus
  - Actinobacillus

## DIFFERENTIAL DIAGNOSIS (CONT'D)

- Cardiobacterium
- Eikenella
- Kinaella
- SPECIAL MEDIA Mycoplasma, Chlamydia, Legio nella, Brucella, Bartonella, Coxiella burnetii (Q fever), Histoplasma, Tropheryma whippelii

**MARANTIC ENDOCARDITIS** non bacterial throm botic endocarditis secondary to malignancy (usually adenocarcinoma) or SLE (Libman Sacks endocarditis)

Endocarditis 53

#### PATHOPHYSIOLOGY

**SUBTYPES** important to classify infective endocar ditis 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* endo carditis also have neoplasms of the GI tract

#### RISK FACTORS FOR ENDOCARDITIS

- HIGH RISK complex cyanotic congenital heart dis ease (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, dur ing 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 reci pients who develop cardiac valvulopathy
- MODERATE RISK most other congenital heart dis eases, acquired valvular disease (rheumatic heart disease, mitral/aortic/pulmonary/tricuspid stenosis or regurgitation), mitral valve prolapse with valv ular regurgitation or leaflet thickening, hyper trophic cardiomyopathy
- LOW OR NO RISK secundum ASD or surgically repaired ASD, VSD, PDA, mitral valve prolapse with thin leaflets in the absence of regurgitation, ischemic heart disease, previous CABG
- NON-CARDIAC IDU, poor dental hygiene, long term hemodialysis, long term indwelling catheter, procedures (GU, GI, surgical wound infection), dia betes, HIV

## CLINICAL FEATURES

**HISTORY** fever, murmur, dyspnea, chest pain, anorexia, weight loss, malaise, night sweats, compli cations (painful nodules, rash, stroke, myocardial infarction, any infections), past medical history (struc tural heart disease, recent procedures [dental, Gl, 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 pustular lesions

## CLINICAL FEATURES (CONT'D)

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, pul monary embolism, splenic infarction, glomerulone phritis, septic arthritis, and osteomyelitis

#### INVESTIGATIONS

#### BASIC

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

#### DIAGNOSTIC AND PROGNOSTIC ISSUES

## MODIFIED DUKE'S CRITERIA

- MAJOR positive blood culture ×2 (or positive blood culture ×1 for *C. burnetii*), echocardio graphic evidence (oscillating intracardiac mass, abscess, new partial dehiscence of a prosthetic valve), new murmur
- MINOR fever (>38°C [100.4°F]), risk factor (car diac conditions, IDU), vascular phenomena (major arterial emboli, septic pulmonary infarct, mycotic aneurysm, intracranial hemorrhage, con junctival hemorrhages, Janeway lesions), immu nologic 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 echocardio gram (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, diag nosing prosthetic valve endocarditis, and for differ entiating 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

54 Peripheral Vascular Disease

## **Related Topics**

Aortic Regurgitation (p. 49) Mitral Regurgitation (p. 51) Tricuspid Regurgitation (p. 51)

#### MANAGEMENT

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

TARGETED ANTIBIOTIC THERAPY (please refer to the Sanford guide to antimicrobial therapy) Streptococci (penicillin G 2 3MU IV q4h or ceftriax one 2 g IV/IM g24h ×4 weeks. Gentamicin 1 mg/kg IV q24h  $\times$ 2 weeks may be added in certain circum stances to shorten the course by 2 weeks). Penicil lin sensitive Enterococci (ampicillin 2 q IV q4h or vancomycin 1 q IV q12h ×4 6 weeks, plus gentami cin 1 mg/kg IV  $\alpha$ 8h  $\times$ 4 6 weeks for native valve). Penicillin resistant Enterococci (vancomvcin 1 a IV q12h ×6 weeks, plus gentamicin 1 mg/kg IV q8h ×6 weeks for native valve). S. aureus (cloxacillin 2 g IV q6h or nafcillin or oxacillin 3 g IV q6h or cefazolin 2 g IV q8h ×2 6 weeks (depending on right or left sided valve)  $\pm$  gentamicin 1 mg/kg IV g8h ×3 5days: for native valve). MRSA (vancomycin 1 g IV q12h ×6 weeks for native valve). HACEK (ceftriaxone 2 g IV/IM q24h or ampicillin sulbactam 3 g IV q6h or *ciprofloxacin* 500 mg PO BID  $\times$ 4 weeks). For prosthetic valve infection, therapy is usually longer (by 2 4 weeks) with gentamicin

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

#### TREATMENT ISSUES

**INDICATIONS FOR SURGERY** in the acute period, refractory congestive heart failure is the most impor tant indication. Other indications include perivalvular extension of infection, abscess, microbiologic failure, infection with fungi or untreatable pathogens, Sta phylococci on a prosthetic valve, two major emboli events and one major embolus event with residual large mobile vegetation

## OVERALL RECOMMENDATIONS FOR ENDOCARDI

**TIS 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, car diac transplant recipients with valvulopathy, pre vious endocarditis
- PROCEDURES
  - ORAL CAVITY manipulation of gingival or peri pical region of teeth, perforation of oral mucosa
  - RESPIRATORY TRACT tonsillectomy, adenoidect omy, bronchoscopy with a rigid bronchoscope, or flexible bronchoscopy if biopsied
  - GI/GU TRACT prophylaxis generally not recommended
- PROPHYLAXIS REGIMENS give one of the following 30 60 min prior to procedure: amoxicillin 2 g PO/ IM/IV, cefazolin 1 g IV/IM, ceftriaxone 1 g IV/IM, cephalexin 2 g PO, clindamycin 600 mg PO/IM/IV, azithromycin 500 mg PO, clarithromycin 500 mg PO

## **Peripheral Vascular Disease**

NEJM 2007 356:12

#### **DIFFERENTIAL DIAGNOSIS OF CLAUDICATION**

#### ARTERIAL

- ATHEROSCLEROSIS
- INTRALUMINAL OCCLUSION embolism, thrombo sis, dissection, adventitial cystic disease, arterial fibrodysplasia, arterial tumor, occluded limb aneurysm
- VASCULITIS Takayasu's arteritis, temporal arter itis, thromboangiitis obliterans
- VASOSPASM
- DRUGS ergot

## DIFFERENTIAL DIAGNOSIS OF CLAUDICATION (CONT'D)

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

**VENOUS** DVT, thrombophlebitis, venous congestion

**NEUROPATHIC** spinal stenosis, peripheral neuropathy

**OTHERS** arthritis (hips, knees), compartment syndrome

## **CLINICAL FEATURES**

**HISTORY** pain, discomfort, or fatigue that occurs in leg muscle with exercise and improves with resting (ischemic intermittent claudication is NOT sensitive for peripheral vascular disease), maximum walking distance, trauma, DVT risk factors, past medical his tory (CAD, HF, AF, stroke, TIA, renal disease, hyperten sion, cholesterol), medications

#### **PHYSICAL**

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

#### CLINICAL FEATURES (CONT'D)

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

VENOUS INSUFFICIENCY EXAMINATION hemo siderin deposit, pitting edema, dermatitis, cellulitis, ulcer (with prominent granulation tissue over med ial malleolus), superficial venous collaterals (DVT), varicose vein (palpate for tenderness or hardness that may suggest thrombophlebitis), Trendelen burg 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 sug gests incompetence of valves in the superficial venous system)

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

EXTREMIT I FERRI HERAE ARTERIAE DISEASE:	
LR+	LR
History	
Claudication 3.3	0.89
Inspection	
Wounds (ischemic ulcers and gangrene over lateral malleolus, tips of toes, metatarsal heads, 5.9	0.98
bunion)	
Discolouration 2.8	0.74
Atrophy	
Absence of hair	
Palpation	
•	0.38
	0.92
Capillary refill time (firm pressure to planter aspect of great toe for 5 s. Abnormal if >5 s for 1.9	
normal skin)	
Auscultation	
	0.39

**SPECIAL TESTS ankle brachial index** (ankle SBP by palpation/doppler of posterior tibial or dorsalis pedis pulse divided by brachial SBP), **Buerger test** (raise legs to  $90^{\circ}$  with patient in supine position. Check for return of rubor as the legs are lowered. Abnormal if angle of circulation  $<0^{\circ}$  i.e. legs below table), **venous filling time** (raise leg to  $45^{\circ}$  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 (lilac, femoral and popliteal) and the presence of normal peripheral pulses reduce the likelihood of peripheral arterial disease"

JAMA 2006 295:5

56 Peripheral Vascular Disease

#### CLINICAL FEAURES (CONT'D)

## DISTINGUISHING FEATURES OF COMMON CAUSES OF LEG PAIN

Claudication
Pain Cramp, tiredness
Sites Buttock, hip, thigh, calf, foot
Worse Walking

Better Rest

Others Vascular dx, ↓ pulse

## Spinal stenosis

Cramp, tiredness, tingling Buttock, hip, thigh Walking, standing Sitting or change in position

Lower back pain

Venous congestion

Tightness, bursting Groin, thigh Walking Leg elevation History of DVT

#### INVESTIGATIONS

#### BASIC

- LABS CBC, lytes, urea, Cr, fasting glucose, fast ing 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 angio gram if the diagnosis is uncertain or if revascular ization is being considered. Digital subtraction angiograph remains the gold standard

#### MANAGEMENT

#### **RISK REDUCTION ★ABCDEFG★**

neous transluminal angioplasty)

- 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 percuta

#### TREATMENT ISSUES

**REVASCULARIZATION** indicated for patients with significant functional limitations (lifestyle or jobs) despite maximal lifestyle and medical treat ment. Not optimal for patients >40, with non dis abling 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. Preventa tive Services Task Force recommends one time screen ing 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 elec tive repair, 19% for urgent repair, and 50% for repair of a ruptured aneurysm. No driving if AAA >5 cm [>2 in.]

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

PALPATION to detect abnormal widening of the aortic pulsation (sens 50% for AAA 4 4.9 cm [1.6 1.9 in.], sens 76% for AAA ≥5 cm [≥2 in.], LR+ 12 and LR 0.72 for AAA ≥3 cm [≥1.2 in.], LR+ 15.6 and LR 0.51 for AAA ≥4 cm [≥1.6 in.]) APPROACH "abdominal palpation will detect most AAAs large enough to warrant surgery, but it cannot be relied on to exclude the diagnosis. The sensitivity of palpation appears to be reduced by abdominal obesity. When a ruptured AAA is suspected, imaging studies such as ultrasound or computed tomography should be performed regardless of physical findings"

JAMA 1999 281:1

## Hypertension

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

#### DIFFERENTIAL DIAGNOSIS

#### **★0 12 3 4★**

#### **0** ESSENTIAL HYPERTENSION

**1 ANATOMIC** aorta (coarctation, aortic dissection) **2 RENAL** renal parenchymal disease (chronic renal failure, polycystic kidney disease), renal artery stenosis

**3 ADRENAL** pheochromocytoma, Conn's synd rome, Cushing's syndrome

#### 4 SCENTS

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

#### PATHOPHYSIOLOGY

#### CLASSIFICATION OF HYPERTENSION

- MALIGNANT HYPERTENSION chronic marked hyper tension with retinal hemorrhages, exudates, or papilledema
- HYPERTENSIVE URGENCY >220/120 mmHg without findings of hypertensive emergency
- HYPERTENSIVE EMERGENCY acute severe hyperten sion with end organ damage such as pulmonary edema, aortic dissection, myocardial infarction, cerebrovascular hemorrhage, papilledema, fundo scopic 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 sec ondary 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 ventri cular hypertrophy, stroke, TIA, microalbuminuria or proteinuria, and chronic kidney disease

#### HYPERTENSIVE RETINOPATHY

 MILD focal arteriolar narrowing (vasospasm), generalized arteriolar narrowing (increased vas cular tone due to autoregulation, mild intimal hyperplasia, and hyaline degeneration in sclerotic

#### PATHOPHYSIOLOGY (CONT'D)

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 bar rier), microaneurysms (necrosis of the smooth muscles and endothelial cells), hard exudates (exudation of blood and lipids), and soft exudates (cotton wool spots, retinal ischemia)
- MALIGNANT signs of moderate retinopathy plus swelling of the optic disc
- UTILITY the retina provides a window of cerebral circulation. Risk of stroke (and death) increases with degree of retinopathy. Note that the stages may not be sequential

NEJM 2004 351:22

#### **CLINICAL FEATURES**

HISTORY blood pressure levels, ambulatory/home monitoring, complications (ischemic heart disease, peripheral arterial disease, left ventricular hypertrophy, stroke, TIA, microalbuminuria or pro teinuria, and chronic kidney disease), other cardiac risk factors (smoking, diabetes, dyslipidemia, obe sity), past medical history (thyroid, renal, or adrenal disorders), medications (antihypertensives, steroids, illicit drugs)

PHYSICAL vitals (heart rate, blood pressure), obe sity (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 cir cumference (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 com plications including retinopathy, stroke, HF, AAA, and PVD

MEASURING BLOOD PRESSURE NEJM 2009 360:e6

#### INVESTIGATIONS

#### BASIC

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

#### INVESTIGATIONS (CONT'D)

#### **SECONDARY CAUSES WORKUP**

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

#### DIAGNOSTIC ISSUES

## **CLINICAL DIAGNOSIS OF HYPERTENSION**

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

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

#### ACUTE MANAGEMENT

**ACUTE** ABC, O<sub>2</sub>, IV

HYPERTENSIVE EMERGENCY labetalol 20 mg IV bolus initially, then 20 80 mg q10min, or 2 mg/min IV infusion (loading) then 2 8 mg/min, maximum total dose of 300 mg. Nitroprusside 0.25 0.5 μg/kg/min IV initially, increase by 0.5 μg/kg/min increments,

#### ACUTE MANAGEMENT (CONT'D)

to usually target 3  $\mu$ g/kg/min (rarely >4  $\mu$ g/kg/min, maximum 10  $\mu$ g/kg/min). *Nicardipine* 5 mg/hr IV initially, titrate to a maximum of 15 mg/hr. *Fenoldopam* 0.1  $\mu$ g/kg/min IV initially, titrate dose q15min. Con sider 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, spironolac tone 12.5 50 mg PO daily
- α1 AGONISTS clonidine 0.1 0.5 mg PO BID, tera zosin 1 20 mg PO daily
- **OTHERS** minoxidil, phentolamine, hydralazine

**TREAT UNDERLYING CAUSE** renal artery steno sis (angioplasty with stenting, nephrectomy of atrophic kidney  $\pm$  endarterectomy)

#### TREATMENT ISSUES

## ACE INHIBITORS/ANGIOTENSIN RECEPTOR BLOCKERS

- INDICATIONS HF, post MI, diabetes, proteinuria, renal failure (with caution), LVH
- CONTRAINDICATIONS pregnancy, ESRD, bilateral RAS
- ADVERSE EFFECTS cough (less with ARB), angioe dema, hyperkalemia

#### TREATMENT ISSUES (CONT'D)

#### **B BLOCKERS**

- INDICATIONS resting tachycardia, HF, migraine, glaucoma, CAD/post MI
- CONTRAINDICATIONS asthma, severe PVD, Ray naud's phenomenon, depression, bradycardia, sec ond or third degree heart block and hypoglyce mia prone diabetics
- ADVERSE EFFECTS depression, 
   ↓ exercise tolerance, bradycardia, hypotension

#### CALCIUM CHANNEL BLOCKERS

 $\mathsf{CKD} \pm \mathsf{proteinuria}$  Asthma

Perioperative

Thyrotoxicosis
Essential tremor
Postural hypotension

Migraine

Ravnaud's

Osteoporosis

Gout

**BPH** 

- **DIHYDROPYRIDINE** (potent vasodilators) nifedi pine, nicardipine, amlodipine, felodipine
- NON-DIHYDROPYRIDINE (heart rate control) verapa mil (cardiac depressant activity), diltiazem (some cardiac depressant, some vasodilator)
- INDICATIONS angina pectoris, recurrent SVT (ver apamil), Raynaud's phenomenon (dihydropyri dine), migraine, heart failure due to diastolic dys function, 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 (\( \pm \) car diac contractility, conduction, and constipation), diltiazem (both side effects but a lot less severe)

## TREATMENT ISSUES (CONT'D)

#### DIURETICS

All others

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

## BLOOD PRESSURE TREATMENT TRIGGERS AND TARGETS

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

<140/90 CHEP Guidelines 2009 http://www.hypertension.ca

#### OVERALL APPROACH TO CHOICE OF THERAPY Condition **Drug of Choice** HTN without other $A/B/C/D \rightarrow AC/AD/BC/BD \rightarrow ABC/ACD/BCD/ABD \rightarrow ABCD$ indications Avoid B as first line if age >60 ACEi may be less effective in blacks Isolated systolic hypertension $ARB/C1/D \rightarrow ARB$ plus either C1 or D $\rightarrow$ ARB plus C1 plus D Avoid B $ACEi/B \rightarrow ACEi \ plus \ B \rightarrow add \ C1$ **Angina** Prior myocardial infarction $AB \rightarrow ABC$ Heart failure AB → ABD (including spironolactone) → ACEi/ARB/B/D. Avoid hydralazine and minoxidil if LVH Prior cerebrovascular disease $AD \rightarrow add$ other agents Peripheral vascular disease A/B/C/D plus ASA. Avoid B if severe PVD Diabetes without $A/C1/D \rightarrow AC1/AD \rightarrow add B \text{ or } C2$ nephropathy Diabetes with nephropathy $A \rightarrow AC/AB/AD$

 $A \rightarrow AD \rightarrow add$  other agents

B (if moderate to high risk)

Avoid vasodilators and diuretics

A/C/D. Avoid B

C (dihydropyridine)

α blockers

B R

D

D

## TREATMENT ISSUES (CONT'D)

Condition Drug of Choice

Hyperkalemia A/B/C/D. Avoid aldosterone antagonists

Hyponatremia A/B/C. Avoid D

Pregnancy B/methyldopa/vasodilators. Avoid ACE inhibitors and ARB

where A=ACE inhibitors/ARBs, B= $\beta$  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 inva sive and high sensitivity/specificity), CT angio gram, duplex U/S (anatomic and functional infor mation), 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 inhibit tors/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 (con sider if severe or refractory hypertension, recurrent flash pulmonary edema, acute significant decline in renal failure due to renal artery stenosis. Unlikely to reverse renal failure if small kidneys or high creatinine >300 µmol/L [3.4 mg/dL]), surgery

## NEJM 2001 344:6

## **DIFFERENTIAL DIAGNOSIS OF ABDOMINAL BRUITS**

- CARDIOVASCULAR abdominal aortic aneurysm, aortocaval fistula
- RENAL VASCULAR renal artery stenosis
- GI VASCULAR celiac artery compression syn drome, mesenteric ischemia
- HEPATIC VASCULAR cirrhosis, hepatoma, AV malforma tion, arterioportal fistula, Cruveilhier Baumgarten sign (cirrhosis, portal hypertension, and caput medusa)
- SPLENIC VASCULAR splenic AV fistula, splenic artery dissection, splenic enlargement
- PANCREATIC VASCULAR pancreatic carcinoma

#### SPECIFIC ENTITIES (CONT'D)

## RATIONAL CLINICAL EXAMINATION SERIES: IS LISTENING FOR ABDOMINAL BRUITS USEFUL IN THE EVALUATION OF RENOVASCULAR HYDEOTENSION?

HYPERIENSION?					
	Sens	Spc	LR+	LR	
Systolic and diastolic abdominal bruit	39%	99%	39	0.6	
Any epigastric or flank	63%	90%	6.4	0.4	
bruit, including					
isolated systolic					
bruit					
Systolic bruit	78%	64%	2.1	3.5	
APPROACH "given the	he high	prevale	nce (7	31%)	

APPROACH "given the high prevalence (7 31%) of innocent abdominal bruits in the younger age groups, it is recommended that if a systolic abdom inal 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 hyperten sion. In view of the high specificity, the presence of a systolic bruit (in particular a systolic diastolic bruit) in a hypertensive patient is suggestive of renovascular hypertension. In view of the lack of evidence to support characterizing bruits as to pitch, intensity and location, bruits should be reported only as systolic or systolic/diastolic"

JAMA 1995 274:16

## **Related Topics**

Aortic Dissection (p. 25)

Hyperaldosteronism (p. 349)

Pheochromocytoma (p. 349)

Hyperlipidemia 61

## Hyperlipidemia

## Canadian Cardiovascular Society Dyslipidemia Guidelines 2006

## DIFFERENTIAL DIAGNOSIS OF HYPERCHOLESTEROLEMIA

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

**SECONDARY** obesity, diabetes, hypothyroidism, nephrotic syndrome, medications (estrogen, tamoxifen,  $\beta$  blockers, glucocorticoids)

## DIFFERENTIAL DIAGNOSIS OF HYPERTRIGLYCERIDEMIA

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

**SECONDARY** obesity, diabetes, nephrotic syn drome, hypothyroidism, alcoholism, drugs (tamox ifen, cyclosporine, glucocorticoids)

#### DIFFERENTIAL DIAGNOSIS OF LOW HDL

#### **PRIMARY**

SECONDARY obesity, smoking, inactivity

#### **CLINICAL FEATURES**

TELLTALE SIGNS						
Lesions	1	lla	IIb	Ш	IV	٧
Tendon xanthoma (LDL)		$\checkmark$				
Palmer xanthoma				$\checkmark$		
Eruptive xanthoma	$\checkmark$				$\checkmark$	$\checkmark$
Xanthelasma	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$
Tuberous xanthoma		$\checkmark$	$\checkmark$	$\checkmark$		
(LDL)						

#### INVESTIGATIONS

#### BASIC

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

#### MANAGEMENT

**LIFESTYLE CHANGES diet** ( $\uparrow$  fruit and vegetable intake,  $\uparrow$  mono and polyunsaturated fats,  $\downarrow$  saturated fats and trans fatty acid to <7% of calories,  $\uparrow$  omega 3 fatty acid from fish and plant sources, *salmon oil* 3 9 g can  $\downarrow$ TGL). **Exercise** 

## **RISK REDUCTION MEDICATIONS**

- RESINS (↓ LDL, ↑ cholesterol synthesis) Cholestyr amine 2 24 g PO daily, colestipol 5 30 g PO daily in divided doses. Main side effects include constipa tion, ↓ vitamin K deficiency, and drug interactions (bind to other drugs and prevent absorption)
- HMG-COA REDUCTASE INHIBITORS (
   \precedent LDL) atorvas
   tatin 10 80 mg daily, pravastatin 10 40 mg daily,
   rosuvastatin 2.5 40 mg daily, simvastatin
   10 80 mg daily. Main side effects include hepato
   toxicity, myalgia and myopathy
- NIACIN (↓ LDL, ↑↑ HDL, ↓ TGL) nicotinic acid 1 3 g. Main side effects include ↑ blood sugar; flushing, hepatotoxicity, and gastric irritation
- ASPIRIN ASA 81 mg PO daily

TREAT SECONDARY CAUSES/METABOLIC SYN DROME IF PRESENT

#### TREATMENT ISSUES

## TREATMENT TARGETS BASED ON RISK CATEGORY (CCS 2009 Guideline) High risk Moderate risk

LDL  $<2 \text{ mmol/L} [<77 \text{ mg/dL}] \text{ or } \ge 50\% \downarrow \text{LDL}$ 

ApoB <0.80 g/L [<80 mg/dL]

 Moderate risk
 Low risk

 <2 mmol/L</td>

 [<77 mg/dL] or ≥50% ↓ LDL</td>
 ≥50% ↓ LDL

 <0.80 g/L</td>

 [<80 mg/dL]</td>

#### TREATMENT ISSUES (CONT'D)

#### **RISK CATEGORIES**

- HIGH ≥20% 10 year Framingham risk or estab lished CAD, diabetes, CVD, or PVD. All high risk patients require treatment
- MODERATE 10 19% 10 year CAD risk. Consider initiating treatment if LDL >3.5 mmol/L [135 mg/ dL], TChol/HDL >5.0, high sensitivity CRP >2 mg/L,

## TREATMENT ISSUES (CONT'D)

- men age >50, women age >60, or significant family history
- 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 Fra mingham 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]
- $\downarrow$  **HDL**  $\circlearrowleft$  <1.3 mmol/L [<50 mg/dL],  $\circlearrowleft$  <1.0 mmol/L [<40 mg/dL]

## SPECIFIC ENTITIES (CONT'D)

- INSULIN RESISTANCE fasting glucose ≥5.6 mmol/L
   [>110 mg/dL]
- HYPERTENSION ≥130/85 mmHg or on treatment Other features include hyperuricemia and pro thrombotic state

FAMILIAL DYSLIPIDEMIA				
			Cardiac	
Туре	Mechanism	Lipid profile	risk	Treatment(s)
<b>Type I</b> . Hyperchylomicronemia	lipoprotein lipase deficiency	↑ chylo, ↑↑ TAG		Low fat diet
Type IIa. Hypercholesterolemia	↓ LDL receptor. Tendon xanthoma is essential for diagnosis	↑ LDL, ↑ CE	$\uparrow \uparrow$	Resin, statin, niacin
<b>Type IIb</b> . Familial combined hyperlipidemia	↑ liver VLDL production	↑ VLDL, ↑ LDL, ↑ TAG, ↑ CE	1	Resin, statin, niacin
Type III. Dysbetalipoproteinemia	apoE Δ. Classically associated with palmer xanthoma	↑ chylo r, ↑ IDL, ↑ TAG, ↑ CE	1	Niacin, statin
Type IV. Hypertriglyceridemia	↑ hepatic VLDL production	↑ VLDL, ↑ TAG	1	Low fat diet, weight loss, fibrate, statin, niacin
<b>Type V</b> . Mixed hypertriglyceridemia	↑ production and ↓ clearance VLDL/chylo	$\uparrow$ VLDL, $\uparrow$ chylo, $\uparrow\uparrow$ TAG, $\uparrow$ CE		Low fat diet, niacin, statin

## **Smoking Issues**

See SMOKING ISSUES (p. 418)

## Approach to ECG

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

## TEN STEPS TO ECG

- 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 com plex, sinus, atrial, atrioventricular, ventricular
- 4. AXIS deviation, rotation
- 5. **PR INTERVAL** normal 120 200 ms; first, second, third degree AV block
- QRS INTERVAL normal 80 110 ms, intraventri cular 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
- ISCHEMIA ST elevation/depression, T wave inversion
- 10. INFARCTION Q waves
- 11. SPECIAL CONDITIONS

## CHEST LEADS PLACEMENT

- **V1** 4<sup>th</sup> intercostal space, right sternal border
- **V2** 4<sup>th</sup> intercostal space, left sternal border
- V3 halfway between V2 and V4
- **V4** 5<sup>th</sup> intercostal space, left mid clavicular line
- V5 5<sup>th</sup> intercostal space, left anterior axillary line
- V6 5<sup>th</sup> 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, ventri cle) 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 junc tional tachycardia

#### **IRREGULAR NARROW COMPLEX TACHYCARDIA**

sinus tachycardia/arrhythmia, premature atrial con tractions, multifocal atrial tachycardia, ectopic atrial tachyarrhythmia with variable block, atrial flutter with variable block atrial fibrillation

**REGULAR WIDE COMPLEX TACHYCARDIA** ventri cular 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 CONDUC

**TION** older age, history of coronary artery disease, AV dissociation (dissociated P waves, fusion beats, capture beats), concordance of precordial leads, QRS width >160 ms in LBBB or >140 ms in RBBB, atypical BBB, extreme LAD ( 90° to 180°)

### BRADYCARDIA AND PROLONGED PR

**SINUS** sinus bradycardia, sick sinus syndrome with sinus pause, bradycardia tachycardia syndrome (SSS+AF usually)

AV BLOCK prolonged PR interval

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

## PROLONGED QRS BUNDLE BRANCH BLOCK AND HEMIBLOCK

**ANATOMY** SA node (RCA 59%, LAD 38%, both 3%)  $\rightarrow$  AV node (RCA 90%, LCX 10%)  $\rightarrow$  bundle of His (RCA)  $\rightarrow$  right bundle (LAD), left anterior fascicle (LAD, RCA), and left posterior fascicle (RCA, LAD)

**RBBB** QRS >120 ms, slurred S wave in I and V6 and rSR' in V1 3 with R' taller than r. May also see QR' complex in V1 (suggestive of old or new infarct). QRS polarity positive in V1 2. Causes include LAD 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 2. Causes include hypertension, CAD, dilated cardio myopathy, rheumatic heart disease, infiltrative dis eases, benign or idiopathic

**LEFT ANTERIOR HEMIBLOCK** QRS 100 120 ms, left axis deviation 30° to 90°, qR in I, rS in III, II, and aVF. May be benign, LAD involvement/anterior infarction. Shortcut to diagnosis I up, II down, aVF down

**LEFT POSTERIOR HEMIBLOCK** right axis deviation 90 180°, normal or slightly widened QRS, rS in I, and qR in III. RCA involvement/anterior infarction

BIFASCICULAR BLOCK RBBB+LAHB, RBBB+LPHB
TRIFASCICULAR BLOCK first degree AV block +
bifascicular block

#### PROLONGED QT

NORMAL QTc=square root (QT in seconds/RR interval in seconds); QT <50% of RR interval; normal QTc 390 460 ms (women), 390 450 ms (men)

CAUSES genetic, metabolic (hypokalemia, hypo magnesemia, hypocalcemia), antiarrhythmics (qui nidine, procainamide, amiodarone, sotalol), antibio tics (macrolide, trimethoprim sulfamethoxazole, fluoroquinolone), psychotropics (TCA, SSRI, haloper idol, risperidone), analgesics (methadone), struc tural 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), overd 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

**LVH** tall R in aVL (>11 mm); R in V5 or V6 (whichever is taller) plus S in V1 >35 mm; R in V5 or R in V6 >27 mm; poor R wave progression in precordial leads;

#### HYPERTROPHY CRITERIA (CONT'D)

ST depression and T wave inversion in lateral leads (I, aVL, V5 6) suggestive of ventricular strain; R in aVL plus S in V3 > 28 mm in male or > 20 mm in female (Cornell criteria). Diagnosis difficult with LBBB, consider LVH if S in V1 + R in V5 > 45 mm (Klein criteria) RVH right axis deviation (>110°); R>S wave in V1 and R > 7 mm; persistent S waves V5 6; ST depres sion 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. Con
sider 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 ORS

ACCELERATED IDIOVENTRICULAR RHYTHM sug gests 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 sug gestive of infarction include concordant ST segment changes (ST elevation  $\geq 1$  mm in leads with positive QRS complex and ST depression  $\geq 1$  mm in V1 3), disconcordant ST segment changes (ST elevation  $\geq 5$  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	N ZONES			
Territory		Leads	Artery	Comment
Inferior		II, III, aVF <sup>a</sup>	RCA, LAD <sup>b</sup>	RV, SA, AV nodes
Lateral		I, aVL, V5, V6	LCX, RCA	
Posterior		V1i, V2i, V8, V9 <sup>c</sup>	RCA	
Anterior		V1 V4 <sup>d</sup>	LAD	Massive LV
RV		R leads (V1), V4R	RCA	Preload
a			 	 

<sup>&</sup>lt;sup>a</sup>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

binferior infarcts may be related to either RCA (ST elevation in III) 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)

<sup>&</sup>lt;sup>c</sup>i=inverted. ST depression in V1 V2 in a regular ECG should trigger one to automatically request for posterior leads to check for posterior MI. Posterior infarct may be associated with inferior and lateral infarct as these territories are all supplied by RCA

<sup>&</sup>lt;sup>d</sup>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 procaina mide. 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

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## Notes

# 3

## NEPHROLOGY

Section Editor: Dr. Alan McMahon

## Acute Renal Failure: Pre-renal

NEJM 2007 357:8

#### DIFFERENTIAL DIAGNOSIS

#### TRUE INTRAVASCULAR FLUID LOSS

- HEMORRHAGE
- GI LOSS diarrhea, vomiting
- RENAL LOSS diuretic, osmotic
- SKIN LOSS increased insensible losses, sweating, burns

#### **DECREASED EFFECTIVE CIRCULATING FLUID**

- HEART FAILURE
- HYPOALBUMINEMIA protein losing enteropathy, nephrotic, cirrhosis, malnutrition
- THIRD SPACING
- SEPSIS

#### RENAL HEMODYNAMICS

- AFFERENT renal artery stenosis (RAS), renal vein thrombosis, fibromuscular dysplasia, ASA, NSAIDs, cyclosporin, tacrolimus, cocaine, hyper calcemia (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 CBCD, lytes, urea, Cr, Ca, urinalysis, urine lytes, urine Cr
- MICROBIOLOGY blood C&S, urine C&S
   SPECIAL
- RENAL ARTERY STENOSIS WORKUP renal dopplers, captopril renogram, CT/MR renal angiogram (use with caution in renal failure)

#### DIAGNOSTIC ISSUES

## **COCKCROFT GAULT FORMULA**

- CREATININE CLEARANCE (SI UNITS) CrCl=(140 age)
   ×(weight in kg)/(Cr in μmol/L), multiply by 1.2 if male
- CREATININE CLEARANCE (US UNITS) CrCl=(140 age)  $\times$  (weight in lbs  $\times$ 0.37)/(Cr in mg/dL $\times$ 88.4), multi ply by 1.2 if male
- NOTE creatinine is used to estimate GFR, but 5% of creatinine is secreted and thus overestimates GFR. At low GFR, proportion of creatinine secreted becomes higher, so overestimates even more

#### **FEATURES SUGGESTING PRE RENAL CAUSES**

- UREA:CR RATIO (urea in mmol/L×10) > Cr in μmol/L [or in US units: (urea in mg/dL/20) > Cr in mg/dL].
   Urea reabsorption increases during pre renal failure, resulting in a disproportionally high serum urea level
- 10–20–30 RULE urine Na $^+$  <10 mmol/L or Cl <20 mmol/L and K $^+$  >30 mmol/L
- **FENA**  $(U_{na}/P_{na})/(U_{cr}/P_{cr}) \times 100\%$ , <1%
- URINALYSIS bland, high specific gravity

#### DISTINGUISHING FEATURES BETWEEN PRE RENAL FAILURE AND ATN

## Pre renal ATN

 Increase in Cr
 Variable
 <44 μmol/L/day [<0.5 mg/dL/day]</th>

 Urinalysis
 Normal
 Heme granular casts

 Urine Na
 <20 mmol/L</td>
 >30 mmol/L

Urine Na <20 mmol/L >30 |
FEND <1% >2%

Urine osmo >500 mOsm/kg <350 mOsm/kg

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#### MANAGEMENT

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

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

#### TREATMENT ISSUES

## CRITERIA FOR DIALYSIS IN ACUTE RENAL FAILURE ★AEIOU★

- ACIDOSIS persistent despite medical treatment
- ELECTROLYTES persistent severe hyperkalemia despite medical treatment
- INTOXICATION ASA, Li, methanol
- OVERLOAD persistent fluid overload despite medical treatment
- UREMIA pericarditis, encephalopathy

## **Acute Renal Failure: Renal**

#### DIFFERENTIAL DIAGNOSIS

#### VASCULAR

- EMBOLI atherothrombotic, cholesterol
- MICROANGIOPATHIC HEMOLYTIC ANEMIA TTP, HUS, scleroderma, malignant hypertension
- VASCULITIS PAN, Takayasu's
- HYPERTENSION chronic

#### **TUBULAR**

- ACUTE TUBULAR NECROSIS (ATN) ischemia, con trast dye, aminoglycosides, amphotericin, acy clovir, myoglobin, hemoglobin, uric acid
- INTRA-TUBULAR OBSTRUCTION uric acid, indina vir, 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 prolifera tive GN, RPGN
  - ANTI GBM ANTIBODY Goodpasture's, anti GBM antibody nephritis
  - IMMUNE COMPLEX SLE, HBV, HCV, endocar ditis, post strep/infectious GN, IgA, cryoglo bulinemia, 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, nephro toxins, past medical history (recent infections, HBV, HCV, HF, diabetes, hypertension, malignancy, connec tive tissue disease), medications (ACE inhibitors, ARB, NSAIDs, ASA, cyclosporine, penicillins, cephalospor ins, acyclovir, amphotericin)

**PHYSICAL** orthostatic vitals especially heart rate and blood pressure, respiratory and cardiac examination (JVP, heart failure), abdominal examination (masses, renal bruit), ankle edema, cholesterol emboli

## **Related Topic**

Glomerulonephritis (p. 70)

#### INVESTIGATIONS

#### **BASIC**

- LABS CBCD, lytes, urea, Cr, urinalysis, urine lytes, urine Cr
- ETIOLOGY WORKUP ANA, anti dsDNA, ENA, p anca, c anca, anti GBM antibody, C3, C4, CK, uric acid, ASO titer, HBV/HCV serology, RF, cryoglobu lin, quantitative lg, 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

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#### INVESTIGATION ISSUES

## DISTINGUISHING FEATURES BETWEEN VARIOUS RENAL ETIOLOGIES

#### Urinalysis Other tests

Bland

Vascular

Urinary eosinophils (cholesterol emboli)

Tubular Muddy brown casts (ATN)

Interstitial WBC casts, urinary eosinophils

Glomerular **RBC** casts

Acanthocyte (dysmorphic RBC)

Oval fat body Fatty cast

Peripheral smear (TTP)

p anca (PAN)

ANA, ENA (lupus) CK (rhabdomyolysis)

Uric acid (gout) Systemic eosinophilia c anca (Wegener's)

p anca (PAN) Eosinophilia (Churg Strauss)

Anti GBM (Goodpasture's syndrome)

ANA, anti dsDNA (SLE) ASO titer (PSGN)

Blood C&S, echo (infectious endocarditis) HBV/HCV serology, SPE, UPE (multiple myeloma)

Cryoglobulins, rheumatoid factor

(cryoglobulinemia)

#### MANAGEMENT

PREVENTION avoid contrast dye, nephrotoxins if possible

TREAT UNDERLYING CAUSE nephrotic syndrome (low salt diet and furosemide for volume regulation if needed; statin if needed to correct hyperlipidemia) RENAL REPLACEMENT dialysis (peritoneal, hemodialysis)

#### SPECIFIC ENTITIES

PSEUDO RENAL FAILURE cimetidine and tri methoprim may reduce tubular secretion of creati nine causing a small but significant increase in serum creatinine in the absence of | GFR

#### **MULTIPLE MYELOMA AND RENAL FAILURE**

- PRE-RENAL N&V, renal vein thrombosis, calcium induced vasospasm, nephrogenic diabetes insipi dus (hypercalcemia)
- RENAL secondary amyloidosis (λ), light chain deposition disease (x), myeloma kidney (tubuloin terstitial damage due to increased light chain absorption through proximal tubule), Bence Jones/cast nephropathy, plasma cell infiltration, cryoglobulinemia, pyelonephritis, sepsis
- POST-RENAL renal stones (hypercalcemia), neuro genic bladder

## **NSAIDS INDUCED RENAL FAILURE**

- PRE-RENAL inhibition of prostaglandin synthesis leading to afferent vasoconstriction, hypertensive nephropathy
- RENAL acute interstitial nephritis, nephrotic syn drome (minimal change disease, membranous)

## ACUTE TUBULAR NECROSIS (ATN)

 PATHOPHYSIOLOGY tubular damage → decreased reabsorption of Na  $\rightarrow$  vasoconstriction  $\rightarrow$ 

### SPECIFIC ENTITIES (CONT'D)

decreased GFR. Also may be related to tubular blockage from damaged epithelial cells. Risk fac tors include elderly (GFR ↓ by 1 mL/min/year after age 40), pre existing renal dysfunction, decreased cardiac function, diabetes, dehydration, and multi ple nephrotoxins

TREATMENTS after the insults are stopped, may start to recover in 3 5 days. Generally takes 7 21 days (some up to 8 weeks) for full recovery

#### CONTRAST NEPHROPATHY

- PATHOPHYSIOLOGY contrast induced vasospasm, hyperosmolar load and oxygen free radical gen eration  $\rightarrow$  acute tubular injury  $\rightarrow \uparrow$  Cr or  $\downarrow$  GFR by 25%. Usually develops immediately after expo sure to contrast, peaks in 48 72 h. Risk factors and recovery time course same as ATN. Key dif ferential 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 osmolal (iodixanol) non ionic agents. Hydration options include (1) IV 1/2 NS at 1 mL/kg/h starting 12 h before until 12 h after contrast exposure; (2) IV NS or NaHCO3 154 mmol/L at 3 mL/kg/h starting 1 h

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#### 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
- EXTRALUMINAL cancer, retroperitoneal fibrosis, pregnancy

#### INVESTIGATIONS

#### BASIC

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

#### INVESTIGATIONS (CONT'D)

#### SPECIAL

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

#### DIAGNOSTIC ISSUES

RENAL U/S hydronephrosis suggests post renal causes. However, retroperitoneal fibrosis and acute post renal obstruction may not show hydronephrosis

#### MANAGEMENT

TREAT UNDERLYING CAUSE Foley catheter. For BPH (tamsulosin 0.4 mg PO daily or TURP) RENAL REPLACEMENT dialysis (peritoneal, 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 endothe lium involvement in nephritic syndrome), circulating antigen antibody complexes, and/or cell mediated

#### PATHOPHYSIOLOGY OF GLOMERULOPATHIES (CONT'D)

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**

nephritis (RPGN)

#### CLINICAL MANIFESTATIONS OF GLOMERULAR DISEASES

Clinical manifestation

FSGS, mesangial proliferative GN, diabetic nephropathy Asymptomatic proteinuria 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

See text

Antiglomerular basement membrane antibody disease, immune Pulmonary renal syndrome

complex vasculitis, pauci immune (ANCA) vasculitis

Chronic renal failure Sclerosed glomerular disease Glomerulopathies 71

## CLINICAL FEATURES (CONT'D)

#### DISTINGUISHING FEATURES BETWEEN NEPHROTIC AND NEPHRITIC SYNDROMES

	Nephrotic	Nephritic
Onset	Slower	Faster
Edema	++++	++
Blood pressure	N/↓	<b>↑</b>
Volume/JVP	N/↓	<b>↑</b>
Proteinuria	>3 g/day	May be <3 g/day
Hematuria	May occur	+++
Urine sediment	Hyaline casts, lipid droplets (oval fat	Dysmorphic RBC, WBC, RBC casts, granular
	body)	casts
Albumin	$\downarrow\downarrow\downarrow$	N/mild ↓
Creatinine	N/↑	Usually ↑
Serum Na	May be ↓↓	N/mild ↓
NOTE I .:		

**NOTE**: nephrotic syndrome  $\neq$  nephrotic range proteinuria (proteinuria >3 g/day without other symptoms and signs)

#### NEPHROTIC SYNDROME

**DIFFERENTIAL DIAGNOSIS** minimal change dis ease, membranous GN, focal segmental glomerulo sclerosis, membranoproliferative GN, diabetes, amy loidosis, 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

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

#### NEPHRITIC SYNDROME

 $\begin{array}{ll} \textbf{DIFFERENTIAL} & \textbf{DIAGNOSIS} & \text{membranoprolifera} \\ \text{tive GN (type 2), rapidly progressive/crescentic GN} \\ (\alpha \text{GBM, immune, pauci immune), IgA nephropathy} \end{array}$ 

**CLINICAL FEATURES** hematuria, proteinuria, hypertension

**INVESTIGATIONS** CBCD, lytes, urea, Cr, ANA, anti dsDNA, ENA, p anca, c anca, anti GBM, C3, C4 (com plements low except for IgA nephropathy), CK, uric acid, ASO titer, HBV serology, HCV serology, cryoglo

#### NEPHRITIC SYNDROME (CONT'D)

bulin, quantitative lg, serum protein electrophoresis, renal biopsy

**TREATMENTS** steroid, cyclophosphamide, myco phenolate mofetil

#### SPECIFIC ENTITIES

#### MINIMAL CHANGE DISEASE (MCD)

- PATHOPHYSIOLOGY T cell abnormality → ↑ glo merular 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), immuno fluorescence (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, autoim mune thyroiditis, syphilis, HBV, HCV, chronic trans plant rejection)
- **CLINICAL FEATURES** pure nephrotic (minimal hematuria, no RBC casts)
- PATHOLOGY light microscopy (basement mem brane thickening, spikes), immunofluorescence (immune complexes IgG, and complements in sub epithelial space), electron microscopy (same as immunofluorescence)
- TREATMENTS steroid, cyclophosphamide, cyclo sporin

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#### 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, lympho mas, 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 com plexes), electron microscopy (effacement of podo cyte foot processes)
- TREATMENTS steroid, cyclophosphamide, cyclo sporin
- **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 comple ment 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, lym phomas, 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 mem brane thickening, mesangial cell hypercellularity), immunofluorescence (complements along capil lary walls), electron microscopy (type 1 shows dis crete deposits in mesangium, type 2 shows depos its as continuous ribbon in glomerular basement membrane)
- TREATMENTS steroid, cyclophosphamide, cyclo sporin
- 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 anti body nephritis
- CLINICAL FEATURES nephritic (hematuria, protei nuria, ARF). Goodpasture syndrome also has lung

#### SPECIFIC ENTITIES (CONT'D)

- involvement whereas anti GBM antibody nephritis affects kidnev alone
- PATHOLOGY immunofluorescence (linear staining)
- TREATMENTS plasmapheresis with IV pulse ster oids followed by PO steroids with PO cyclopho sphamide for 1 year

## RAPIDLY PROGRESSIVE GN (RPGN) IMMUNE COMPLEX

- PATHOPHYSIOLOGY deposition of circulating immune complex in glomeruli, usually in suben dothelial location
- CAUSES SLE, HBV, HCV, endocarditis, post strep GN, post infectious GN, IgA nephropathy, cryoglo bulinemia, shunt nephritis
- CLINICAL FEATURES nephritic (hematuria, protei nuria, ARF)
- PATHOLOGY immunofluorescence (granular staining)
- TREATMENTS IV pulse steroids followed by PO ster oids with IV monthly cyclophosphamide for 1 year

## RAPIDLY PROGRESSIVE GN (RPGN) PAUCI IMMUNE COMPLEX

- causes Wegener's (c anca), microscopic polyan giitis (p anca), Churg Strauss
- CLINICAL FEATURES nephritic (hematuria, protei nuria, 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, malignan cies, seronegative spondyloarthropathies)
- CLINICAL FEATURES 50% recurrent macroscopic hematuria with URTI, 30 40% persistent microhe maturia and proteinuria, 10% rapidly progressive renal failure, <10% nephrotic syndrome</li>
- PATHOLOGY light microscopy (focal or diffuse mesangial hypercellularity and matrix expansion), immunofluorescence (extensive IgA deposition in mesangium and capillary walls), electron micro scopy (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

Chronic Kidney Disease 73

#### SPECIFIC ENTITIES (CONT'D)

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

#### **Related Topics**

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

## **Chronic Kidney Disease**

## NEJM 2007 357:13

#### DIFFERENTIAL DIAGNOSIS

CAUSES OF ACUTE RENAL FAILURE pre renal, renal, post renal (see ACUTE RENAL FAILURE p. 68)
CHRONIC KIDNEY DISEASES

- RENOVASCULAR DISEASE atherosclerosis, hyper tensive 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 irrever sible component

#### CLASSIFICATION OF CHRONIC KIDNEY DISEASE

- **STAGE I** (GFR 90 100 mL/min/1.73 m², protei nuria) observe, consider ACE inhibitor
- STAGE II (GFR 60 90 mL/min/1.73 m<sup>2</sup>) consider ACE inhibitor, nephrology referral
- STAGE III (GFR 30 60 mL/min/1.73 m<sup>2</sup>) nephrol ogy referral
- stage IV (GFR 15 30 mL/min/1.73 m<sup>2</sup>) consider renal replacement therapy (dialysis or transplantation)
- STAGE V (GFR <15 mL/min/1.73 m<sup>2</sup>) dialysis, transplantation, or palliation

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

#### CLINICAL FEATURES

## SIGNS AND SYMPTOMS OF CHRONIC KIDNEY DISEASE

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

#### CLINICAL FEATURES (CONT'D)

- CALCIUM/PHOSPHATE BALANCE 
   ↓ 1,25(OH)<sub>2</sub> vitamin D3 synthesis in kidney, ↑ PO<sub>4</sub> due to decreased filtration → ↓ Ca → ↑ PTH → renal osteodystrophy (osteitis fibrosa with increased bone resorption from secondary hyperparathyroidism; osteomala cia with decreased bone resorption and unminer alized 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 concen tration, slow and slurred speech, myotonic jerks, seizures, altered smell and taste, periph eral neuropathy, sleep disturbances, restless leg syndrome
  - GASTROINTESTINAL anorexia, nausea and vomiting, gastritis
  - HEMATOLOGIC anemia, platelet dysfunction, and bleeding
  - MUSCULOSKELETAL bone disorders, arthropa thy, muscle cramps
  - **DERMATOLOGIC** pruritus, uremic frost, sallow
  - SEXUAL amenorrhea, sexual dysfunction, infertility

#### INVESTIGATIONS

#### BASIC

 LABS CBCD, lytes, urea, Cr, glucose, HbA1C, Ca, PO<sub>4</sub>, Mg, PTH, albumin, fasting lipid profile, uri nalysis, 24 h urinary albumin collection, 24 h urinary protein collection

#### SPECIAL

• MYELOMA WORKUP serum protein electrophor esis, urinary protein electrophoresis

#### DIAGNOSTIC ISSUES

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

74 Proteinuria

#### DIAGNOSTIC ISSUES (CONT'D)

anemia, small kidneys from renal U/S (except dia betes, amyloidosis, acromegaly, renal vein thrombo sis, HIV nephropathy), renal osteodystrophy are all consistent with CKD. Renal biopsy is also helpful

#### MANAGEMENT

#### SLOW PROGRESSION

- LIMIT PROTEIN INTAKE 0.8 1 g/kg/day
- ACE INHIBITION blood pressure and proteinuria control (ramipril 1.25 10 mg PO daily)
- LIPID CONTROL
- AVOID NEPHROTOXINS
- SMOKING CESSATION
- TREAT DIABETES MELLITUS

#### TREAT COMPLICATIONS

- VOLUME OVERLOAD low sodium diet, diuretics
- HYPERKALEMIA (K >5.5 mmol/L) low potassium diet, hydrochlorothiazide 12.5 mg PO daily, kayex alate 30 g PO daily QID, decrease ACE inhibitor
- METABOLIC ACIDOSIS consider NaHCO<sub>3</sub> if low pH or HCO<sub>3</sub>
- ANEMIA (Hb <100 g/L [Hb <10 g/dL]) epoetin alfa 50 200 U/kg/week SC/IV div 2 3×/week, dar bepoetin alfa 0.45 μg/kg SC every week, ferrous fumarate 600 mg PO qhs, goal to keep Hb 100 120 g/L [10 12 g/dL]
- CALCIUM/PHOSPHATE BALANCE keep Ca normal, PO<sub>4</sub> <1.5 mmol/L [<4.6 mg/dL], PTH <2 3× nor mal, dietary phosphate restriction, phosphate bin der CaCO<sub>3</sub> 500 mg PO TID, calcitriol 0.25 1 μg PO daily, parathyroidectomy

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

#### TREATMENT ISSUES

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

#### TREATMENT ISSUES (CONT'D)

**ACE INHIBITORS IN RENAL FAILURE** ACE inhibition leads to vasodilation of efferent arterioles  $\rightarrow \downarrow$  intraglomerular pressure  $\rightarrow \downarrow$  long term remodeling/stress  $\rightarrow$  slow progression of chronic kidney disease. Other positive effects of ACE inhibition include  $\downarrow$  blood pressure,  $\downarrow$  proteinuria, and  $\downarrow$  mediators of glomerular tubule hypertrophy and fibrosis. Should start in all patients with chronic kidney disease  $\pm$  hypertension  $\pm$  proteinuria. If <30% rise in creatinine after starting ACE inhibitor, should continue as long term benefit important. Expect GFR to return to pre ACE inhibitor baseline after 3 4 months due to remodeling

## SPECIFIC ENTITIES

#### DIABETIC NEPHROPATHY

- NORMOALBUMINURIA (<30 mg/day) lasts 8 10 years, treatment with glycemic/blood pressure/ lipid control, smoking cessation
- MICROALBUMINURIA (30 300 mg/day) lasts 5 10 years, same treatment as above plus ACE inhibitor, protein restriction
- OVERT NEPHROPATHY (>300 mg/day) CrCl declines by 2 20 mL/min/year, same treatment as above
- PERCENTAGES 25 40% of type 1 or 2 diabetics develop nephropathy: 99% of type 1 diabetics with chronic kidney disease are related to diabetes, while this is true only for 30% of type 2 diabetics

#### Related Topics

Acute Renal Failure (p. 68) Diabetes Mellitus (p. 337) Glomerulonephritis (p. 70) Hypertension (p. 57) Multiple Myeloma (p. 178) Polycystic Kidney Disease (p. 76)

#### **Proteinuria**

## DIFFERENTIAL DIAGNOSIS

**FUNCTIONAL** (<1 g/day) infection, fever, exer cise, 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 glo merular proteinuria), while small proteins such as  $\beta_2$  microglobulin filter through but are reabsorbed at proximal tubules (affected in tubular proteinuria)

Hematuria 75

#### CLINICAL FEATURES

HISTORY ankle swelling, fever, strenuous exercise, urinary tract infections (dysuria, frequency), past medical history (myeloma, diabetes, glomerulone phropathies, lupus), medications (antibiotics, NSAIDs) PHYSICAL vitals particularly blood pressure, abdominal examination (cystic kidney), ankle edema

## INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, HbA1C, fasting glu cose. albumin
- URINALYSIS inaccurate and dependent on urine volume, detects mainly negative charged pro teins 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

 $\eth$ =ratio $\times$ 0.14 0.16 mg/kg/day $\times$ weight in kg  $\Im$ =ratio $\times$ 0.18 0.20 mg/kg/day $\times$ weight in kg

#### INVESTIGATIONS (CONT'D)

- 24-H URINARY PROTEIN most accurate but cum bersome method to quantify urinary protein

  SPECIAL
- MYELOMA WORKUP urinary protein electrophor esis, serum protein electrophoresis
- KIDNEY BIOPSY

#### MANAGEMENT

**TREAT UNDERLYING CAUSE** observe if <1 g/day, urine benign and creatinine normal. Consider biopsy otherwise

**SLOW PROGRESSION** ACE inhibitors

#### SPECIFIC ENTITIES

**ORTHOSTATIC/POSTURAL PROTEINURIA** mainly in healthy young people. Split upright and recum bent urine collections could reveal protein loss mainly with upright position. Usually disappears with time and is of no clinical significance

## Hematuria

## NEJM 2003 348:23

#### DIFFERENTIAL DIAGNOSIS

**PIGMENTS** beets, myoglobinuria, hemoglobi nuria, porphyrin, rifampin, food coloring **TRANSIENT** menstruation, urinary tract infec

**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, medul lary sponge kidney

## PATHOPHYSIOLOGY

**DEFINITION OF HEMATURIA** >1 2 RBC/high power field

#### CLINICAL FEATURES

**HISTORY** blood clots, other sources of bleeding (GI, hemoptysis, epistaxis), beets, fever, strenuous

#### CLINICAL FEATURES (CONT'D)

exercise, urinary tract infections (dysuria, frequency), last menstrual period, past medical history (tumors, renal stones, cystic kidney disease, lupus, Alport's syndrome), medications (ASA, NSAIDs, anticoadulants)

**PHYSICAL** vitals (particularly blood pressure), check hearing, abdominal examination (cystic kidney)

#### INVESTIGATIONS

#### BASIC

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

#### DIAGNOSTIC ISSUES

## DIFFERENTIATING FEATURES FOR SOURCE OF BLEEDING

- GLOMERULAR cola urine, proteinuria, dysmorphic RBC (acanthocytes), RBC casts, no clot
- EXTRA-GLOMERULAR bright red urine, no protei nuria, no dysmorphic RBC, clots, no RBC casts

**76** Cystic Kidney Diseases

#### MANAGEMENT

#### TREAT UNDERLYING CAUSE

#### SPECIFIC ENTITIES

**ISOLATED PERSISTENT HEMATURIA** predisposi tion to stones, IgA nephropathy, Alport's syndrome, thin basement membrane disease, Loin pain hema turia syndrome

#### ALPORT'S SYNDROME

- PATHOPHYSIOLOGY X linked defect in α5 chain of type IV collagen
- CLINICAL FEATURES hematuria without protei nuria, may have hearing loss. End stage renal

#### SPECIFIC ENTITIES (CONT'D)

disease by age 30 45 in males. Persistent micro hematuria but rarely renal failure in female carriers

#### THIN BASEMENT DISEASE

- **PATHOPHYSIOLOGY** autosomal dominant; defect of type IV collagen (usually  $\alpha 3$  or  $\alpha 4$  chain)
- CLINICAL FEATURES hematuria without protei nuria. Normal GFR

#### **Related Topics**

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

## **Cystic Kidney Diseases**

#### CAUSES

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

MEDULLARY CYSTIC KIDNEY DISEASE

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, Cr/urea, urinalysis
- IMAGING U/S renal, IVP (medullary sponge kidney)

#### MANAGEMENT

**TREAT COMPLICATIONS** infections, stones, dialy sis 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 bleed ing and infections. Risk factors for progression include younger age at diagnosis, male, black, hypertension, and PKD1
- CLINICAL FEATURES symptoms may include abdom inal pain/fullness, microscopic hematuria (gross hematuria if cyst hemorrhages), hypertension, renal stone disease, recurrent UTI (cyst infections). Extrarenal involvements include cysts in other

## SPECIFIC ENTITIES (CONT'D)

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 end stage renal disease

## NEJM 2008 359:14 MEDULLARY CYSTIC KIDNEY DISEASE

- PATHOPHYSIOLOGY genetic abnormality with diffuse tubulointerstitial cysts at corticomedullary border
- CLINICAL FEATURES symptoms include hematuria and hypertension. Frequently progress to end stage renal disease by age 20 50
- TREATMENTS dialysis if endstage renal disease MEDULLARY SPONGE KIDNEY
- PATHOPHYSIOLOGY malformation of terminal collecting ducts bilaterally
- CLINICAL FEATURES usually asymptomatic, but may see kidney stones, microscopic hematuria, or infections. Renal failure not likely. May see "brush like" appearance of calyces in IVP
- TREATMENTS treatment of stones and infections as needed

#### SIMPLE CYSTS

- **PATHOPHYSIOLOGY** 30% of men, 15% of women by age 70
- CLINICAL FEATURES cortex affected. May be single or multiple. Usually round, well demarcated, smooth walls, no echoes within cyst, strong posterior wall echo. Asymptomatic and renal failure unlikely
- DIAGNOSIS U/S renal every 6 12 months to help distinguish from cystic malignancy

77 Metabolic Acidosis

## **Metabolic Acidosis**

#### DIFFERENTIAL DIAGNOSIS

#### ANION GAP (NORMOCHLOREMIC)

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

#### NON ANION GAP (HYPERCHLOREMIC)

- . HCL GAIN drinking HCl
- HCO3 LOSS renal (proximal RTA, acetazola mide), GI (diarrhea, ostomy loss)
- ↓ HCO<sub>3</sub> PRODUCTION distal RTA, aldosterone deficiency/resistance
- ★HARD POPS★
  - HYPERALIMENTATION (resulting from amino acid load in TPN)
  - AMPHOTERICIN, ACETAZOLAMIDE
  - RENAL FAILURE, RTA (type I, II, IV)
  - DIARRHEA
  - PANCREATITIS, PANCREATIC FISTULA
  - OBSTRUCTIVE UROPATHY (RTA IV)
  - PEE (ureteroenteric drain/ileal conduit)
  - SALINE

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, lactate, ketone, serum alcohol/methanol, serum osmol ality, urinalysis, urine lytes
- ABG

#### SPECIAL

· URINE OXALATE CRYSTALS if suspect ethylene glycol ingestion

#### **Related Topics**

Osmolar Gap (p. 104) Overdose (p. 102) Respiratory Acidosis (p. 18)

Respiratory Alkalosis (p. 18)

#### DIAGNOSTIC ISSUES

## APPROACH TO ARTERIAL BLOOD GAS (ABG)

- 1. Check accuracy of data. H<sup>+</sup>=24×PCO<sub>2</sub>/HCO<sub>3</sub> (modified Henderson Hasselbalch formula). Recollect ABG and lytes if discrepancy found
- 2. Identify primary acid/base disturbance
  - Acidemia pH <7.35
  - **Alkalemia** pH >7.45
  - Acidosis/alkalosis disturbance in PCO2 or HCO<sub>3</sub>, irrespective of pH, that may result in acidemia/alkalemia, respectively
  - Metabolic initiated by change in HCO<sub>3</sub>
  - Respiratory initiated by change in PCO<sub>2</sub>
- 3. Check compensation

J. 4	5. 44						
	Primary Change HCO <sub>3</sub>	Compensation pCO <sub>2</sub>					
MAA -	•						
MAc	↓ 10	↓ 10 13					
MAlk	↑ 10	↑57					
	pCO <sub>2</sub>	HCO₃					
RAIk	↓ 10	↓ 5 (chronic) 2 (acute)					
RAc	↑ 10	↑ 3 (chronic) 1 (acute)					

Normal pCO<sub>2</sub> = 40 mmHg,  $HCO_3$  = 24 mmol/L 4. Calculate anion gap (↑ anion gap in MAc, ↓ anion gap may be due to hypoalbuminemia [10:2.5] ratio], paraproteinemia (e.g. myeloma), halide ingestion (e.g. lithium) or laboratory error)

ANION GAP = Na Cl HCO<sub>3</sub>; normal is between 8 and 12 mmol/L

- 4a. If anion gap metabolic acidosis, calculate osmolar gap to differentiate between causes **OSMOLAR GAP** = (Glucose + Urea + Na<sup>+</sup>  $\times$ 2) observed osmolality ★GUN2★ (see p. 104 for more details)
- 4b. Calculate "delta ratio" (also known as "delta delta") to check for any superimposed metabolic disorder

 $\Delta AG/\Delta HCO_3 = (AG 10)/(24 HCO_3)$ 

$\Delta$ AG/ $\Delta$ HCO <sub>3</sub>	Interpretation
< 0.4	Combined ↑ AG MAc + non AG
	MAc
	(i.e. $\downarrow$ HCO <sub>3</sub> $>>\uparrow$ AG)
0.4 0.8	Possible ↑ AG MAc + non AG
	MAc; typical for renal failure
1.0 2.0	Isolated ↑ AG MAc
	Lactic acidosis usually 1.6
	DKA usually 1.0
>2.0	Combined ↑ AG MAc + MAlk, or
	Pre existing compensated RAc
	(i.e. $\uparrow$ AG $>>\downarrow$ HCO <sub>3</sub> )

NOTE: be wary of over interpretation, use clinical judgment

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#### DIAGNOSTIC ISSUES (CONT'D)

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,  $O_2$ , IV, intubation, NaHCO<sub>3</sub> 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 CI. A negative UNC suggests unmeasured cation, imply ing that NH<sub>4</sub><sup>+</sup> is present (i.e. type II RTA, not type I RTA). In the presence of acidosis, UNC should be negative (i.e. NH<sub>4</sub><sup>+</sup> present). Therefore, look for GI losses (neGUTive)

#### RENAL TUBULAR ACIDOSIS TYPE I (distal)

- PATHOPHYSIOLOGY inability to make NH<sub>4</sub><sup>+</sup>. Causes include H<sup>+</sup>/ATPase mutation (associated with hypokalemia), back leakage of hydrogen ions due to increased luminal membrane perme ability (Sjogren's syndrome, rheumatoid arthritis, amphotericin B, cirrhosis; associated with hyperka lemia) and decreased distal tubular Na reab sorption resulting in reduced electrical gradient for proton secretion (obstructive uropathy, sickle cell anemia; associated with hyperkalemia). Urine pH elevated because of ↓ H<sup>+</sup> in urine. Serum K ↓ in most cases
- **DIAGNOSIS** +ve UNC, urine pH relatively high despite metabolic acidosis
- TREATMENTS treat underlying cause. HCO<sub>3</sub> and K supplement, or potassium citrate

#### SPECIFIC ENTITIES (CONT'D)

RENAL TUBULAR ACIDOSIS TYPE II (proximal)

- PATHOPHYSIOLOGY inability to reabsorb HCO<sub>3</sub> at the proximal tubule. Causes include Fanconi's syndrome (multiple myeloma, carbonic anhy drase inhibitor, ifosfamide), genetic disorders (Wilson's disease, cystinosis), vitamin D defi ciency, and renal transplant
- DIAGNOSIS low serum K, negative urine net charge. Confirmation is done by HCO<sub>3</sub> challenge → check urine pH every 2 h → measure serum HCO<sub>3</sub> level when urine pH >7 (expect relatively "low" serum HCO<sub>3</sub> in type II RTA). Urinary pH initially ↑ due to HCO<sub>3</sub> loss, but then ↓ as serum HCO<sub>3</sub> becomes low
- TREATMENTS usually self limiting in adults. HCO<sub>3</sub> supplement has limited utility due to HCO<sub>3</sub> wast ing and may even lead to hypokalemia

#### RENAL TUBULAR ACIDOSIS TYPE IV

- PATHOPHYSIOLOGY causes include hyporenine mic hypoaldosteronism (renal failure, frequently diabetic nephropathy and sometimes acute glo merulonephritis, ACE inhibitors, NSAIDs), primary aldosterone deficiency (Addison's, congenital adrenal hyperplasia), and aldosterone resistance (amilloride, spironolactone, tubulointerstitial disease)
- DIAGNOSIS high serum K
- TREATMENTS K restriction in diet, diuretics. Flu drocortisone may be used with caution

#### DISTINGUISHING FEATURES FOR RENAL TUBU LAR ACIDOSIS Type I Type IV Type II Pathology Distal Proximal Ald deficiency 1/↑ Serum K Serum Variable 10 20 >17 HCO<sub>3</sub> Variable Urine pH >5.3 < 5.3 UNC **Positive** Negative Variable

## **Metabolic Alkalosis**

#### **DIFFERENTIAL DIAGNOSIS**

HCO<sub>3</sub> GAIN HCO<sub>3</sub> administration (IV/PO), citrate (transfusion), acetate (TPN)
H<sup>+</sup> LOSS

- GI Loss vomiting, NG suction
- PHYSIOLOGIC ALDOSTERONE-MEDIATED RENAL LOSS (volume sensitive)
  - FLUID INTAKE
  - RENAL LOSS diuretics, Bartter's, Gitelman's, hypomagnesemia

### DIFFERENTIAL DIAGNOSIS (CONT'D)

- GI Loss vomiting, ileus, villous adenoma, stool CI loss
- SKIN LOSS sweat, burn
- INTRACELLULAR ACIDOSIS hypokalemia
- PATHOLOGICAL ALDOSTERONE-MEDIATED RENAL LOSS (volume insensitive)
  - ↑ RENIN renal artery stenosis, tumor
  - ↑ ALDOSTERONE Conn's
  - † ALDOSTERONE-LIKE Cushing's

Hyponatremia 79

## 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 ALKA LOSIS ↓ effective circulating fluid volume, hypoka lemia, hyperaldosteronism, chloride deficiency

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, serum osmolality, uri nalysis, urine lytes, magnesium, urine osmolality
- ABG

#### **SPECIAL**

SERUM ALDOSTERONE AND RENIN

#### DIAGNOSTIC ISSUES

#### LYTES AND URINE LYTES

	U Na	UK	U CI	Rh
Vomit HCI loss	1	1	$\downarrow$	1
Burn NaCl loss	1	<b>↑</b>	1	$\downarrow$
Physiologic renal loss	1	1	1	$\downarrow$
Pathologic renal loss	1	1	1	1

## DIAGNOSTIC ISSUES (CONT'D)

#### URINE CHLORIDE

- INCREASED (>20 mmol/L, "Cl resistant") diuretic use (decreased Cl reabsorption), Bartter's and Gitelman's syndrome (decreased Cl reabsorption), mineralocorticoid excess (Conn's), Cushing's syndrome, licorice, severe hypokalemia (impaired Cl transport), hypomagnesemia, alkali load, idiopathic
- DECREASED (<10 mmol/L, "Cl responsive") decreased chloride intake, vomiting, NG drainage, post diuresis, cystic fibrosis, villous adenoma, laxa tive abuse, persistent post hypercapnia, RTA (decreased NH<sub>4</sub> excretion)

#### MANAGEMENT

ACUTE ABC, O2, IV

**TREAT UNDERLYING CAUSE volume sensitive** (fluids, replete K), **volume insensitive** (spironolac tone, 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 CI transporter in the distal tubule (similar to inhibition by thiazide diuretics). Characterized by hypocalciuria

## Hyponatremia

## DIFFERENTIAL DIAGNOSIS OF HYPOOSMOLAR HYPONATREMIA

## **HYPOVOLEMIC (VOLUME DEPLETION)**

- RENAL LOSS diuretics, hypoadrenalism, hypo magnesemia, Bartter's
- GI LOSS vomiting, diarrhea, third spacing
- SKIN LOSS sweat burns
- BLOOD LOSS

#### **EUVOLEMIC**

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

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

## DIFFERENTIAL DIAGNOSIS OF HYPOOSMOLAR HYPONATREMIA (CONT'D)

- CANCER SCLC, pancreatic, duodenum, thy moma, lymphoma
- LUNG DISEASE TB, abscess, empyema, pneu monia, viral pneumonitis
- CNS PROBLEMS skull fracture, subarachnoid hemorrhage, subdural hemorrhage, cerebral atrophy, encephalitis, meningitis, Guillain Barre syndrome, lupus, acute intermittent porphyria
- DRUGS morphine, carbamazepine, TCA, chlorpropamide, vincristine, vinblastine, clofi brate, oxytocin, general anesthesia

**HYPERVOLEMIC** (edema) cardiac failure, cirrho sis, Gl losing enteropathy, nephrotic syndrome, malnutrition

80 Hyponatremia

#### PATHOPHYSIOLOGY

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

#### INVESTIGATIONS

#### BASIC

 LABS lytes, urea, Cr, glucose, TSH, cortisol, urine lytes, urine Cr, serum and urine osmolality (e.g. to rule out pseudohyponatremia)

#### DIAGNOSTIC ISSUES

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

**SIADH CRITERIA** diagnosis of SIADH requires the following: cause available, clinically euvolemic, hypo natremic, increased urine osmolality (>100 mmol/L and usually >300 mmol/L), specific gravity (>1.003), increased urine Na (>40 mmol/L), and low uric acid. Also need to rule out hypothyroidism, adrenal insufficiency, diuretic use, and psychogenic polydipsia. See

## NEJM 2007 356:20 for more details CALCULATING CORRECTION RATE

- CHANGE IN SERUM NA
  - =  $(Na_{infusate} Na_{serum})/(total\ body\ water + 1)$ where total body water  $\approx 0.5 \times body\ weight\ (kg)\ in$ women and  $0.6 \times body\ weight\ (kg)$  in men
- VOLUME OF INFUSATE NEEDED (in liters) = intended change in serum Na over a defined period of time (usually 8 mmol/L over 24 h)/change in serum Na
- In patients with chronic hyponatremia, the daily limit of increase in serum Na should be ≤8 mmol/L to minimize the risk of central pontine myelinolysis. The initial rate of correction can still be 1 2 mmol/L per hour for several hours in patients with severe symptoms. In patients with acute hyponatremia, the daily limit can be more flexible
- INFUSATE SODIUM CONTENT D5W (5% dextrose in water) 0 mmol/L, ½ NS (0.45% NaCl in water) 77 mmol/L, Ringer's lactate 130 mmol/L, NS (0.9% NaCl in water) 154 mmol/L, 3% hypertonic saline 513 mmol/L, 5% hypertonic saline 855 mmol/L

#### MANAGEMENT

**HYPOVOLEMIC NS** infusion. 3 oxo cubes/L water daily  $\times 3$  days. Hypertonic saline or furosemide if severe (be extremely cautious)

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

#### MANAGEMENT (CONT'D)

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

#### TREATMENT ISSUES

**VAPTANS** ("AQUARETICS") oral V2 receptor antago nists → block ADH action → water diuresis. For correction of euvolemic and hypervolemic hypona tremia, 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 hyperglyce mia (correct Na by adding 3 mmol/L for every 10 mmol/L increase in glucose), hypertonic 3 mmol/L mannitol

**ISOOSMOLAR HYPONATREMIA** glycine or sorbi tol 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 (mor phine, 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
- DIAGNOSIS CT head, MRI head
- TREATMENTS dismal prognosis with no effective therapy. Prevention is key

Hypokalemia 81

## **Hypernatremia**

## NEJM 2000 342:20

#### **DIFFERENTIAL DIAGNOSIS**

**HYPOVOLEMIC** decreased thirst, decreased water access

**EUVOLEMIC** (diabetes insipidus)

- NEUROGENIC trauma, tumors, infections (TB, meningitis, encephalitis), infiltrative (sarcoido sis), vascular, idiopathic
- NEPHROGENIC renal disorders (polycystic kid neys, infiltration, infection, ischemia), hypercal cemia, medications (lithium, demeclocycline, amphotericin B), idiopathic

**HYPERVOLEMIC** drink seawater, excessive IV fluid, primary hyperaldosteronism

#### PATHOPHYSIOLOGY

**DEFINITION OF HYPERNATREMIA** Na > 145 mmol/L

#### CLINICAL FEATURES

**SYMPTOMS** may include intense thirst, muscle weakness, confusion, and coma. Brain shrinkage could potentially cause vascular rupture, leading to cerebral bleeding, subarachnoid hemorrhage, perma nent neurologic deficit, and death

### INVESTIGATIONS

#### **BASIC**

- LABS lytes, urea, Cr, glucose, Ca, serum osmolal ity, urinalysis, urine lytes, urine Cr, urine osmolality SPECIAL
- **DDAVP TEST** to distinguish between nephro genic and neurogenic diabetes insipidus

## DIAGNOSTIC ISSUES

#### CALCULATING CORRECTION RATE

- WATER DEFICIT (in liters)
  - =  $(Na_{current}/Na_{goal} 1) \times total body water$
- CHANGE IN SERUM NA
  - =(Na<sub>infusate</sub> Na<sub>serum</sub>)/(total body water + 1) where total body water  $\approx 0.5 \times$  body weight in women and  $0.6 \times$  body weight in men
- VOLUME OF INFUSATE NEEDED (in liters) = intended change in serum Na over a defined period of time (usually 10 mmol/L over 24 h) divided by change in serum Na + 1.5 L to compensate for obligatory daily water losses
- INFUSATE SODIUM CONTENT D5W (5% dextrose in water) 0 mmol/L, ½NS (0.45% NaCl in water) 77 mmol/L, Ringer's lactate 130 mmol/L, NS (0.9% NaCl in water) 154 mmol/L. Avoid using NS for correction of hypernatremia unless hemody namic instability/fluid resuscitation

**OSMOLALITY** urine osmolality is usually lower than serum osmolality in diabetes insipidus, whereas urine osmolality is usually higher than serum osmol ality in hypovolemic hypernatremia

#### MANAGEMENT

**HYPOVOLEMIC hypotonic fluid** infusion. Treat underlying cause

**EUVOLEMIC ADH** if central diabetes insipidus. Free water hydration. Treat underlying cause (see POLY URIA p. 347)

## Hypokalemia

#### DIFFERENTIAL DIAGNOSIS

**INTAKE** rare

**SHIFT INTO CELL** metabolic alkalosis, hyperinsu lin states,  $\uparrow \beta$  adrenergic states, hypothermia

#### ↑ OUTPUT

- GI Loss diarrhea, vomiting, tube drainage
- RENAL LOSS diuretics, hypomagnesemia, type I or II RTA, hyperaldosteronism, Conn's, renal artery stenosis

#### PATHOPHYSIOLOGY

 $\begin{array}{ll} \textbf{DEFINITION OF HYPOKALEMIA} & K < 3.5 \text{ mmol/L} \\ \textbf{PHYSIOLOGY} & \text{daily intake of potassium is usually} \\ 40 & 120 \text{ mEq/day (banana contains 1 mEq of K every} \\ \end{array}$ 

## PATHOPHYSIOLOGY (CONT'D)

2.5 cm [1 in.]), which is mostly excreted by the kid neys. 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 HYPOVOLE

**MIA** 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)

82 Hyperkalemia

#### CLINICAL FEATURES

SYMPTOMS usually not present unless <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 ammo nia production due to intracellular acidosis, and hypokalemic nephropathy

#### INVESTIGATIONS

#### BASIC

 LABS lytes, magnesium, urea, Cr, glucose, CK, serum osmo, urinalysis, urine lytes, urine osmo

## SPECIAL

ECG

#### INVESTIGATIONS (CONT'D)

• HYPERALDOSTERONISM WORKUP serum aldoster one and plasma renin activity

#### DIAGNOSTIC ISSUES

**TRANSTUBULAR K GRADIENT** indirect indicator of aldosterone activity

- TTKG = (U<sub>K</sub>/U<sub>osmo</sub>)/(P<sub>K</sub>/P<sub>osmo</sub>)
- TTKG >4 = renal loss (hyperaldosteronism)
- TTKG <2 = GI or non renal loss</li>
- Note: TTKG only valid if U<sub>osmo</sub> >P<sub>osmo</sub> and U<sub>Na</sub> >25 mmol/L

#### MANAGEMENT

**ACUTE** (K <3.0 mmol/L) **KCI** 10 mEq in 100 mL D5W IV bolus  $\times$ 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*<sub>4</sub> 5 g IV over 4 h)

#### TREAT UNDERLYING CAUSE

## Hyperkalemia

#### **DIFFERENTIAL DIAGNOSIS**

**PSEUDOHYPERKALEMIA** hemolysed sample, leukocytosis, thrombocytosis

↑ **INTAKE** rare

 $\begin{array}{ll} \textbf{SHIFT OUT OF CELL} & \text{metabolic acidosis, diabetes} \\ \text{(insulin deficit), } \beta \text{ blockade} \end{array}$ 

↑ **RELEASE** rhabdomyolysis, tumor lysis, strenu ous exercise, intravascular hemolysis

#### **⊥** OUTPUT

- ↓ DISTAL TUBULAR FLOW renal failure, ↓ effective circulating fluid volume

#### PATHOPHYSIOLOGY

**DEFINITION OF HYPERKALEMIA** K >5.0 mmol/L

#### CLINICAL FEATURES

## **SYMPTOMS**

- MUSCULAR weakness and even paralysis of extre mities, but rarely respiratory muscle involvement
- CARDIAC tall, peaked T wave (especially precor dial leads), widen QRS, wide and flat P wave, VF

#### INVESTIGATIONS

#### BASIC

blood

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

#### **SPECIAL**

- ABG/VBG quick way to get serum K level
- HYPOALDOSTERONISM WORKUP serum aldoster one 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 hyper kalemic patient (kidneys not secreting K appropriately
- TTKG <5 = very suggestive of hypoaldosterism in hyperkalemic patient (adrenal insufficiency)

Hypophosphatemia 83

#### MANAGEMENT

**ACUTE** (K >6.0 mmol/L with ECG changes)

- STABILIZE MEMBRANE calcium chloride 10% 10 mL IV push, calcium gluconate 10% 10 mL IV push, do not give if hyperkalemia related to digoxin
- SHIFTING K INTO CELLS (temporizing measure)
  - INSULIN D50 50 mL IV push followed by Humu lin R 10 U in 50 mL of D50% IV bolus. Consider dextrose drip or second amp of D50W as hypo glycemia occurs up to 70% of cases when only 1 amp of D50 given
  - ALKALOSIS NaHCO<sub>3</sub> 45 mEq IV over 5 min, repeat in 30 min PRN for acidosis

#### MANAGEMENT (CONT'D)

 β-AGONIST salbutamol 10 20 mg via NEB, monitor heart rate

**REMOVAL OF K** *kayexalate* 30 g PO daily QID (avoid if HF/Na retention), each dose followed by lactulose 30 mL PO. *Ca resonium* 30 40 g in 50 mL 20% sorbitol. **Diuretics** (*furosemide* 40 mg IV, doses up to 200 mg may be needed in ARF). **Dialysis** 

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

## Hypomagnesemia

#### DIFFERENTIAL DIAGNOSIS

↓ INTAKE malnutrition, malabsorption, maldigestion SHIFT INTO BONE hungry bone syndrome ↑ OUTPUT

- Gl Loss diarrhea, small bowel bypass surgery, acute pancreatitis
- RENAL LOSS thiazide, loop diuretics, alcohol, hypercalcemia, tubular dysfunction (alcohol, aminoglycosides, amphotericin B, cisplatin, cyclosporine, acute tubular necrosis in diuretic phase, primary renal magnesium wasting)

#### PATHOPHYSIOLOGY

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

#### CLINICAL FEATURES

#### SYMPTOMS

LYTES/CA/PO<sub>4</sub> ↓ K, ↓ Ca, PTH resistance, vitamin D deficiency

#### CLINICAL FEATURES (CONT'D)

 HEART ventricular arrhythmias, widening of the QRS, peaking or diminution (severe) of T waves, prolongation of PR interval, and torsade de pointes

#### INVESTIGATIONS

#### BASIC

 LABS lytes, urea, Cr, Ca, Mg, PO<sub>4</sub>, serum osmol ality, urinalysis, urine Mg, urine Cr

### DIAGNOSTIC ISSUES

FeMg =  $(U_{Mg}/U_{Cr})/(0.7 \times P_{Mg}/P_{Cr})$ , <3 suggests extra renal loss

#### MANAGEMENT

**MG SUPPLEMENT**  $MgSO_4$  5 g IV over 5 h, Mg gluconate 500 mg PO TID

**TREAT UNDERLYING CAUSE** amphotericin B induced hypomagnesemia (amiloride)

## Hypophosphatemia

## DIFFERENTIAL DIAGNOSIS

↓ INTAKE alcoholism, inadequate intake, antacids SHIFT INTO CELL acute respiratory alkalosis (DKA, hyperventilation), hyperinsulin (especially refeeding syndrome), hungry bone syndrome

#### ↑ OUTPUT

- PRIMARY HYPERPARATHYROIDISM
- SECONDARY HYPERPARATHYROIDISM (vitamin D deficiency/resistance) hereditary hypophosphatemic rickets, oncogenic osteomalacia, Fanconi syndrome, osmotic diuresis, acetazolamide, acute volume expansion, steatorrhea, chronic diarrhea

#### PATHOPHYSIOLOGY

**DEFINITION OF HYPOPHOSPHATEMIA** PO<sub>4</sub> <0.8 mmol/L [<2.5 mg/dL]

## CLINICAL FEATURES

#### SYMPTOMS

- CNS (intracellular ATP falls) metabolic ence phalopathy
- HEMATOLOGIC (RBC 2,3 DPG falls) hemolysis, ↓ WBC activity, ↓ clot retraction, thrombocytopenia

#### Related Topics

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

#### INVESTIGATIONS

#### BASIC

 LABS Ca, Mg, PO<sub>4</sub>, PTH, CK, 24 hour urinary PO<sub>4</sub> collection (<100 mg), urine PO<sub>4</sub>, urine Cr

#### DIAGNOSTIC ISSUES

 $FePO_4 = (U_{PO4}/U_{Cr})/(P_{PO4}/P_{Cr}), < 5$  suggests not due to  $\uparrow$  output

#### MANAGEMENT

PO<sub>4</sub> SUPPLEMENT potassium phosphate (22 mmol K<sup>+</sup>, 15 mmol PO<sub>4</sub>) in 250 mL NS over 4 h, or sodium phosphate (20 mmol Na<sup>+</sup>, 15 mmol PO<sub>4</sub>) in 250 mL NS over 4 h, or sodium phosphate 1 g PO TID (replaces ∼100 mmol/day)

**TREAT UNDERLYING CAUSE vitamin D defi** ciency (vitamin D 800 U PO daily)

## **Ureteral Calculi**

NEJM 2004 350:7

#### **CAUSES**

**CALCIUM** (80%) calcium oxalate or calcium phosphate, radiodense

**URIC ACID** (10 15%) 20% of patients also have gout, radiolucent

**STRUVITE** (10 15%) urea splitting bacteria (*Proteus, Klebsiella*), infected stone. Staghorn calculi if filled entire renal pelvis, radiodense

**CYSTINE** (1%) autosomal recessive disorders of renal tubular absorption of dibasic amino acids, radiodense

#### **PATHOPHYSIOLOGY**

#### STONE FORMATION

- PROMOTERS low urine volumes, urine cystine, pH (distal RTA), uric acid, Ca/oxalate/PO<sub>4</sub>, ana tomic defects (medullary sponge kidney)
- INHIBITORS high urine volumes, urine citrate, Mg, Tamm Horsfall proteins, nephrocalcin, uro pontin, orthophosphates
- **COMPLICATIONS** obstruction, renal failure, infection, urosepsis, ureteral stricture

#### **INVESTIGATIONS**

#### BASIC

- LABS CBCD, lytes, urea, Cr, Ca, PO<sub>4</sub>, 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

#### SPECIÁL

- URINE TEST 24 hour urinary Ca/PO<sub>4</sub>, oxalate, urate, Mg, citrate, and Na
- CYSTOSCOPY

## DIAGNOSTIC ISSUES

**RADIODENSE STONES** ★**COLAS**★ Calcium, Cystine, Ornithine, Lysine, Arginine, Struvite

**RADIOLUCENT STONES** uric acid, matrix (organic substances associated with urea producing bacteria), indinavir (radiolucent on X ray and CT)

#### MANAGEMENT

ACUTE pain control (ketorolac 30 60 mg IV/IM, then 15 mg IV/IM q6h or 10 mg PO q6h, diclofenac 50 mg PO BID TID, or morphine 5 mg SC q4h). N&V (dimenhydrinate 25 50 mg PO/IV/SC q4h PRN), meto clopramide 10 mg PO/IV q4h PRN). Urology consult (if stone does not pass spontaneously or >5 mm, consider shock wave lithotripsy, ureteroscopy, percu taneous nephrolithotomy. If obstructed, infected upoer 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). Hyper calciuria (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, alkaliniza tion of urine with K citrate or NaHCO₃). Hypomagne suria (Mg gluconate 500 mg PO TID)

## Hypertension

Approach to Dialysis 85

## **Approach to Dialysis**

#### HEMODIALYSIS

**PRINCIPLES OF CLEARANCE** fluid removal (ultra filtration  $\pm$  osmotic gradient), solute removal (small toxins, middle molecules, electrolytes. Dialysis by osmotic gradient). Urea is a surrogate marker and is not toxic itself

FACTORS AFFECTING EFFICIENCY countercurrent exchange, blood pump speed, dialysate speed (500 mL/min), size of membrane, time (4 h 3× week) VASCULAR ACCESS temporary (double lumen internal jugular/femoral. Avoid subclavian placement if possible to minimize risk of subclavian stenosis), intermediate (PermCath internal jugular), permanent (AV graft, AV fistula)

#### **ORDERS**

- GOAL WEIGHT DETERMINATION symptoms, clinical fluid status, blood pressure
- FILTER low efficiency for new patients, high flux, high efficiency filters for most other patients
- BLOOD PUMP SPEED usually 400 450 mL/min for CRF. May start at 200 250 mL/min for new patients
- DIALYSATE FLOW 500 mL/min
- DURATION usually 4 h. May start at 2.5 h for new patients
- FLUID REMOVAL net weight gain + fluid given during dialysis. Try to attain dry weight
- NA<sup>+</sup> 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 sim ply set Na at 137 mmol/L or 140 mmol/L throughout the run. If hyponatremia, set Na at 132 135 mmol/L
- K<sup>+</sup> as a general rule, [dialysate K] = 7 mmol/L [serum K]
- HCO<sub>3</sub> 25 40 mmol/L (usually 35 mmol/L)
- ca<sup>2+</sup> 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 intravascu larly, 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,

#### HEMODIALYSIS (CONT'D)

- 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, hemody namically stable. Consider switching to intermittent hemodialysis

## ADVANTAGES OF CONTINUOUS RENAL REPLACE MENT COMPARED TO INTERMITTENT HEMODIA

**LYSIS** 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 REPLA CEMENT** requires anticoagulation (heparin, citrate, NS flush q30 min), removes more solute, and requires replacement

## PERITONEAL DIALYSIS (PD)

ADVANTAGES OF PERITONEAL DIALYSIS COM PARED TO INTERMITTENT HEMODIALYSIS bet ter middle molecular clearance, better control of fluid and blood pressure, preserves residual renal function better, cheaper, increased patient autonomy

METHODS OF CLEARANCE continuous ambula tory peritoneal dialysis (4×2 L exchanges/day for 30 40 min during the day, with one indwelling exchange overnight), continuous cycler PERITO NEAL DIALYSIS (reverse timing of CAPD)

**FACTORS AFFECTING EFFICIENCY** volume of exchanges, time of exchange, efficiency of peritoneal membrane (high average transporter vs. low average transporter)

**DIALYSATE Dianeal** (standard with Na 132 mmol/L, Cl 95 mmol/L, Mg 0.25 mmol/L [5 mEq/L], osmol ality 395 mmol/kg, pH 5.2, dextrose 0.5%, 1.5%, 2.5%, or 4.25%), **Extraneal** (icodextrin), **Nutrineal** (1.1% amino acid solution. Good nutrition). Concentration of glucose affect fluid removal

**ADEQUACY** goal KT/V 1.7/week and creatinine clearance 60 L/week

## PERITONEAL DIALYSIS (PD) (CONT'D)

## **COMPLICATIONS OF PERITONEAL DIALYSIS**

 PERITONITIS once every 2 years. Triad of abdominal pain, cloudy dialysate, and >100 WBC/mm<sup>3</sup>. Treat with intraperitoneal ceftazi dime and vancomycin empirically until cul tures available

## PERITONEAL DIALYSIS (PD) (CONT'D)

- MECHANICAL blockage (causes include constipa tion, 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

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## Notes

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# Notes

# 4

# CRITICAL CARE

Section Editor: Dr. Wendy Sligl

#### **Intensive Care Issues**

#### ICU ADMISSION CRITERIA

NEED FOR FREQUENT OR CONTINUOUS MONI TORING 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 postitoning, 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 coagulo pathy. Prophylaxis with  $\rm H_2$  blockers (e.g. *ranitidine* 50 mg IV q8h or 150 mg PO/NG q12h) preferred unless high risk as use of proton pump inhibitors is associated with increased risk of ventilator associated pneumonia **VENOUS THROMBOEMBOLISM** particularly in patients with trauma and prolonged bed rest. Pro phylaxis includes heparin SC, LMWH, fondaparinux, or pneumatic compression stockings

#### SEDATION, ANALGESIA, PARALYSIS IN THE ICU

SEDATION/AMNESIA propofol 0.5 mg/kg/h initial infusion, titrate to 0.5 3.0 mg/kg/h by continuous IV infusion, typical infusion range 0 300 mg/h. Appropriate for short term sedation, monitor for acidosis and increased CK with prolonged use, rapid onset, short duration; mid azolam 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

**ANALGESIA** *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  $\mu$ g/h, 100 $\times$  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,  $5\times$ more potent than morphine

**NEUROMUSCULAR BLOCKAGE** *rocuronium* 0.5 mg/kg IV PRN, onset 1 min, duration 30 min; *pancuro nium* 0.06 0.15 mg/kg IV PRN, onset 2 3 min, duration 60 120 min, may run continuous infusion 0.01 0.05 mg/kg/h, vagolytic effect may cause tachy cardia; *cisatracurium* 0.15 0.2 mg/kg IV PRN, onset 2 3 min, duration 30 min, may run continuous infusion 3 μg/kg/min, undergoes Hoffman degradation; *succinylcholine* 0.5 1.5 mg/kg IV, onset 1 min, duration  $\sim$ 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, hypomagnese mia, hypocalcemia, organophosphates, botulism **MYOPATHY** critical illness myopathy, acute necrotizing myopathy, hypokalemia, hypopho sphatemia, hypocalcemia, hypomagnesemia, ster oid, muscular dystrophy, polymyositis

#### PROCEDURES

# RADIAL ARTERIAL LINE INSERTION (NEJM 2006 354:e13)

 LANDMARK palpate radial artery immediately proximal to scaphoid. Insert 20 gauge (48 mm length) catheter at 30° 90 Intensive Care Issues

#### 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 ingu inal 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 (CAO<sub>2</sub>)

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

#### VENOUS OXYGEN CONTENT (CvO<sub>2</sub>)

- $C_vO_2 = O_2$  carried by hemoglobin  $+ O_2$  dissolved in blood
- $C_vO_2 = 1.36 \times Hb \times S_vO_2 + 0.003 \times P_vO_2$ where  $S_vO_2 =$  mixed venous Hb saturation ( $S_{cv}O_2$  if using central venous saturation)

#### OXYGEN FLUX (DO<sub>2</sub>)

- DO<sub>2</sub> = amount of oxygen delivered to tissues/min
- DO<sub>2</sub> = CO × C<sub>a</sub>O<sub>2</sub>, where C<sub>a</sub>O<sub>2</sub> ~ 1.36×Hb×S<sub>a</sub>O<sub>2</sub> since 0.003 × P<sub>a</sub>O<sub>2</sub> is negligible

#### OXYGEN CONSUMPTION (VO<sub>2</sub>)

- VO<sub>2</sub> = the arteriovenous oxygen content differ ence multiplied by cardiac output
- VO<sub>2</sub> = CO × (C<sub>a</sub>O<sub>2</sub> C<sub>v</sub>O<sub>2</sub>) ≅ constant (the body normally extracts ~25% of the delivered oxygen except in fever, sepsis, hyperthyroidism, i.e. VO<sub>2</sub>/ DO<sub>2</sub>=0.25)

#### INTERPRETATION

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

#### PROGNOSTIC ISSUES

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

- CLINICAL age, GCS, organ failure (biopsy proven cirrhosis, NYHA class IV, severe COPD, chronic hemodialysis, immunocompromise), procedure (non surgical, elective, emergency operation)
- VITALS HR, RR, MAP, temp
- ABG pH, A a gradient or PaO<sub>2</sub>
- CBC Hct, WBC
- CHEMISTRY Na, K, Cr

**VENTILATION** 95% of patients with acute respiratory failure can be weaned within 7 days of intubation. 5% are unable to be weaned from the ventilator and require tracheostomy and long term ventilatory support

#### CARDIOPULMONARY RESUSCITATION

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

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#### CARDIOPULMONARY RESUSCITATION (CONT'D)

hypoxia, anemia, chronic renal failure), **poor base line function** (dependent on ADLs), **scene of CPR** (>10 min of CPR without the return of at least a single vital sign, unwitnessed arrest)

PROGNOSIS respiratory arrest better than cardiac arrest. VT/VF/bradycardia better than asystole/PEA (patients with VF/VT witnessed arrest and response within 5 min of resuscitation have the highest probability of survival to discharge). If resuscitated promptly, 95% of survivors will return to their baseline level of function after CPR, but 5% will be left in a chronic vegetative state. Survival to discharge 1 5% for out of hospital CPR and 15% for in hospital CPR

#### BRAIN DEATH

#### **EXAMINATION OF THE UNRESPONSIVE PATIENT**

- VITALS include GCS
- 5N neurological, noggin, neck, nose, needle
- EYES fundoscopy, pupil reflex, corneal reflex, oculocephalic reflex, oculovestibular reflex
- **OTHERS** gag reflex, tone, limb reflexes, Babinski

#### **GLASGOW COMA SCALE**

- EYES OPENING 1=none, 2=to pain, 3=to voice, 4=voluntary
- LANGUAGE 1=none, 2=sounds, 3=words, 4=disor ganized 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</li>

#### **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 con scious patient instilled with Cold water, nystag mus fast phase moves toward Opposite side;

#### BRAIN DEATH (CONT'D)

with **W**arm water, nystagmus fast phase moves toward **S**ame side)

#### ANOXIC BRAIN INJURY SPECTRUM

- 1. Good recovery (mild disability)
- 2. Moderate disability (independent with ADLs)
- 3. Severe disability (dependent for ADLs)
- 4. Persistent vegetative state (unawareness but awake at times)
- 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 irreversibil ity, absence of drug intoxication or poisoning, absence of hypothermia, absence of metabolic causes for encephalopathy
- PHYSICAL core temperature ≥34°C [≥93.2°F], absence of motor response to painful stimulus, absence of brain stem reflexes (corneal, pupillary, gag, cough, doll's eyes, calorics), apnea testing
- IMAGING perfusion brain scan (most sensitive test), cerebral angiogram, EEG, transcranial dop pler ultrasound
- CRITERIA need both history and physical features to confirm brain death. If apnea testing cannot be performed or indeterminate, need imaging test to verify
- BRAIN DEATH MIMICS locked in syndrome (focal injury to pons), hypothermia (light reflex lost 28 32°C [82.4 89.6°F], other brain stem reflexes lost <28°C [82.4°F]), drug intoxication, Guillain Barre syndrome

#### Related Topics

Dialysis Issues (p. 85)

Critical Illness Neuromuscular Disorders (p. 332) Palliative Care (p. 389)

Resuscitation Status (p. 399)

#### APNEA TESTING

- 1. Obtain ABG just prior to test
- Pulse oximetry on, ventilator off, 100% oxygen 6 L/min into trachea or place patient on bagger
- Observe for respiratory movements. Obtain ABG after 8 min. Reconnect ventilator immediately and draw ABG if SBP <90 mmHg, marked decrease in SaO<sub>2</sub>, or arrhythmia
- 4. Apnea present if respiratory movements are absent, PaCO<sub>2</sub> ≥60 mmHg (and increased ≥20 mmHg above baseline) and pH ≤7.28

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#### BRAIN DEATH (CONT'D)

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

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

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

JAMA 2004 291:7

### Hypoxemia

#### DIFFERENTIAL DIAGNOSIS

**R TO L SHUNT** (unresponsive to supplemental  $O_2$ , V/Q <1) ARDS, HF, pneumonia, alveolar hemor rhage, atelectasis, pulmonary arteriovenous malfor mation, intracardiac shunt (ASD, VSD, PFO)

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

**DIFFUSION DEFECTS** interstitial lung disease, PJP, atypical pneumonia

#### **HYPOVENTILATION (A a normal)**

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

**LOW O<sub>2</sub> PARTIAL PRESSURE** (A a normal) high altitude

#### PATHOPHYSIOLOGY

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

#### INVESTIGATIONS

#### BASIC

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

#### DIAGNOSTIC ISSUES

#### **OXIMETRY**

- NORMAL >90% is normal. Dyspnea may occur ~85%. Pulmonary hypertension may develop from chronic alveolar hypoxia if saturations <80%</li>
- 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). Contin uous oximetry is better than spot measurements</li>
- CORRELATION S<sub>p</sub>O<sub>2</sub> 50% = P<sub>a</sub>O<sub>2</sub> 27 mmHg, 75% = 40 mmHg, 90% = 60 mmHg, 92% = 80 mmHg, 95% = 90 mmHg. ABG is the gold standard for diagnosing hypoxemia

# OVERALL APPROACH TO DETERMINING THE CAUSE OF HYPOXEMIA

- 1. Confirm ABG shows low P<sub>a</sub>O<sub>2</sub>
- 2. Exclude diffusion defects and low partial pressure of O<sub>2</sub>
- Check PaCO<sub>2</sub>. If normal or low, then hypoventila tion is excluded. This leaves either shunt or V/Q mismatch, which can be distinguished with response to O<sub>2</sub> (absence of response suggests shunt. V/Q mismatch should respond to O<sub>2</sub>)
- 4. If high PaCO<sub>2</sub>, then hypoventilation is present. Check A a gradient to determine if co existing shunt or V/Q mismatch (presence of A a gradient suggests yes and should check response to O<sub>2</sub> to distinguish between these two possibilities)

#### DIAGNOSTIC ISSUES (CONT'D)

#### ALVEOLAR ARTERIAL (A A) O2 GRADIENT

- NORMAL A a gradient <age/4 + 4, or <0.4 × age. Usually <15 mmHg in young, up to ~30 mmHg in elderly
- CALCULATION A a gradient =  $P_AO_2$   $P_aO_2 = [(P_B 47) \times 0.21 PaCO_2/0.8] P_aO_2$ , where  $P_B$ =baro metric pressure  $\approx 760$  mmHg if at sea level
- INTERPRETATION calculation used when FiO<sub>2</sub> is 21% (room air). Normal range changes with sup plemental oxygen. If A a gradient normal, consider hypoventilation or low inspired O<sub>2</sub> as causes of hypoxemia. If A a gradient high, consider V/Q mis match, R to L shunt, and/or diffusion defects

 $P_aO_2/P_AO_2$  RATIO when FiO<sub>2</sub> >21% (i.e. on sup plemental O<sub>2</sub> therapy),  $P_aO_2/P_AO_2$  ratio should be used instead of A a gradient

- NORMAL  $P_aO_2/P_AO_2 \ge 0.99$  (0.003 × age), usually > 0.82
- INTERPRETATION unlike A a gradient, P<sub>a</sub>O<sub>2</sub>/P<sub>A</sub>O<sub>2</sub> ratio decreases in the presence of V/Q mismatch, R to L shunt, and/or diffusion defects

#### MANAGEMENT

ACUTE ABC, O<sub>2</sub>, IV, mechanical ventilation if severe respiratory failure (invasive or non invasive) TREAT UNDERLYING CAUSE

#### TREATMENT ISSUES

**AVOID OVER CORRECTING O<sub>2</sub> SATURATION IN HYPOVENTILATION** O<sub>2</sub> displaces  $CO_2$  from Hb, causing elevated  $CO_2$  in blood. In addition, O<sub>2</sub> may change V/Q relationship and may decrease hypoxic drive. For patients with chronic hypoven tilation ( $\uparrow$  HCO<sub>3</sub>), O<sub>2</sub> to keep saturation between 88 and 92% only

#### SPECIFIC ENTITIES

HYPOXEMIC RESPIRATORY FAILURE (P<sub>a</sub>O<sub>2</sub> <50 mmHg even with F<sub>1</sub>O<sub>2</sub> >50) failure to oxyge nate, see DIFFERENTIAL DIAGNOSIS OF HYPOXEMIA HYPERCARBIC RESPIRATORY FAILURE (P<sub>a</sub>CO<sub>2</sub> greater than baseline with concomitant acidosis) failure to ventilate, see hypoventilation under DIF FERENTIAL DIAGNOSIS OF HYPOXEMIA

### **Acute Respiratory Distress Syndrome**

#### DIFFERENTIAL DIAGNOSIS

#### PULMONARY EDEMA

- CARDIOGENIC ischemic cardiomyopathy, valvular disease
- **NON-CARDIOGENIC** ARDS, toxic inhalation, drug reaction, aspiration, fat embolism

**INFECTION** bacterial, viral, mycobacterial, fungal **HEMORRHAGE** pulmonary embolism, pulmonary contusion, bleeding diathesis, DIC, anticoagulation, vasculitis (Wegener's granulomatosis, Goodpasture's, SLE)

#### PATHOPHYSIOLOGY

#### **DEFINITION OF ARDS**

- ACUTE ONSET
- BILATERAL ALVEOLAR INFILTRATES usually asym metric/patchy, peripheral >central
- **HYPOXEMIA**  $P_aO_2/F_iO_2 \le 200$
- 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 syn drome of severe lung injury due to systemic inflam mation. 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

#### PATHOPHYSIOLOGY (CONT'D)

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

**HYPOXEMIA IN ARDS** caused mainly by right to left shunt, thus the  $P_aO_2/F_iO_2$  ratio is low. V/Q mis match and hypoventilation may also contribute

**CAUSES** over 80% of ARDS are caused by infections, aspiration, and trauma

- PULMONARY pneumonia (bacterial, viral, fungal, PJP), aspiration, drowning, inhalation injury (O<sub>2</sub>, smoke, NO<sub>2</sub>), reperfusion injury (post lung trans plant or cardiopulmonary bypass)
- GI acute pancreatitis
- CNS neurogenic (intracerebral hemorrhage)
- SYSTEMIC sepsis, transfusion reaction, major trauma, drugs (heroine, cocaine, aspirin, chemotherapy)

#### INVESTIGATIONS

### **BASIC**

- LABS CBCD, lytes, urea, Cr, troponin/CK, 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

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#### DIAGNOSTIC AND PROGNOSTIC ISSUES

**ACUTE LUNG INJURY** milder form of ARDS with  $P_aO_2/F_1O_2 < 300$ 

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

#### MANAGEMENT

# **ABC O**<sub>2</sub> to keep sat >90%, IV **MECHANICAL VENTILATION**

- LUNG-PROTECTIVE VENTILATION (low tidal volumes to minimize ventilation induced lung injury) set tidal volume ~4 8 mL/kg, based on ideal body weight, maintain plateau pressure <30 cmH<sub>2</sub>O
- PEEP should be employed to keep FiO<sub>2</sub> in pre sumed 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<sub>2</sub>O PEEP for 40 s

#### MANAGEMENT (CONT'D)

- PERMISSIVE HYPERCAPNIA generally tolerate pH >7.25, may need to run HCO<sub>3</sub> infusion to maintain nH
- 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 pro phylaxis. Some clinicians still use in non resolving cases (start 7 14 days after onset. *Methylprednisolone* 2 mg/kg load, then 2 mg/kg/day from days 1 to 14, then taper by 50%/week to 0.125 mg/kg/day, monitor for infection). **Nitric oxide** (selectively dilates pulmonary vessels of ventilated alveoli, improving V/Q matching. Reduces pulmonary artery pressures and intrapulmonary shunting with an increase in  $P_aO_2/F_iO_2$ )

TREAT UNDERLYING CAUSE

#### **Ventilation Issues**

#### MECHANICAL VENTILATION

# INDICATIONS FOR MECHANICAL VENTILATION • DECREASED COMPLIANCE (stiff lungs) pulmonary

- fibrosis, pulmonary edema, ARDS

   INCREASED RESISTANCE (narrowed airways, air trap
- INCREASED RESISTANCE (narrowed airways, air trap ping) 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

#### 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 oxygena tion and ventilation

#### INVASIVE MECHANICAL VENTILATION

- INDICATIONS severe hypoxemia, acute hypercap nia, need for airway protection (GCS ≤8), impend ing 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<sub>peak</sub> or decreased V<sub>-</sub>
- COMPLIANCE ease with which lungs expand.
   Normal ~50 mL/cmH₂O
- 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

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#### MECHANICAL VENTILATION (CONT'D)

- POSITIVE END-EXPIRATORY PRESSURE (PEEP) mainte nance of positive pressure throughout exhalation. PEEP improves P<sub>a</sub>O<sub>2</sub> mainly by augmenting mean airway pressure. Other potential mechanisms include recruitment of collapsed alveoli, increased functional residual capacity, and improvement in V/Q matching. Usually set at 5 cmH<sub>2</sub>O. >15 cmH<sub>2</sub>O may cause barotrauma
- PEAK AIRWAY PRESSURE (P<sub>peak</sub>) maximal inspira tory pressure to distend alveoli and to overcome airway resistance. P<sub>peak</sub> is dependent on inflation volume, airways resistance, and lung/chest wall compliance. Happens about halfway through inspiration phase
- PLATEAU PRESSURE (P<sub>plat</sub>) pressure to prevent lungs from deflating at end inspiration. Related to lung/chest wall compliance. Normal is 33±9 cmH<sub>2</sub>O
- 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 antici pate 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** pro minent 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 breaths)
- MOUTH OPENING <4 cm [<1.6 in.] (2 3 finger breaths)
- MANDIBULAR LENGTH <9 cm [3.5 in.]
- MALLAMPATI SCORE III/IV may indicate difficult air way for intubation
  - I = visualization of the soft palate, fauces, uvula, anterior and posterior pillars
  - II = visualization of the soft palate, fauces, and uvula
  - III = visualization of the soft palate and the base of the uvula
  - IV = soft palate is not visible at all

#### ARTIFICIAL AIRWAYS

**ORAL AIRWAYS** used in unconscious patients without a gag reflex to prevent airway collapse/

#### 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 tra cheostomy tube allowing weaker patients to tolerate plugging trials easier), disposable inner cannula (seal fenestration, allows easier exchange of tracheostomy tube if plugged), cuff (balloon that occludes airway surrounding tracheostomy tube)
- PLUGGING PROCEDURE provide alternate source of
  O<sub>2</sub> (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 sponta neously without ventilator assistance, consistent cough and ability to expectorate secretions, awake enough to protect airway, on minimal  $F_1O_2$  (<40% or <5 6 l/min), no evidence of upper air way obstruction

**TRACHEOSTOMY BUTTONS** to maintain stoma during weaning. Less resistance than plugged tra cheostomy 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 pres sure breath is delivered. In volume cycled modes only

**PRESSURE SUPPORT** ranges from 6 cmH<sub>2</sub>O (almost no support) to 30 cmH<sub>2</sub>O (max). Normal = 14 16 cmH<sub>2</sub>O. In pressure limited modes only

96 Ventilation Issues

#### VENTILATORY SETTINGS (CONT'D)

**INSPIRATORY TIME** determines duration over which the pressure is delivered. In pressure limited modes only

 $\mathbf{F_{i}O_{2}}$  range 0.21 1.0. Normal = 0.4 or keep satura tion >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 con trol breaths at set rate. Patient may breathe spon taneously (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<sub>high</sub> and P<sub>low</sub>). This mode attempts to maximize mean airway pressure and thus alveolar recruitment at P<sub>high</sub>, while dropping briefly to P<sub>low</sub> for CO<sub>2</sub> elimination. Used in refrac tory 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 recruit
  ment and to minimize ventilator induced lung

#### VENTILATORY SETTINGS (CONT'D)

- 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 com
   mon) 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<sub>2</sub>O, up to 20 cmH<sub>2</sub>O) and expiratory positive airway pressure phase (EPAP, start at 6 cmH<sub>2</sub>O, up to 10 cmH<sub>2</sub>O). IPAP leads to ↑ airflow which ↑ Ve and helps to ↓ PCO<sub>2</sub>, whereas EPAP leads to ↑ FRC and mainly ↑ PO<sub>2</sub>. 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, mini mal sedation, no metabolic acidosis, clear CXR, adequate hemoglobulin, adequate nutrition
- $F_iO_2$  **SETTING** effective oxygenation at  $F_iO_2$  0.5 or less
- PEEP SETTING effective gas exchange at PEEP 7.5 cmH<sub>2</sub>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<sub>2</sub>O, RSBI <100 (even better if <70)</li>

#### PROCESS FOR WEANING VENTILATED PATIENTS

- MEASURES PSV trial builds endurance. Cold nebu lizer trial builds strength. The less time the patient is on ventilator, the more normal their lung func tion, the simpler and shorter the weaning process. Daily spontaneous breathing trials significantly shorten the weaning process
- **QUICK** switch directly to CPAP, cold neb, or bag ger 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

Shock 97

#### VENTILATOR ASSOCIATED PNEUMONIA

#### PATHOPHYSIOLOGY

- DEFINITION pneumonia in patient mechanically ventilated ≥48 h
- RISK FACTORS prolonged mechanical ventilation, need for reintubation, aspiration of gastric con tents, acid suppression therapy, supine position ing, poor oral/dental hygiene
- MICROBIOLOGY predominantly *S. aureus* (including MRSA), Enterobacteriaceae, *Pseudomonas aer uginosa*. Other common microorganisms include *Stenotrophomonas*, *Acinetobacter*, anaerobes

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

#### **TREATMENTS**

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

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

	LR+	LR
Physical and investigations		
Fever	1.2	0.86
Leukocytosis	1.3	0.74
Purulent sputum	1.3	0.63

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

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

JAMA 2007 297:14

#### Shock

#### DIFFERENTIAL DIAGNOSIS

#### **★SHOCK**★

**SEPTIC** pneumonia, bacteremia, UTI, intra abdominal infection, meningitis, necrotizing fasciitis

**HYPOVOLEMIC/HEMORRHAGIC** blood loss (trauma, Gl bleed, retroperitoneal hemorrhage), Gl losses, renal losses, burns

**OBSTRUCTIVE** pulmonary embolism, tension pneumothorax, cardiac tamponade

**CARDIOGENIC** ischemic, hypertensive, valvular, arrhythmia, peripartum, toxic, infiltrative, idio pathic, familial, autoimmune

#### DIFFERENTIAL DIAGNOSIS (CONT'D)

#### KLASSIFIED CAUSES

- MEDICATIONS antihypertensives, AV nodal block ing agents
- ANAPHYLACTIC
- LIVER hepatic failure
- ENDOCRINE adrenal insufficiency, myxedema
- SPINAL cord compression

#### PATHOPHYSIOLOGY

**DEFINITION** hypotension leading to cellular hypo perfusion, hypoxia, lactic acidosis, and subsequent

98 Shock

#### PATHOPHYSIOLOGY (CONT'D)

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

#### IT'S SIMPLE MATH

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

#### CLINICAL FEATURES

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

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

#### ASSESSMENT OF VOLUME STATUS

- VITALS postural heart rate and blood pressure
- SKIN skin turgor (inner aspect of thigh, sternum), oral mucosa
- CARDIOPULMONARY JVP or CVP, crackles, S<sub>3</sub>
- URINE urine output
- EXTREMITIES peripheral pulses, skin temperature, capillary refill

#### **FEET EXAMINATION**

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

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, INR, PTT, AST, ALT, ALP, bilirubin, Ca, Mg, PO<sub>4</sub>, TSH, D dimer, lactate, CK, troponin, urinalysis
- MICROBIOLOGY blood C&S, sputum C&S, urine C&S
- IMAGING depends on suspected source; CXR, AXR, echocardiogram, CT where appropriate (e.g. CT abdomen if intra abdominal source suspected)
- ECG
- ABG

#### DIAGNOSTIC ISSUES

#### **PULMONARY ARTERY CATHETERIZATION**

 INDICATIONS diagnosis (shock states, primary pul monary hypertension, valvular disease, intracardiac shunts, cardiac tamponade, pulmonary embolus), hemodynamic monitoring (complicated AMI, multi organ system failure, post cardiac surgery),

#### DIAGNOSTIC ISSUES (CONT'D)

- treatment (aspiration of air emboli). No mortality difference with use of PA catheter
- CONTRAINDICATIONS tricuspid or pulmonary mech anical valve, tricuspid or pulmonary valve endocardi tis, right heart mass (thrombus and/or tumor)
- SITES OF ENTRY right internal jugular vein (has shortest and straightest path to the heart) >left subclavian vein >right subclavian vein >left inter nal jugular vein >femoral veins
- NORMAL VALUES
  - CENTRAL VENOUS PRESSURE (CVP) = 5 8 mmHg, may accept higher values in patients ventilated with high PEEP
  - RIGHT ATRIAL PRESSURE (RAP) = 5 8 mmHq
  - RIGHT VENTRICULAR PRESSURE (RVP) = 20 30/ 2 8 mmHg
  - PULMONARY ARTERY PRESSURE (PAP) = 20 30/ 5 15 mmHg, mean 10 22 mmHg
  - PULMONARY CAPILLARY WEDGE PRESSURE (PCWP) = pulmonary artery occlusion pressure (PAOP) ~ LA pressure = 8 12 mmHg (PCWP >18 mmHg suggests interstitial edema, PCWP >24 mmHg suggests alveolar edema)
  - LEFT VENTRICULAR PRESSURE (LVP) = 120/8 mmHg
  - AORTIC PRESSURE = 120/80 mmHg, MAP 70 110 mmHa
  - SYSTEMIC VASCULAR RESISTANCE INDEX (SVRI) = 900 1200 dynes/s/cm<sup>2</sup>
  - CARDIAC INDEX = 2.4 4.2 L/min/m<sup>2</sup>, CO = 4 7 L/min
  - $DO_2 = 400 650 \text{ mL/min/m}^2$
  - $VO_2 = 125 \ 175 \ mL/min/m^2$
  - COMPLICATIONS arterial puncture, hemothorax, pneumothorax, venous or air embolus, sustained ventricular tachycardia, ventricular fibrillation, heart block (most commonly RBBB, or complete heart block in the setting of pre existing LBBB), infection, pulmonary artery thrombosis/embo lism/infarction/rupture, knotting of catheter (requires fluoroscopic removal), pulmonary or tricuspid valve insufficiency

# DISTINGUISHING FEATURES BETWEEN SHOCK

JIAILS				
	co	CVP	PCWP	SVR
Distributive	1	↓/N	↓/N	1
Hypovolemic	$\downarrow$	$\downarrow$	$\downarrow$	1
Cardiogenic	$\downarrow$	1	1	1
Isolated RHF	$\downarrow$	1	$\downarrow$	1
Isolated LHF	$\downarrow$	↓/N	1	1
Tamponade <sup>a</sup>	1	1	1	1
3.				

<sup>a</sup>In tamponade or tension pneumothorax, observe equalization of pressures, i.e. CVP=RA=RV EDP=PCWP; cardiogenic shock gives heart failure picture on CXR, whereas tamponade usually has clear CXR with cardiomegaly only Sepsis and Septic Shock 99

#### **Related Topics**

Anaphylaxis (p. 372) Myocardial Infarction (p. 26) Sepsis (p. 99)

Tamponade (p. 32)

#### MANAGEMENT

**ACUTE** ABC, **O**<sub>2</sub>, cardiac and oximetry monitoring, **IV fluid resuscitation** (1 5 L), **ICU consult**, consider intubation/mechanical ventilation, **inotropes/vaso pressors** (*Norepinephrine* 1 30 μg/min IV. *Vasopres sin* 0.01 0.04 U/min IV. *Epinephrine* 1 20 μg/min IV. *Ephedrine* 5 25 mg IV q5 10min until blood pressure stable. *Phenylephrine* 20 200 μg/min IV. *Dobutamine* 

#### MANAGEMENT (CONT'D)

2.5 15 μg/kg/min IV. *Milrinone* 0.375 0.75 μg/kg/min IV. *Dopamine* start 1 4 μg/kg/min IV, titrate to maximum 20 μg/kg/min. *Midodrine* 5 10 mg PO TID). **Correct coagulopathy** (transfuse PRBC, FFP, cryoprecipitate)

TREAT UNDERLYING CAUSE

#### TREATMENT ISSUES

#### INOTROPES/VASOPRESSORS

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

Agent	Mechanism of action	Special note			
Norepinephrine	$\alpha$ 1 mainly, $\beta$ 1 $\rightarrow$ ↑ PVR, ↑ CO	First line for septic shock			
Vasopressin	V1, V2 → dilates renal, pulmonary,	Second line for sepsis;			
	cerebral, coronary arteries and constricts others	AE: Gut ischemia, skin necrosis			
Epinephrine	$\beta$ 1, $\beta$ 2, $\alpha$ 1 $\rightarrow$ $\uparrow$ CO, $\uparrow$ PVR	Salvage for sepsis, first line for			
		anaphylaxis;			
		AE: ischemia			
Phenylephrine	$\alpha 1 \rightarrow \uparrow PVR$	Sepsis, counteract spinal/epidural			
		anesthesia			
Ephedrine	$\beta$ 1, $\beta$ 2, $\alpha$ 1 $\rightarrow$ $\uparrow$ CO, $\uparrow$ PVR	Bolus therapy pending CVC			
·		placement for continuous			
		vasopressor therapy			
Dobutamine	$\beta$ 1, $\beta$ 2 $\rightarrow$ ↑ CO, $\downarrow$ PVR	First line for cardiogenic shock			
Milrinone	Phosphodiesterase inhibitor →	First line for cardiogenic shock with			
	↑ CO, ↓ PVR	pulmonary HTN			
Dopamine 1 2 μg/kg/min	DA → dilates renal, mesenteric,	↑ renal perfusion/GFR			
	cerebral arteries and airways	(controversial)			
Dopamine 5 10 μg/kg/min	DA, $\beta 1 \rightarrow \uparrow CO$	HF/sepsis;			
	2.7, p. 1 33	AE: tachycardia			
Dopamine >10 μg/kg/min	$\alpha 1 \rightarrow \uparrow PVR$	Sepsis/HF;			
Σοραπιτίο > το μg/ κg/ πιτί	3.1 7   1 VIII	AE: tachycardia			
Midadrina	1 . ↑ DVD	•			
Midodrine	$\alpha 1 \rightarrow \uparrow PVR$	Sepsis; oral			
where AE=adverse effects, CO=cardiac output, CVC=central venous catheter, DA=dopamine, HF=heart					

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

### **Sepsis and Septic Shock**

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

#### PATHOPHYSIOLOGY

#### **DEFINITIONS**

• sirs  $\ge$ 2 of temperature >38.3°C [>100.9°F] or <36°C [<96.8°F], heart rate >90 beats min, respiratory rate >20 or  $P_aCO_2 < 32$  mmHg, WBC >12 $\times$ 10°/L or <4  $\times$ 10°/L or >10% bands

#### PATHOPHYSIOLOGY (CONT'D)

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

100 Sepsis and Septic Shock

#### PATHOPHYSIOLOGY (CONT'D)

 SEPTIC SHOCK sepsis induced hypotension (i.e. SBP <90 mmHg) despite adequate fluid resuscita tion or vasopressor dependence.

**SIMPLIFIED MECHANISM OF INJURY** infection  $\rightarrow$  systemic inflammation (SIRS)  $\rightarrow$  complement activa tion,  $\downarrow$  fibrinolytics  $\rightarrow$  endothelial dysfunction, micro vascular coagulopathy and thrombosis  $\rightarrow$  organ fail ure. Too little or too much host response

#### **MECHANISM OF ACUTE KIDNEY INJURY IN SEPSIS**

- 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
- Disseminated microvascular coagulation → glo merular 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 >0.7×10<sup>9</sup>/L, com monly seen in infections
- "SEVERE" LEFT SHIFT cells as immature as meta myelocytes may be seen in left shift in response to infection, but unusual to see more immature cells (myelocytes, promyelocytes, blasts). When pre sent, suggestive of myeloproliferative disorder (chronic myelogenous leukemia, agnogenic mye loid metaplasia, or one of the various forms of acute leukemia)

#### INVESTIGATIONS

#### **BASIC**

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

#### **SPECIAL**

- ScvO<sub>2</sub> MONITORING with internal jugular or subclavian central line insertion
- LUMBAR PUNCTURE if altered level of consciousness
- THORACENTESIS if significant pleural effusion(s)
- PARACENTESIS if ascites

#### MANAGEMENT

**ACUTE** ABC,  $\mathbf{O_2}$ ,  $\mathbf{IV}$ , consider intubation/mechanical ventilation

#### MANAGEMENT (CONT'D)

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

#### NEJM 2001 345:19

**ANTIMICROBIALS** early **empiric antimicrobials, should be administered ASAP, order STAT.** If sus pect pulmonary source, macrolide plus  $\beta$  lactam for community acquired pneumonia, anti pseudomonal plus aminoglycoside or fluoroquinolone  $\pm$  vancomy cin (if high level MRSA endemicity) for nosocomial pneumonia. If suspect urinary source, third genera tion cephalosporin, fluoroquinolone, or aminoglyco side. If suspect intra abdominal source,  $\beta$  lactam/ $\beta$  lactamase inhibitor or carbapenem. **Tailor antimi crobials** 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], maintain ing euglycemia *may* improve outcomes; however, must avoid hypoglycemia

**ACTIVATED PROTEIN C** for patients at high risk of death (APACHE score  $\geq$ 25, sepsis induced multiple organ failure, septic shock, or sepsis induced ARDS, with no absolute contraindications related to bleed ing 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 mortal ity 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  $S_{cv}O_2$  during the first 6 h of resuscitation, the target hematocrit should be 30%. In stable patients, the threshold for transfusion should be hemoglobin <70 g/L, with a target of 70 90 g/L

PROPHYLAXIS DVT (unfractionated heparin SC, LMWH, fondaparinux, pneumatic stockings), stress ulcer (ranitidine 50 mg IV q8h or 150 mg PO/NG q12h) SPECIFICS ARDS (lung protective ventilation), acute kidney injury (avoid nephrotoxins, supportive renal replacement therapy), early enteral feeding

Rhabdomyolysis 101

#### **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 (etha nol, methanol, ethylene glycol, paraldehyde, cyanide, nitroprusside, isoniazid, epinephrine
- B3 (inborn errors of metabolism) defects of pyruvate metabolism, defects of NADH oxida tion, disorders of gluconeogenesis (type 1 glyco gen storage disease), fatty acid oxidation defects, defects of organic acid metabolism

#### PATHOPHYSIOLOGY

**DEFINITION** >4 mmol/L [>36 mg/dL] (normal  $\sim$ 1 mmol/L [9 mq/dL]) + metabolic acidosis

**LACTIC ACID PRODUCTION** part of the glycolytic pathway as pyruvate is converted to lactate to gen erate NAD from NADH. As anaerobic metabolism increases ( $\downarrow$  O<sub>2</sub> delivery,  $\uparrow$  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 appro priate (e.g. CSF, pleural, pericardial, ascites)
- IMAGING AXR  $\pm$  CT abdomen (if suspect bowel ischemia)
- ABG

#### SPECIAL

• INBORN ERROR OF METABOLISM (mitochondrial disorder) if suspected, consider LP for CSF lactate level  $\pm$  muscle biopsy

#### MANAGEMENT

**ACUTE** ABC,  $O_2$  to keep sat >94%, IV, HCO<sub>3</sub> 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, neuro leptic 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  $>5\times$  of upper normal limit

**HYPOCALCEMIA AND HYPERCALCEMIA** calcium initially decreases due to ↑ deposition in muscle and ↓ bone responsiveness to PTH. May see rebound

#### PATHOPHYSIOLOGY (CONT'D)

hypercalcemia in 20% of patients when rhabdomyo lysis resolves

COMPLICATIONS acute kidney injury, DIC

#### INVESTIGATIONS

#### BASIC

 LABS lytes, urea, Cr, CK, AST, ALT, Ca, PO<sub>4</sub>, Mg, uric acid, troponin, urine myoglobin

#### DIAGNOSTIC ISSUES

**MONITORING IN RHABDOMYOLYSIS** CK, urine output, Cr, Ca, PO<sub>4</sub> should be checked regularly (q4 24h) until CK normlized

#### MANAGEMENT

**ACUTE ABC**, O<sub>2</sub> 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

102 Toxicology

#### MANAGEMENT (CONT'D)

kidney injury. However, if acute kidney injury already established be careful not to cause fluid overload. **Alkaline diuresis** (add 3 amps NaHCO<sub>3</sub> 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 typi cal, and sometimes atypical, antipsychotic agents. The syndrome typically occurs within a few days of treatment, with drug levels usually within thera peutic 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. Check CK
- TREATMENTS discontinue all antidopaminergic medications. Supportive measures. Specific

#### SPECIFIC ENTITIES (CONT'D)

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), neuro muscular 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 medica tions. Supportive measures. In mild cases, symptoms usually resolve within 24 h. Consider cyproheptadine in select cases

### Toxicology

#### APPROACH TO OVERDOSE

**BASIC** ABC, O<sub>2</sub>, IV, monitor, vitals (HR, RR, BP, temp, O<sub>2</sub> sat, blood sugar, GCS)

#### INVESTIGATIONS

- **BLOOD TESTS** CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, Ca, Mg, PO<sub>4</sub>,  $\beta$ hCG, alcohol level, methanol, ethylene glycol, salicylates, acetaminophen, other drug levels (especially patient's own medications such as digoxin, iron, theophylline, lithium), serum osmolality, and osmolar gap
- URINE TESTS urine pregnancy test (if female <50), urine drug screen (as appropriate, e.g. narcotics, benzodiazepines, cocaine, ampheta mines, 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, hallucina tions, mydriasis, urinary retention, decreased bowel sounds), **serious** (seizures, coma, respiratory failure, arrhythmias, cardiovascular collapse). ECG findings may include sinus tachycardia, prolonged PR, QRS, and QT intervals, RBBB and ST elevation in leads V1 V3

TREATMENTS supportive measures, charcoal, HCO<sub>3</sub> if cardiac arrhythmia, sedation with benzodia zepines PRN

#### SYMPATHOMIMETIC SYNDROMES

**CAUSES** cocaine, amphetamines, LSD, PCP, metham phetamine, phenylpropanolamine, ephedrine, pseu doephedrine, methylphenidate, nicotine, theophylline **CLINICAL FEATURES common** (fever, tachycardia, hypertension, *diaphoresis*, delusions, paranoia,

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#### SYMPATHOMIMETIC SYNDROMES (CONT'D)

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

**TREATMENTS** supportive measures, sedation with benzodiazepines. Avoid  $\beta$  blockers (unopposed  $\alpha$  effect)

#### CHOLINERGIC SYNDROMES

**CAUSES** organophosphate and carbamate insecti cides, pilocarpine, physostigmine, edrophonium, some mushrooms

CLINICAL FEATURES common (delirium, saliva tion, lacrimation, miosis, diaphoresis, emesis, urinary and fecal incontinence), serious (pulmonary edema, seizures, coma)

TREATMENTS supportive measures, atropine

#### METHANOL AND ETHYLENE GLYCOL OVERDOSE

See METHANOL and ETHYLENE GLYCOL OVERDOSE on p. 105

#### ACETAMINOPHEN OVERDOSE

**PATHOPHYSIOLOGY** 5% of acetaminophen is metabolized to *N* acetyl p benzoquinoneimine (NAPQI) which is highly toxic to liver, but is normally rapidly inactivated via conjugation with glutathione. With acetaminophen overdose, NAPQI accumulates due to depletion of glutathione stores, causing hepatic necrosis and acute kidney injury. *N* acetylcysteine, the antidote, regenerates hepatic glutathione stores leading to enhanced conjugation and clearance of NAPQI. A single dose of 10 15 g acetaminophen (twenty 500 mg tablets) can produce liver injury. Fulminant hepatic failure (FHF) usually associated with >25 g

★The rule of 140's★ toxic dose = 140 mg/kg, nomogram blood level vs. time (>140  $\mu$ g/mL 4 h after ingestion) → >5  $\mu$ g/mL 24 h after ingestion). First dose of N acetylcysteine 140 mg/kg PO (IV infusion may also be used: 150 mg/kg in 200 mL D5W over 15 min, then 50 mg/kg in 500 mL D5W over 4 h, then 100 mg/kg in 1L D5W over 16 h; may continue third stage until liver enzyme normalization in FHF)

**CLINICAL FEATURES** first few hours, nausea and vomiting, RUQ pain, diarrhea. Symptoms disappear 24 h after ingestion. Liver failure († INR, bilirubin, and transaminases) may start at 24 72 h with or without AKI or cardiotoxicity

**POOR PROGNOSTIC SIGNS** coagulopathy (most important), acidosis, acute kidney injury, hypopho sphatemia, encephalopathy

TREATMENTS supportive, N acetylcysteine
KING'S COLLEGE CRITERIA FOR LIVER TRANS
PLANTATION IN TYLENOL OVERDOSE ★The rule

#### ACETAMINOPHEN OVERDOSE (CONT'D)

of 3's  $\star$  either pH <7.3 or grade III/IV encephalo pathy plus Cr >300  $\mu$ mol/L [>3.3 mg/dL] plus INR >6.5 (~5% survival with medical therapy alone)

NEJM 2008 359:3

#### SALICYLATE OVERDOSE

**CAUSES** (★**The rule of 3's**★) a single dose of 10 **3**0 g (**3**0 tablets of **3**25 mg) can be fatal. Symp toms may occur with salicylate >**3.0** mmol/L [>40 mg/mL]

**CLINICAL FEATURES common** (tinnitus, vertigo, N&V, diarrhea, tachypnea, metabolic acidosis, respira tory alkalosis), **serious** (hyperthermia, pulmonary edema, delirium, seizure, coma)

**DIAGNOSIS** salicylate level (every 2 h until decreased level), ABG (every 2 h until stable)

**TREATMENTS supportive** measures (avoid intu bation if possible. Consider gastric lavage. *Glucose* 100 mL of D50W IV if altered mental status regardless of serum glucose level. **Activated charcoal** (50 100 g PO/NG q4h ×3doses). **Alkalinize** serum and urine; maintain urine pH 8 8.5 (*NaHCO*<sub>3</sub> 1 3 amps IV push, then 3 amps of NaHCO<sub>3</sub> in 1 L D5W at 250 mL/h). Consider **hemodialysis** if altered menta tion, 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 clin ical deterioration

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

# OPIATE, SEDATIVE OR ETHANOL INTOXICATION SYNDROMES

**CAUSES** narcotics, barbiturates, benzodiazepines, ethanol, clonidine

**CLINICAL FEATURES common** (decrease in all vitals, hypothermia, stupor, miosis, dry skin, urinary retention, decreased bowel sounds, hyporeflexia), **serious** (seizures, coma, respiratory depression). Note vitals may be relatively normal, particularly for benzodiazepine overdose

**TREATMENTS** supportive measures, naloxone (if opiates), flumazenil (if benzodiazepines), urinary alkalinization (if barbiturates)

#### β BLOCKER OVERDOSE

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

**TREATMENTS supportive** measures, **fluid** resusci tation, **glucagon** (initial dose 0.05 0.15 mg/kg up to

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#### β BLOCKER OVERDOSE (CONT'D)

a max dose of 10 mg over 2 min, then infusion 0.07 mg/kg), IV calcium, phosphodiesterase inhi bitor (milrinone or amrinone), epinephrine, dialysis for atenolol or sotalol, insulin/glucose infusions, atropine, or pacing not usually effective

#### CALCIUM CHANNEL BLOCKERS OVERDOSE

**CAUSES** dihydropyridine calcium channel blockers (nifedipine, amlodipine, isradipine) affect mainly vas cular tone and may cause hypotension with reflex tachycardia. Non dihydropyridine calcium channel blockers (diltiazem, verapamil) usually lead to SA/AV slowing and negative inotropy

**CLINICAL FEATURES common** (hypotension, arrhy thmias, delirium, hypokalemia, lactic acidosis, hyper glycemia)

**TREATMENTS** supportive measures. Fluid resuscita tion. **IV** calcium (calcium gluconate 10% 50 mL or calcium chloride 10% 20 mL). **Glucagon. Insulin/glu cose infusions** 

#### LITHIUM TOXICITY

**CAUSES** usually related to chronic drug accumula tion, 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, leukocy tosis, hypercalcemia). Chronic toxicities include dia betes insipidus, leukocytosis, and goiter

**TREATMENTS supportive** measures, gastric lavage if within 60 min of ingestion, **hypotonic solu tion** infusion, Kayexalate (binds lithium), whole bowel irrigation, **hemodialysis** (if Li >3.5 mEq/L in acute ingestion or >2.5 mEq/L in chronic ingestion AND significant symptoms, or persistently high Li levels, beware of rebound effect after hemodialysis due to redistribution)

#### **Related Topics**

ABG (p. 77)

Alcohol Abuse (p. 105) Delirium/Coma (p. 380)

ECG (p. 62)

Seizures (p. 309)

#### DIAGNOSTIC ISSUES FOR OVERDOSE

**OSMOLAR GAP** measured osmolality calculated osmolality, where Osmo<sub>calc</sub> ★**GUN2**★

- Osmo<sub>calc</sub> = (Glucose in mmol/L) + (Urea in mmol/L) + 2×(Na mmol/L)
- or in US units: Osmo<sub>calc</sub> = (Glucose in mg/dL)/18 + (Urea in mg/dL)/2.8 + 2×(Na mEg/L)
- NORMAL OSMOLAR GAP typically 2 to +6 mOsm/ kg
- INCREASED OSMOLAR GAP AND ANION GAP ethylene glycol, methanol, diabetic or alcoholic ketoacido sis, lactic acidosis, chronic renal failure (other small solutes), severe lactic acidosis ("idiogenic osmole"), severe sepsis (some inflammatory mediators are believed to be osmotically active)
- INCREASED OSMOLAR GAP BUT NORMAL ANION GAP ethanol, isopropyl alcohol, diethyl ether, sorbitol, mannitol, severe hyperproteinemia, severe hyperlipidemia

**ANION GAP (AG)** Na CI  $HCO_3$ . AG >12 mEq/L is abnormal and can be caused by methanol, ethylene glycol, uremia, ketoacidosis, paraldehyde, INH, iron, lactic acidosis, cyanide, arsenic, toluene, salicylates (see METABOLIC ACIDOSIS p. 77). Decreased anion gap can be caused by excessive cations such as in Li toxicity. Remember to adjust AG in hypoalbuminemia by adding 2.5 3 mmol/L for every 10 g/L [1.0 g/dL] decrease in serum albumin). A 'normal' AG may 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

- ACUTE ABC, O<sub>2</sub>, 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 hypoxe mia/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)

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

- 3. ALKALINIZATION AND/OR HEMOPERFUSION/HEMODIALY-SIS forced alkaline diuresis will accelerate excretion of acids (aspirin, barbiturates). Give 3 amps of NaHCO<sub>3</sub> in 1 L D5W at 250 mL/h. Monitor urine output and for volume overload, alkalosis and hypokalemia. Goal pH for urine is 7.5 8 and for serum is 7.5 7.6. Consider hemodialysis if the patient is toxic with barbiturate, bromides, chloral hydrate, alcohols (ethanol, isopropanol, acetone, methanol, ethylene glycol), lithium, procainamide, theophylline, salicylates, heavy metals, trichlor oethanol, atenolol, or sotalol
- 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 1L D5W IV over 16 h. Alternatively, N acetylcysteine 140 mg/kg PO/NG, followed by 70 mg/kg q4h for 17 doses). Opiates (naloxone 0.4 2 mg IV, repeat PRN). Benzodiazepines (flumazenil 0.2 mg over 30 s, then 0.5 mg q1min PRN. Maximum total dose

#### MANAGEMENT OF OVERDOSES (CONT'D)

3 mg). Methanol/ethylene glycol (10% ethanol in D5W 10 mL/kg IV over 30 min, then 1.5 mL/kg/h, goal EtOH level 22 28 mmol/L [100 128 mg/dL]. Fomepizole 15 mg/kg IV, followed by 10 mg/kg q12h until ethylene glychol level <3.2 mmol/L [<20 mg/dL]). Digitalis (Digibind 10 20 vials IV if life threatening arrhythmia). Calcium channel **blockers** (CaCl<sub>2</sub> 1 g over 5 min, repeat if life threatening disease).  $\beta$  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 (pyr idoxine given gram to gram of INH ingested). Tri cyclic antidepressant (NaHCO<sub>3</sub> 1 2 mmol/kg IV if cardiac arrhythmia). Anticholinergics (lorazepam 2 10 mg IV q5min, physostigmine). **Iron** (*deferox* amine 1 g IM or IV, then 500 mg g4h  $\times$ 2, then 500 mg q4 12hr PRN. Maximum total dose 6 g/ day). Cholinergics (atropine 0.5 2 mg IV, repeat a5 30min PRN)

- ANTICIPATE COMPLICATIONS delirium, aspiration pneumonia, respiratory failure, electrolyte imbal ance, 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 neu ropathy, myopathy
  - **PSYCHIATRIC** dependence, depression, homi cide, 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, thrombocy topenia, splenomegaly
- CANCER oral cavity, esophagus, pharynx, lar ynx, 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, **A**nnoyed by criticisms, **G**uilty about drinking, **E**ye opener. LR+ for heavy drinking (>8 drinks/day): 0=0.14, 1=1.5, 2=4.5, 3=13.2, 4=101

OTHERS MAST, AUDIT

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

JAMA 1994 272:22

#### CLINICAL FEATURES (CONT'D)

#### DSM IV CRITERIA FOR ALCOHOL WITHDRAWAL

- A. Cessation/reduction of alcohol use that has been heavy and prolonged
- B. Two or more of the following within several hours to a few days of cessation: autonomic hyperactivity (e.g. sweating, tachycardia), tremor, insomnia, nau sea or vomiting, transient visual, tactile, or auditory hallucinations or illusions, psychomotor agitation, anxiety, grand mal seizures
- Symptoms causing clinically significant distress or impairment in social or occupational function
- D. Rule out general medical conditions or other men tal disorders

#### MINOR WITHDRAWAL

- TIMING occurs within 6 h of cessation, resolves in 24 48 h
- SYMPTOMS due to CNS and sympathetic hyperac tivity, may include insomnia, tremulousness, mild anxiety, gastrointestinal upset, headache, diaphor esis, 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/alobal 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, tachy cardia, 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

#### BASIC

- LABS CBCD (macrocytosis, cytopenias), lytes, urea, Cr, glucose, TSH, AST, ALT (AST/ALT >2), ALP, bilirubin, GGT, Ca, Mg, PO<sub>4</sub>, osmolality
- MICROBIOLOGY blood C&S, urinalysis, urine C&S (if delirious)
- IMAGING CXR
- ECG
- ABG
- URINE DRUG SCREEN

#### INVESTIGATIONS (CONT'D)

#### SPECIAL

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

#### ACUTE MANAGEMENT OF ALCOHOL WITHDRAWAL

**ACUTE** ABC,  $O_2$  to keep sat >94%, IV (NS 1 L bolus, then 100 mL/h). Consider causes of patient's 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)
   chlordiazepoxide 50 100 mg PO q6h and PRN ×1 day, then 25 50 mg q6h and PRN ×2 days.

   Alternatively, consider CIWA Ar scale below
- LOW RISK FOR WITHDRAWAL (as needed dosing) diazepam 10 20 mg PO q2h or lorazepam 1 2 mg PO q1h until no symptoms then PRN doses
- AGITATION add haloperidol 0.5 5 mg PO/IM/IV q1 4h PRN (but may lower seizure threshold)
- TREMORS β blockers

**NUTRITIONAL SUPPLEMENT thiamine defi ciency** (*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  $\times 1$  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?"

Hypothermia 107

# TREATMENT ISSUES FOR ALCOHOL WITHDRAWAL (CONT'D)

- AUDITORY DISTURBANCES (0 7) "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?"
- VISUAL DISTURBANCES (0 7) "Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?"
- HEADACHE, FULLNESS IN HEAD (0 7) "Does your head feel different? Does it feel like there is a band around your head?"
- ORIENTATION AND CLOUDING OF SENSORIUM (0 4)
   'What day is this? Where are you? Who am !?"
- UTILITY mild withdrawal ≤8/67 points, moderate withdrawal 9 15 points, severe withdrawal >15 points (higher risk of delirium tremens and sei zures). 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 dura tion of treatment

#### SPECIFIC ENTITIES

#### THIAMINE DEFICIENCY SYNDROMES

- WERNICKE'S ENCEPHALOPATHY encephalopathy (profound disorientation, indifference, inattentive ness, delirium, altered level of consciousness), ocu lomotor dysfunction (nystagmus, lateral rectus palsy, and conjugate gaze palsies), gait ataxia
- KORSAKOFF'S AMNESIA (irreversible) selective ante rograde 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

#### SPECIFIC ENTITIES (CONT'D)

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 meta bolic acidosis with associated Kussmaul breathing, hypotension, seizures, and altered level of con sciousness. Methanol specifically is associated with mydriasis, afferent pupillary defect, optic disc hyperemia, retinal edema resulting in perma nent 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 acti vated charcoal). NaHCO<sub>3</sub> 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 pene tration and damage). Alcohol dehydrogenase inhibition (fomepizole 15 mg/kg IV, followed by 10 mg/kg q12h) or continuous ethanol (IV 8 mL/kg 10% ethanol in D5W over 30 min then 1.5 2 mL/kg/h to maintain serum ethanol >21 mmol/L, increase rate to 3 mL/kg/h on dialy sis; alternatively PO 1 mL/kg 95% ethanol then 0.15 mL/kg/h  $\approx$  4 oz Scotch loading dose with 2 oz g1h maintenance). Cofactor therapy includes folic acid 50 mg IV g4h until methanol no longer measurable (accelerates formic acid  $\rightarrow$  CO<sub>2</sub> + H<sub>2</sub>O); thiamine 100 mg IV q6h and pyridoxine 50 mg IV q6h until ethylene glycol no longer measurable (accelerates glycoxylate  $\rightarrow$  glycine +  $\alpha$  hydroxy  $\beta$ ketoadipate. This reaction requires magnesium sup plementation). **Hemodialysis** 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, vaso dilation (drugs, alcohol, sepsis, pancreatitis)
- IATROGENIC cold fluid infusion, CPR, renal repla cement therapy

#### **DECREASED METABOLISM**

 ENDOCRINE hypothyroidism, hypopituitarism, adre nal insufficiency, hypoglycemia

#### CAUSES (CONT'D)

- METABOLIC anorexia nervosa, malnutrition
   ALTERED REGULATION
- CENTRAL stroke, Parkinson's disease, multiple sclerosis, hypothalamic dysfunction, anorexia ner vosa, drugs (barbiturate, TCA, sedatives, alcohol)
- PERIPHERAL neuropathies, diabetes

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#### PATHOPHYSIOLOGY

**DEFINITION OF HYPOTHERMIA** internal tempera ture <35°C [<95°F] (by rectal, tympanic, or esopha geal thermometer). Hypothermia may be mild (34 35°C [93 95°F]), moderate (30 34°C [86 93°F]), or severe (<30°C [<86°F])

**RISK FACTORS** extremes of age, alcoholism, mal nutrition, homelessness, mental illness

**COMPLICATIONS** hypothermia affects most organs, causing cognitive (coma), neuromuscular (rigidity), respiratory (pulmonary edema), cardiac (arrhythmia), and cutaneous complications (frost bite). Sepsis, pneumonia, hypokalemia, hypoglyce mia, and rhabdomyolysis may also occur

#### CLINICAL FEATURES

**HISTORY** exposure to cold (duration, environ ment), shivering, confusion, delirium, palpitations, weakness, ulcers, frostbite, fever, weight loss, past medical history (hypothyroidism, diabetes, alcohol ism, psoriasis), medications, social history

**PHYSICAL** vitals (bradycardia, apnea, hypertension/hypotension, hypoxemia), GCS, respiratory and cardio vascular examination (arrhythmia), rigidity, hypore flexia, skin examination (frostbite, burns, psoriasis)

#### <u>INVES</u>TIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, CK, tropo nin, AST, ALT, ALP, bilirubin, TSH, urinalysis
- MICROBIOLOGY blood cultures
- ECG Osborn wave (elevated J point), pro longed RR, PR, QRS, and QT intervals

#### MANAGEMENT

**ACUTE** ABC,  $O_2$  to keep sat >94%, IV. Caution with fluid overload (decreased cardiac output in hypother mic patients) and vasopressors (arrhythmogenic potential). Resuscitation should continue until patient completely rewarmed

**MONITORING** continuous cardiac monitoring. Also closely monitor electrolytes and glucose. Vagotonic maneuvers (e.g. intubation or suctioning) may pre cipitate asystole

#### MANAGEMENT (CONT'D)

**REWARMING environment** (remove cold cloth ing. Warming blanket). **Active rewarming** (warm IV fluids ~40 42°C [104 108°F]. If severe hypothermia, consider colonic/bladder irrigation, peritoneal or pleural lavage, extracorporeal blood rewarming. Goal of rewarming is 0.5 2°C/ħ [1.8°F/h] to minimize risk of VF and hypovolemic shock)

**FROSTBITE** supportive care. Skin grafting and amputation may be required if gangrene develops

#### SPECIFIC ENTITIES

#### **ELECTRICAL INJURY**

- PATHOPHYSIOLOGY causes include lightening, taser, and stun gun
- CLINICAL FEATURES injuries may involve the skin (burns), heart (VF, asystole, cardiac contusion), bones/muscles (deep electrothermal tissue injury, osteonecrosis, compartment syndrome, rhabdo myolysis with renal failure, posterior shoulder dis location), and neurologic system (loss of con sciousness, weakness or paralysis, respiratory depression, autonomic dysfunction)
- DIAGNOSIS clinical. Obtain CBCD, lytes, urea, Cr, glucose, CK, appropriate imaging, drug and alco hol levels, urinalysis, CXR, ABG, ECG
- TREATMENTS ABC, O<sub>2</sub>, IV. Supportive manage ment 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). Com plications include respiratory failure, ARDS, hypothermia, arrhythmia (atrial fibrillation, brady cardia, ventricular tachycardia), acidosis (meta bolic, respiratory), anoxic brain injury, cerebral edema, and seizures
- DIAGNOSIS clinical. Obtain CBCD, lytes, urea, Cr, glucose, osmolality, drug and alcohol levels, urina lysis, CXR, ABG, and ECG
- TREATMENTS ABC, O<sub>2</sub>, IV. Supportive manage ment of complications. 75% of near drowning vic tims survive

### **Smoke Inhalation**

#### PATHOPHYSIOLOGY

**MECHANISM OF INJURY** thermal injury, hypoxic gas inhalation, bronchopulmonary toxins (airway inflammation and possible ARDS), and systemic tox ins (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

Anaphylaxis 109

#### CLINICAL FEATURES (CONT'D)

**PHYSICAL** vitals (tachycardia, tachypnea, hypoten sion, temperature, hypoxemia), GCS, respiratory exam ination (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, carboxyhe moglobin level, cyanide level, methemoglobin level (\( \) with cyanide poisoning), lactate (\( \) with cyanide poisoning)
- IMAGING CXR
- ECG
- ABG to determine PaO<sub>2</sub>, PaCO<sub>2</sub>, and CO Hb levels
- LARYNGOSCOPY/BRONCHOSCOPY if significant burns

#### MANAGEMENT

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

**SPECIFIC POISONING** see CO and CN poisoning **BURNS** fluids, wound care. Plastic surgery consult

#### SPECIFIC ENTITIES

#### CARBON MONOXIDE (CO) POISONING

- PATHOPHYSIOLOGY CO is an odorless, colorless, and non irritating gas. It has a high affinity for hemoglobin, preventing it from releasing O<sub>2</sub>
- CLINICAL FEATURES nausea, malaise, headache, dyspnea, angina, confusion, coma
- TREATMENTS 100% O<sub>2</sub> (decreases t<sub>1/2</sub> 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 contain ing 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)

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# Notes

# GASTROENTEROLOGY

Section Editor: Dr. Winnie Wong

### **Nausea and Vomiting**

#### **DIFFERENTIAL DIAGNOSIS**

#### NEUROLOGIC

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

#### **GASTROINTESTINAL**

- INFECTIONS acute gastroenteritis, food poison ing, 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, hyper calcemia, hyperthyroidism, hyperemesis gravidarum
- OTHERS uremia, pregnancy

### IDIOPATHIC

#### PATHOPHYSIOLOGY

#### **REFLEX PATHWAY**

- AFFERENT (1) humoral drugs, toxins, neurotrans mitter, peptides → area postrema in floor of 4<sup>th</sup> 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) nocicep tive 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

#### PATHOPHYSIOLOGY (CONT'D)

bowel and antrum, abdominal muscle contraction and initial cricopharyngeus contraction followed by relaxation seconds before vomiting

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, Ca, Mg, PO<sub>4</sub>, AM cortisol, urinalysis
- MICROBIOLOGY urine C&S
- IMAGING CXR, AXR

#### **SPECIAL**

- GASTROSCOPY
- CT HEAD

#### MANAGEMENT

#### SYMPTOM CONTROL

- H1 ANTAGONISTS dimenhydrinate 50 mg PO/PR q4h, diphenhydramine 25 50 mg PO/IV/IM q6h, cyclizine 50 mg PO/IM q4h or 100 mg PR q4h, meclizine 25 50 mg PO daily, promethazine 12.5 25 mg PO/IM q4h or 12.5 25 mg PR daily
- D2 ANTAGONISTS benzamides (metoclopramide
   5 10 mg PO/IV/IM q4h), phenothiazine (pro chlorperazine 5 10 mg PO q6 8h, chlorpromazine
   10 25 mg PO q4 6h), butyrophenones (droper idol 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, dolase tron 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)

112 Dysphagia

### Dysphagia

#### **DIFFERENTIAL DIAGNOSIS**

**OROPHARYNGEAL** (upper esophagus and phar ynx, or upper esophageal sphincter dysfunction)

- NEUROLOGICAL stroke, multiple sclerosis, Parkinson's, dementia, amyotrophic lateral sclerosis, Guillain Barre, myasthenia gravis, cer ebral palsy, Huntington's, tardive dyskinesia, brain stem tumors, trauma
- MYOPATHIC myotonic dystrophy, dermatomyo sitis, 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 esopha geal sphincter, cardia)

- STRUCTURAL tumors (benign, malignant), eso phagitis/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 dis ease, diffuse esophageal spasm, hypertensive lower esophageal sphincter, nutcracker esopha gus, non specific esophageal motility disorders
- FUNCTIONAL

#### CLINICAL FEATURES

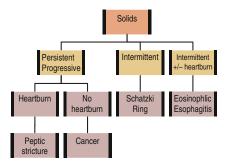
**DIAGNOSTIC CLUES** history of heartburn may sug gest GERD leading to erosive esophagitis, peptic stricture, or esophageal adenocarcinoma. History of atopic diseases especially in a young adult with recur rent dysphagia may suggest eosinophilic esophagitis. Also check for odynophagia, regurgitation,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

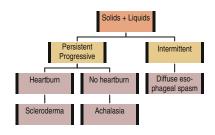
#### PRACTICAL APPROACH TO DYSPHAGIA

 Features of oropharyngeal dysphagia (problems initiating swallowing, extending neck/arms when swallowing, changes in speech, coughing, chok ing, or nasal regurgitation)? Consider workup for oropharyngeal dysphagia. Otherwise, proceed to step 2

#### CLINICAL FEATURES (CONT'D)

- Difficulty swallowing both solids and liquids? If yes, consider motility disorders and proceed to step 3. If progressing from solids to liquids, con sider structural disorders and proceed to step 4
- For motility disorders, is the dysphagia pro gressive? If yes, consider achalasia or sclero derma. If intermittent, consider diffuse esopha geal spasm or non specific esophageal motility disorder
- For structural disorders, is the dysphagia progres sive? 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 achala sia, useful for diffuse esophageal spasm

Dyspepsia 113

#### INVESTIGATIONS (CONT'D)

- **PH MONITORING** for GERD, especially if gastro scopy normal
- FIBEROPTIC NASOPHARYNGEAL LARYNGOSCOPY for oropharyngeal dysphagia

#### MANAGEMENT

**SYMPTOM CONTROL** postural/nutritional/beha vioral modifications, swallowing rehabilitation, eso phageal 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 infarc tion), 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, theo phylline, 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
- **D**rug therapy
- Smokina

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

#### PATHOPHYSIOLOGY

**COMPLICATIONS OF PUD** perforation, hemor rhage, 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, nau sea, and post prandial fullness (indigestion)
- HEARTBURN retrosternal burning sensation sec ondary to lower esophageal sphincter relaxation = more specific for GERD

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

	LR+	LR
Organic dyspepsia		
Diagnosis reached by the clinician	1.6	0.46
or computer model		
Pentic ulcer disease		

2.2

0.45

Diagnosis reached by the clinician

or computer model

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#### CLINICAL FEATURES (CONT'D)

#### LR+ LR

### 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 (car diac, pulmonary, hepatobiliary, colonic, musculos keletal, medications, and dietary indiscretion) and investigate those causes if likely. Otherwise pro ceed 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

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

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, glucose, AST, ALT, ALP, bilirubin, lipase, Ca, albumin, fecal occult blood
- IMAGING upper GI series, U/S abd, CT abd SPECIAL
- UREA BREATH TEST
- H. PYLORI SEROLOGY
- 24-H ESOPHAGEAL PH MONITORING
- ENDOSCOPY WITH BIOPSY urease test, C&S for H. pylori
- PROTON PUMP INHIBITOR TEST sens 78% for **GERD**

#### MANAGEMENT

PEPTIC ULCER DISEASE avoid NSAID use. 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 q 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  $\times$ 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

## NEJM 2008 359:16

#### NSAIDS INDUCED GASTROPATHY

• PATHOPHYSIOLOGY NSAIDs inhibit COX 1 (nor mally protective effect through mucus secretion, Acute Abdominal Pain 115

#### SPECIFIC ENTITIES (CONT'D)

bicarbonate secretion, mucosal circulation) and COX 2 (inducible inflammatory activity, also in kid neys). 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 gluco corticoid or anticoagulant therapy

 TREATMENTS primary prophylaxis includes miso prostol and proton pump inhibitor. If ulcer devel oped while on NSAIDs but must continue, should give proton pump inhibitor

#### **BARRETT'S ESOPHAGUS**

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

#### SPECIFIC ENTITIES (CONT'D)

• **TREATMENTS** high grade dysplasia should be eval uated for esophagectomy or ablative therapy

#### **GASTROPARESIS**

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

#### NEJM 2007 356:8

#### HELICOBACTER PYLORI

- PATHOPHYSIOLOGY chronic inflammation → cau sative 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), serol ogy (sens 90%, spc 80%) is of limited value as it tests for IgG which only indicates previous expo sure, 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 ketoacido sis, uremia, hypercalcemia, porphyria, familial Med iterranean fever

**OTHERS** myocardial infarction, pneumonia, sple nic injury, shingles, musculoskeletal

#### PATHOPHYSIOLOGY

**CAUSES OF ABDOMINAL PAIN** any intra abdom inal organs (e.g. GI, GU, gynecological, spleen) × (ischemia, infection, obstruction, tumors) + systemic causes + referred pain

#### CLINICAL FEATURES

HISTORY characterize abdominal pain (onset, loca tion, duration, severity, radiation), N&V, bleeding, fever, inquire about last menstrual period and pregnancy if female, past medical history (CAD, diabetes, hyperten sion, renal stones), medication history (analgesics)

PHYSICAL vitals, respiratory and cardiac examina tion, abdominal examination, CVA tenderness, pelvic and rectal examination and test for fecal occult blood APPENDICITIS SEQUENCE vague pain initially located in the epigastric or periumbilical region; anor exia, nausea, or unsustained vomiting; migration of the initial pain to the RLQ; low grade fever

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CLINICAL FEATURES (CONT'D)				
RATIONAL CLINICAL EXAMINA	TION SERIES DOES	S THIS DATIENT H	AVE APPENDICIT	157
NATIONAL CLINICAL LAAMINA	Sens	Spc	LR+	LR
History				
Migration of pain to RLQ	64%	82%	3.18	0.5
RLQ pain	81%	53%	8.0	0.15
Pain before vomiting	100%	64%	2.76	
No similar pain previously	81%	41%	1.5	0.32
Physical				
Rigidity	27%	83%	3.76	0.82
Fever	67%	79%	1.94	0.58
Rebound tenderness	63%	69%	3.7	0.4
Psoas sign	16%	95%	2.38	0.90
Obturator sign				
Rectal exam				

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

JAMA 1996 276:19

# CLINICAL FEATURES (CONT'D) DISTINGUISHING FEATURES BETWEEN

# PERITORITIS, SMALL BOWEL OBSTRUCTION, AND ABDOMINAL WALL PAIN

- PERITONITIS rigidity (LR+ 5.1), guarding (LR+ 2.0), rebound tenderness (LR+ 2.0), positive cough test (LR+ 2.0). Other special tests include Rovsing's sign, psoas sign (flexion of hip against resistance increases abdominal pain), obturator sign (internal rotation of hip increases abdominal pain), and rectal/pelvic examination
- SMALL BOWEL OBSTRUCTION visible peristalsis (LR+ 18.8), absent/tinkling/high pitched bowel sounds (LR+ 5.0), abdominal bloating
- ABDOMINAL WALL PAIN
   Carnett's test (palpate area of most intense tenderness while patient supine, then palpate again with patient half sitting up. If pain is intra abdominal, the pain will not increase as tensed rectus muscles protect the underlying viscus)

#### **Related Topic**

Acute Pancreatitis (p. 139)

#### **EXAMINATION OF ABDOMINAL MASSES**

- RIGHT UPPER QUADRANT MASS liver (downward with inspiration, left lobe, bruit/venous hum), right kid ney (downward with inspiration, ballotable, palpable upper border), gallbladder (downward with inspiration, smooth and regular), colon or gastroduode nal (does not move with inspiration, ill defined mass, high pitch bowel sounds), lymphoma (does not move with inspiration, usually more central)
- LEFT UPPER QUADRANT MASS spleen (downward and medially with inspiration, notch, bruit), left

#### CLINICAL FEATURES (CONT'D)

kidney (downward with inspiration, ballotable, palpable upper border), colon (splenic flexure), gastric or pancreatic (ill defined mass, difficult to clearly differentiate these masses on examina tion), 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 (pel vic structures require bimanual examination), lym phoma (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)</li>
- MICROBIOLOGY urine C&S, stool C&S, fecal occult blood
- IMAGING CXR, AXR, U/S abd/pelvic SPECIAL
- IMAGING IVP, barium contrast, CT abd
- **ECG** if suspect cardiac involvement
- ENDOSCOPY

Acute Abdominal Pain 117

#### DIAGNOSTIC ISSUES

#### APPROACH TO ABDOMINAL X RAYS

- FREE AIR pneumoperitoneum suggests perforation. Look for free air under right diaphragm on CXR view or R lateral decubitus view. On supine abd view, look for outline of bowel wall (normally can only see inside of lumen. If also see outside of bowel wall, suggests free air outside bowel)
- **SMALL BOWEL** more central location, valvulae clo ser 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 (pneuma tosis 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 ret roperitoneal structures (rectum, duodenum). Lack of psoas outline suggests retroperitoneal inflam mation (decreased fat)
- BILIARY STRUCTURES common bile duct up to 6 mm in size. Check for air in portal vein or common bile duct (bowel infarction)
- OTHER STRUCTURES liver, spleen, bones

#### MANAGEMENT

**ACUTE** ABC, O<sub>2</sub>, IV hydration. **NPO**, NG if severe N&V/obstruction. *Morphine* 2.5 5 mg SC q4h PRN and 1 2 mg IV q1h PRN. *Dimenhydrinate* 50 mg IM/IV q6h PRN

TREAT UNDERLYING CAUSE early surgical con sult. 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

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

#### **ACUTE CHOLECYSTITIS**

 PATHOPHYSIOLOGY abnormalities of bile acid secretion, mucus generation, and gallbladder motility → gallstone formation → migrate to obstruct the cystic duct and even common bile duct/pancreatic duct → gallbladder inflammation

#### SPECIFIC ENTITIES (CONT'D)

and sometimes secondary infection  $\rightarrow$  gallblad der necrosis and gangrene with perforation in severe cases. Risk factors include older age, obe sity, 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

	Sens	Spc	LR+	LR
Murphy sign	65%	87%	2.8	0.5
RUO 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 probability of cholecystitis from 5% pretest to 60% post test. The evaluation of patients with abdominal pain suggestive of cholecystitis will continue to rely heavily on clinical gestalt and diagnostic imaging"

JAMA 2003 289:1

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

#### NEJM 2008 358:26

### ACUTE MESENTERIC ISCHEMIA

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

118 Upper GI Bleed

#### SPECIFIC ENTITIES (CONT'D)

#### **ISCHEMIC COLITIS**

- PATHOPHYSIOLOGY low flow state in the mesen tery affecting mainly the "watershed" area of the middle colic and inferior mesenteric arteries hematochezia, diarrhea, abdominal pain
- DIAGNOSIS AXR ("thumbprinting" or edematous haustral folds), CT (focal or segmental bowel wall thickening or intestinal pneumatosis with portal vein gas), colonoscopy, laparoscopy
- TREATMENTS supportive (hydration), antibiotics

#### SPECIFIC ENTITIES (CONT'D)

#### CHRONIC MESENTERIC ISCHEMIA

- PATHOPHYSIOLOGY ↓ blood flow from athero sclerosis of the proximal mesenteric vessels → intestinal angina with post prandial abdominal pain → fear of eating, extensive weight loss
- DIAGNOSIS CT, abdomen/pelvis (initial), mesen teric duplex U/S (sens 90% for stenosis of >50%), CT, or mesenteric angiography
- TREATMENTS angioplasty, surgical revascularization

### **Upper GI Bleed**

NEJM 2008 359:9

#### DIFFERENTIAL DIAGNOSIS

PEPTIC ULCER DISEASE (PUD) gastric, duodenum INFLAMMATION esophagitis (CMV, medica tions), 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 malfor
mation, aortoduodenal fistula, hemobilia

OTHERS epistaxis. hemoptysis

#### CLINICAL FEATURES

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

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

#### CLINICAL FEATURES (CONT'D)

**BLACK STOOL THAT MAY MIMIC MELENA** bis muth subsalicylate, iron, spinach, charcoal

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

	Sens	Spc		
For moderate blood loss		•		
Postural pulse increment ≥30/min	22%			
or severe postural dizzines				
Postural hypotension ≥20 mmHg	9%	94%		
SBP drop				
Supine tachycardia	0%	96%		
Supine hypotension	13%	97%		
For large blood loss				
Postural pulse increment ≥30/min	97%	98%		
or severe postural dizziness				
Supine tachycardia	12%	96%		
Supine hypotension	33%	97%		
NOTE: postural change is measure	ed first	with		
supine vitals counting pulse for 30 s (after waiting				

supine vitals counting pulse for 30 s (after waitin 2 min), then standing vitals (after waiting 1 min)

Related Topic Shock (p. 97)

HYPOVOLEMIA DUE TO VOMITING, DIARRHEA, DECREASED INTAKE, DIURETICS				
Symptoms	Sens	Spc	LR+	LR
* •	420/	750/	1 71	0.0
Postural pulse increment ≥30/min	43%	75%	1.71	0.8
Postural hypotension ≥20 mmHg	29%	81%	1.5	0.9
Dry axilla	50%	82%	2.8	0.6
Dry oral/nasal mucous membrane	85%	58%	2.0	0.3
Dry tongue	59%	73%	2.1	0.6

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

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

JAMA 1999 281:11

#### INVESTIGATIONS

#### BASIC

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

#### PROGNOSTIC ISSUES

#### RISK STRATIFICATION FOR PEPTIC ULCER DISEASE

- CLINICAL ROCKALL SCORING age 60 79=1; age ≥80=2; heart rate >100 beats/min=1; systolic BP <100 mmHg=2; co existing illnesses (ischemic heart disease, HF, other major illness)=2; co exist ing illnesses (renal failure, hepatic failure, meta static cancer)=3
- COMPLETE ROCKALL SCORING in addition to clinical Rockall score, add the following based on endo scopic findings: no lesion observed, Mallory Weiss tear=0; peptic ulcer, erosive disease, esophagi tis=1; cancer of upper Gl tract=2; clean base ulcer, flat pigmented spot=0; blood in upper Gl tract, active bleeding, visible vessel, clot=2
- INTERPRETATION low risk for bleeding or death= clinical Rockall score 0 or complete Rockall score \u22222

#### **RISK OF ULCER RE BLEED**

- HIGH-RISK FEATURES active spurting/oozing dur ing 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 fac tors include size and location of ulcer
- LOW-RISK FEATURES flat spot (10% chance), clean ulcer base (3 5% chance)

#### MANAGEMENT

**ACUTE ABC**, O<sub>2</sub>, **IV hydration** (two large bore IV). **Transfusion** (especially if hematocrit <30%, plate lets  $<50\times10^9$ ). NPO, consider NG tube. **Hold** 

#### MANAGEMENT (CONT'D)

antihypertensive and diuretic therapy. If prolonged PT/PTT, *vitamin K* 10 mg PO/IV (small risk of anaphy laxis 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 para doxical 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 hemor rhage, transfuse platelet and FFP PRN, antibiotics for 7 days (ceftriaxone 1 g IV g24h, 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 erythro mycin 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  $\times$ 72 h [if high risk lesion], switch to 40 mg PO BID  $\times 1$  month then daily). **Varices** (endo scopy within 12 h with ligation/band/glue/sclerother  $\mathsf{apy} \to \mathsf{balloon} \; \mathsf{tamponade} \to \mathsf{TIPPS} \to \mathsf{portacaval}/$ distal splenorenal shunt, or liver transplant. Continue octreotide for 3 5 days. Repeat endoscopy every 2 weeks until varices obliterated, then at 1 3 months and again every 6 12 months afterward. Consider non selective β blocker such as *nadalol* 40 mg PO daily. Mallory Weiss tear (omeprazole 20 mg PO daily). H. pylori (see DYSPEPSIA p. 113 for treatment). Intractable or recurrent bleed (consult surgery. See TREATMENT ISSUES below)

#### TREATMENT ISSUES

CRITERIA FOR SURGICAL CONSULT FOR ULCER
BLEED hemodynamic instability despite

#### TREATMENT ISSUES (CONT'D)

resuscitation (>3 U PRBC), shock, recurrent hemor rhage after two endoscopic attempts, continued slow bleed requiring >3 U PRBC/day), high risk endo scopic lesion

**COMPLICATIONS OF ENDOSCOPY** perforations, bleeding, sedation related respiratory failure

DISCHARGE DECISIONS FOR PATIENTS' PEPTIC **ULCER DISEASE** patients with low risk of re bleed

#### TREATMENT ISSUES (CONT'D)

(complete Rockall score < 2, low risk endoscopic fea tures), 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 dis charged home shortly after endoscopy with follow up, while patients with high risk features should be admitted and monitored closely

### **Lower GI Bleed**

#### **DIFFERENTIAL DIAGNOSIS**

**UPPER GI SOURCE WITH BRISK BLEEDING** (10%) **INFECTIOUS** Salmonella, Shigella, Campylobac ter, 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, intussus ception, Meckel's diverticulum

#### CLINICAL FEATURES

HISTORY volume of bleed, melena, abdominal pain, past medical history (IBD, cancer, diverticulosis), medication history (anticoagulants, NSAIDs)

**PHYSICAL** acute bleeding, sinus tachycardia, supine hypotension (SBP < 95 mmHg), postural pulse increase >30/min or dizziness, anemia (conjunctival, facial or palmar pallor), abdominal tenderness, Perform a rectal examination and test for fecal occult blood

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, type/X match, PTT, INR, AST, ALT, ALP, bilirubin, albumin
- MICROBIOLOGY stool C&S, fecal occult blood

## ENDOSCOPY colonoscopy, gastroscopy

#### SPECIAL

• IMAGING for obscure bleed, consider <sup>99</sup>Tc RBC scan (detects 0.1 mL/min), angiography

#### INVESTIGATIONS (CONT'D)

(detects 0.5 mL/min), capsule endoscopy, push enteroscopy, double balloon enteroscopy, and/or Meckel's scan

#### DIAGNOSTIC ISSUES

OCCULT BLEED no obvious melena or bright red blood per rectum (BRBPR), but possible bleed as fecal occult blood positive

OBSCURE BLEED obvious bleeding but source cannot be found

OVERALL APPROACH gastroscopy and/or colono scopy (start with the end with the most likely source of bleed, then scope the other end if no yield)  $\rightarrow$  if negative, repeat panendoscopy → if negative, small bowel followthrough → if negative, consider angio graphy, RBC scan, capsule, push or double balloon endoscopy, or laparotomy

#### MANAGEMENT

**ACUTE** ABC, O<sub>2</sub>, IV hydration (two large bore IVs). **Transfusion** (especially if hematocrit <30%, plate lets  $<50\times10^9$ /L). NPO. **Hold** antihypertensive and diuretic therapy. If prolonged PT/PTT, vitamin K 10 mg IV (small risk of anaphylaxis) [see above com ment 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 asympto matic, 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

#### PATHOPHYSIOLOGY (CONT'D)

(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				
Degree of involvement	Crohn's disease Segmental	Ulcerative colitis Continuous		
Symptoms	Rectal sparing Abd pain	Bloody diarrhea		
	Diarrhea	Tenesmus		
	Anorexia Perianal disease	Fever		
Serology	Saccharomyces cerevisiae IgG antibody (sens 77%, spec 92%, PPV 82%)	P ANCA (sens 70%, spc 88%, PPV 75%)		
Pathology	Transmural granuloma	Mucosal inflammation No granuloma		
Complications	Obstruction	Toxic megacolon (1 2%)		
	Strictures	Colorectal cancer (1%/year after		
	Fistulas	10 years)		
	Fissures			
	Abscesses			
	Colorectal cancer			

#### CLINICAL FEATURES (CONT'D)

**EXTRAINTESTINAL MANIFESTATIONS** fever, club bing, uveitis, iritis, anemia, jaundice (primary sclerosing cholangitis), aphthous ulcers (Crohn's only), arthritis (spondylitis; type I arthropathy: pauciarticular and related to IBD activity; type II arthropathy: polyarticular and unrelated to IBD activity), erythema nodosum, pyoderma gangrenosum, DVT, amyloidosis

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, ESR, CRP, Fe, TIBC, ferritin, % sat, AST, ALT, ALP, bilirubin, albumin, Ca, Mq, PO<sub>4</sub>, vitamin B12, folate
- MICROBIOLOGY stool C&S, fecal occult blood, stool for C. difficile toxin assay
- IMAGING AXR
- ENDOSCOPY flexible sigmoidoscopy, colonoscopy

#### MANAGEMENT

#### SUPPORTIVE THERAPY

- DIET AND NUTRITION if mild, low fiber diet, ele mental diet; if severe, TPN and bowel rest
- ANTIDIARRHEAL AGENTS contraindicated in severe exacerbation and toxic megacolon

#### **ANTIINFLAMMATORY AGENTS**

• **5ASA SUPPOSITORIES** if localized disease. *Mesala mine* 1 g PR qhs, glucocorticoid enema/supposi tories daily BID

#### MANAGEMENT (CONT'D)

- SYSTEMIC 5ASA for induction and maintenance (sulfasalazine induction 0.5 g PO BID, then titrate to 0.5 1.5 g PO QID, maintenance 1 g PO BID QID; mesalamine 800 1600 mg PO TID maintenance 400 800 mg PO TID; olsalazine)
- GLUCOCORTICOIDS for flares (methylprednisolone 30 mg IV BID, prednisone 50 mg PO daily, reduce by 5 mg/week)
- IMMUNOSUPPRESSIVE AGENTS azathioprine 50 mg PO daily, increase by 25 mg daily every 2 weeks to a max of 2 3 mg/kg/day as tolerated, metho trexate 25 mg IM weekly
- **ANTIBIOTICS** *metronidazole* 500 mg PO TID, *cipro floxacin* 500 mg PO BID
- BIOLOGICAL AGENTS infliximab IV infusions of 5 mg/kg at 0, 2, 6 weeks. Dosing regimens differ for adalimu mab and certolizumab. Drug coverage for anti TNF therapy differs between Canadian provinces

#### **SURGERY**

#### **Related Topics**

Clostridium difficile Colitis (p. 122) Inflammatory Arthritis (p. 282) 122 Acute Diarrhea

#### 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 ther apy. Consider metronidazole and ciprofloxacin for treatment of perianal fistula

#### **ULCERATIVE COLITIS**

- ULCERATIVE PROCTITIS 5ASA suppositories or ene mas for 2 4 weeks for active treatment. If failed, add steroid foams. Consider oral 5ASA if patient cannot tolerate suppositories. Maintenance ther apy may be required
- DISTAL COLITIS/PROTOSIGMOIDITIS AND LEFT-SIDED COLITIS similar treatment to ulcerative procti tis, 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, improve ment of diarrhea may actually suggest onset of megacolon) should prompt investigations for toxic megacolon. Patient usually toxic with fever, hypo tension, delirium, and abdominal pain
- DIAGNOSIS dilated colon on X ray (usually trans verse or right colon, >6 cm), plus three of the following (fever >38°C [100.4°F], tachycardia >120/min, leukocytosis >10.5×10<sup>9</sup>/L, anemia), plus one of the following (dehydration, delirium electrolyte disturbances, hypotension)
- TREATMENTS supportive therapy (NPO, IV fluids, hold all opioids, antidiarrheal and anticholinergic agents). For IBD related toxic megacolon, give hydrocortisone 100 mg IV q6h and antibiotics (ceftriaxone plus metronidazole). For C. difficile related toxic megacolon, treat aggressively with metronidazole or vancomycin. Patients with toxic megacolon who do not respond to therapy within 72h should be considered for colectomy. ICU admission for monitoring. Serial blood tests and AXR daily to assess progress

#### **Acute Diarrhea**

NEJM 2004 350:1

#### **DIFFERENTIAL DIAGNOSIS**

**INFLAMMATORY/INVASIVE** (fever, bloody, tenes mus)

- INVASIVE INFECTIONS Salmonella, Shigella Campylobacter, Yersinia, EHEC, EIEC, Vibrio para haemolyticus, Clostridium difficile, Entamoeba
- INFLAMMATORY ulcerative colitis, Crohn's
- ISCHEMIC COLITIS
- RADIATION COLITIS

#### NON INFLAMMATORY

- NON-INVASIVE INFECTIONS bacterial (Vibrio cho lera, Staphylococcus aureus, Bacillus cereus, Clos tridium 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 nodo sum, 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), Cryp tosporidium (1.4/100,000) Acute Diarrhea 123

#### 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, fre quency, volume, blood, floating), infectious contact, recent food intake, abdominal pain, past medical history (IBD, lactose intolerance), medication history (laxatives, antibiotics), travel history

**PHYSICAL** vitals and check for dehydration. Abdominal tenderness. Perform a rectal examination and test for fecal occult blood. Inspect stool sample if available

**SALMONELLA AND CAMPYLOBACTER** although they are classified as inflammatory, patients usually only develop fever and severe diarrhea and not bloody diarrhea

#### INVESTIGATIONS

#### **BASIC**

- LABS CBCD, lytes, urea, Cr, lactate
- MICROBIOLOGY stool C&S (sens 1.5 5.6%), O&P, C. diff toxin A+B, viral culture

#### SPECIAL

- FECAL TESTING fecal leukocytes (inflammatory, sens 73%, spc 84%), fecal lactoferrin (inflamma tory, sens 92%, spc 79%), Giardia toxin, fecal occult blood
- ENDOSCOPY flexible sigmoidoscopy, colonoscopy

#### MANAGEMENT

**SYMPTOM CONTROL IV hydration. Antidiar rheal agents** if not inflammatory (bismuth subsalicy late 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 Enta moeba (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 (Salmo
  nella, C. perfringens, S. aureus, Candida). Relapse
  occurs in 20 25% of patients and typically
  between 3 and 21 days after discontinuation of
  treatment: 3 5% of patients have more than 6
  relapses. Note emergence of virulent C. difficile
  strain NAP 1/027 characterized by increased secre
  tion of toxins A/B, binary toxin production and
  fluoroquinolone resistance, and associated with
  increased outbreaks and mortality
- RISK FACTORS onset of diarrhea ≥6 days after the initiation of antibiotic therapy, hospital stay ≥2 weeks, fecal leukocytes, semi formed stools, cephalosporin use
- CLINICAL FEATURES usually watery diarrhea (may be bloody if severe colitis), abdominal pain. In patients with severe C. difficile infection, significant leukocytosis, pseudomembranous colitis, toxic megacolon (see p. 120), acute renal failure, and hypotension may develop
- DIAGNOSIS C. difficile toxin A/B, colonoscopy (pseudomembranous colitis). C. difficile toxin levels are usually unnecessary immediately after treat ment completion as up to one third of patients have positive assays despite successful treatment
  - TREATMENTS IV hydration. Discontinue impli cated antibiotics. Avoid use of antiperistaltic agents (opiates, loperamide). C. difficile treat ment (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 mega colon, 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 mini mize use of other antibiotics. For further recur rences, consider tapering doses of vancomycin 125 mg PO QID  $\times 1$  week, then BID  $\times 1$  week, then daily  $\times 1$  week, then every other day  $\times 1$ 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 metronida zole or vancomycin

NEJM 2002 346:5; NEJM 2008 359:18

124 Chronic Diarrhea

# **Chronic Diarrhea**

# NEJM 1995 332:11

#### DIFFERENTIAL DIAGNOSIS

#### **★MISO★**

**MOTILITY** hyperthyroidism, diabetic neuropa thy, bacterial overgrowth, irritable bowel syndrome (IBS), scleroderma

#### INFLAMMATORY

- INFECTIONS Salmonella, Shigella, Yersinia, Campy lobacter, E. coli (EHEC, EIEC), C. difficile, Amoeba
- INFLAMMATORY ulcerative colitis, Crohn's, ischemic, radiation, toxic

#### SECRETORY

- INFECTIONS Cholera, Staphylococcus, B. cereus, C. perfringens, E. coli (ETEC, EPEC), Rotavirus, norovirus, CMV, Giardia, Cryptococcus, Amoeba
- NEUROENDOCRINE TUMORS carcinoid, VIPoma, calcitoninoma, gastrinoma, somatostatinoma
- MEDICATIONS senna, dulcolax
- OTHERS bile salt enteropathy, fatty acid induced, collagenous colitis, lymphocytic colitis
   OSMOTIC
- MALDIGESTION/MALABSORPTION pancreatic insuf ficiency, celiac disease, lactose intolerance, short bowel syndrome, enteric fistula
- MEDICATIONS antacids, antibiotics, Mg citrate, Mg hydroxide, lactulose, sorbitol (i.e. "chewing qum diarrhea"), colchicine

## **Related Topics**

Inflammatory Bowel Disease (p. 120) Irritable Bowel Syndrome (p. 126)

# CLINICAL FEATURES

HISTORY characterize diarrhea (duration, fre quency, volume, blood, floating), infectious contact, abdominal pain, weight loss, past medical history (dia betes, 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),  $\alpha$  1 antitrypsin colonoscopy

#### INVESTIGATIONS (CONT'D)

- IMAGING SBFT, CT abd
- ENDOSCOPY upper and lower, for biopsy

#### INVESTIGATION ISSUES

## DISTINGUISHING FEATURES

- INFLAMMATORY bloody stool, fecal leukocytes
- SECRETORY fecal osmotic gap <50 mOsm/kg, >500 g of stool with fasting
- osmotic fecal osmotic gap >50 mOsm/kg; <500 g of stool with fasting

FECAL OSMOTIC GAP 280 2×(stool Na+K)

#### MANAGEMENT

**SYMPTOM CONTROL hydration** and **nutritional support**. Empiric treatment with **antidiarrheal** agents if not inflammatory (*bismuth subsalicylate* 2 tab PO q1h PRN or *loperamide* 4 mg ×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 Bar ley, Rye, Oat, Wheat ★BROW★→ T cell mediated immune reaction to gliadin → intest inal 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 gastrointest inal blood loss, nutritional deficiency, osteoporo sis and sometimes osteomalacia (Looser zones on radiography), diarrhea (sometimes)
- plagnosis 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 atro phy, 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

NEJM 2007 357:17

# **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 obstruc tion, terminal ileal resection

PANCREAS (lipase, amylase, HCO<sub>3</sub>; 90% of extra colo nic causes) cancer, chronic pancreatitis, cystic fibrosis SMALL INTESTINE (brush border/enterocytes) celiac disease, lymphoma, infectious colitis, inflam matory colitis, ischemic colitis, radiation colitis OTHERS β lipoprotein (abetalipoproteinemia), lymphatics (lymphoma)

#### PATHOPHYSIOLOGY

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

## CLINICAL FEATURES

HISTORY diarrhea (watery, steatorrhea), flatus, abdominal distension, abdominal pain (suggests chronic pancreatitis, Crohn's disease, or pseudo obstruction as otherwise uncommon in malabsorp tion), N&V, symptoms in relation to meals (may occur within 90 min of carbohydrate ingestion), anorexia, weight loss, diet, past medical history (type 1 diabetes, celiac disease, IBD, recurrent peptic ulcer disease previous surgery, psychiatric disorders, alcohol), medications (laxatives, diuretics, illicit drugs)

# **Related Topics**

Cachexia (p. 397) Celiac Disease (p. 124) Vitamin B12 Deficiency (p. 405)

## RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT MALNOURISHED?

HISTORY weight change (overall loss in past 6 months, change in past 2 weeks), dietary intake change relative to normal (duration, types include suboptimal solid diet, hypocaloric liquids, full liquid diet, starvation), gastrointestinal symptoms >2 weeks (nausea, vomiting, diarrhea, anorexia), functional capacity (duration, working suboptimally, ambulatory, bedridden)

PHYSICAL loss of subcutaneous fat (triceps, chest), muscle wasting (quadriceps, deltoids), swelling (ankle edema, sacral edema, ascites)

RISK OF MAJOR POSTOPERATIVE COMPLICATIONS BASED ON SUBJECTIVE GLOBAL ASSESSMENT (SGA)

LR+ Well nourished

Defined as <5% weight loss or >5% total weight loss but recent gain and improvement in appetite 0.66

## Moderately malnourished

Defined as 5 10% weight loss without recent stabilization or gain, poor dietary intake, and mild 0.96 (1+) loss of subcutaneous tissue

#### Severely malnourished

Defined as ongoing weight loss of >10% with severe subcutaneous tissue loss and muscle wasting often with edema 4.44

**APPROACH** "SGA is an accurate predictor of patients who are at higher risk of developing complications such as infection or poor wound healing"

JAMA 1994 271:1

## INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, fasting lipid profile, Ca, Mg, PO<sub>4</sub>, albumin, pre albumin, carotene, Fe, ferritin, antitransglutaminase antibody, vitamin B12, RBC folate
- IMAGING U/S abd

#### **SPECIAL**

• COLONOSCOPY for Crohn's

# INVESTIGATIONS (CONT'D)

- GASTROSCOPY for Celiac disease
- ERCP/MRCP if suspect chronic pancreatitis
- **STOOL FAT** >6 g/day suggests steatorrhea
- **D-XYLOSE TEST** if suspect malabsorption
- BREATH TEST for carbohydrate malabsorption and lactose intolerance, including H<sub>2</sub>, <sup>14</sup>CO<sub>2</sub>, or <sup>13</sup>CO<sub>2</sub>
- ANTIINTRINSIC FACTOR ANTIBODY for vitamin B12 deficiency (has replaced historical Schilling test)

126 Constipation

#### 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, weak ness, fractures due to osteomalacia

## SPECIFIC ENTITIES (CONT'D)

 VITAMIN E DEFICIENCY skeletal myopathy, spino cerebellar ataxia, pigmented retinopathy, and hemolysis

#### WATER SOLUBLE VITAMIN DEFICIENCY

- VITAMIN B1 (THIAMINE) DEFICIENCY Wernicke syn drome, Korsakoff syndrome, Leigh's syndrome (subacute necrotizing encephalomyopathy)
- VITAMIN B3 (NIACIN, NICOTINIC ACID) DEFICIENCY
   DDDD\* Dermatitis (photosensitive, pigmen ted, pellagra), Diarrhea, Dementia, Death
- VITAMIN B6 (PYRIDOXINE) DEFICIENCY cheilosis, painless glossitis, acrodermatitis, angular stomatitis
- VITAMIN C DEFICIENCY scurvy with impaired col lagen synthesis leading to ecchymoses, gum bleeding, petechiae, hyperkeratosis, impaired wound healing, arthralgia, weakness, neuropathy, and depression

# Constipation

NEJM 2003 349:14

## DIFFERENTIAL DIAGNOSIS

## **★DUODENUM**★

**DIET** low fiber, dehydration

**ψSYCHIATRY** depression, somatization, obses sive compulsive disorder

**OBSTRUCTION** cancer, strictures, adhesions **DRUGS** opioids, TCAs, neuroleptics, antihista mines, calcium channel blockers, iron, antacids **ENDOCRINE** diabetes, hypothyroidism, hypercal cemia, 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, trans verse, 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 cer eals, psyllium/Metamucil 2 3 teaspoon/day, exer cise, 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 con stipation causing medications if possible

#### SPECIFIC ENTITIES

## **IRRITABLE BOWEL SYNDROME (IBS)**

- PATHOPHYSIOLOGY heightened response to nox ious visceral stimuli, such as balloon distenstion of the rectum and sigmoid colon
- CLINICAL FEATURES Rome criteria define IBS as >3 months of abdominal pain relieved with defe cation, associated with a change in the frequency or consistency of stool, plus two of the following

Constipation 127

# SPECIFIC ENTITIES (CONT'D)

for >25% of days: disturbed defecation (>3 bowel movements/day or <3 bowel movements/ week), altered stool formation, altered stool pas

## SPECIFIC ENTITIES (CONT'D)

sage (straining, urgency, or feeling of incomplete evacuation), passage of mucus, bloating, or feeling of abdominal distenstion

# RATIONAL CLINICAL EXAMINATION SERIES: WILL THE HISTORY AND PHYSICAL EXAMINATION HELP ESTABLISH THAT IRRITABLE BOWEL SYNDROME IS CAUSING THIS PATIENT'S LOWER GASTROINTESTINAL TRACT SYMPTOMS?

**MANNING CRITERIA** abdominal pain relieved by defecation, more frequent stools with onset of pain, looser stools with onset of pain, passage of mucus per rectum, feeling of incomplete emptying, patient reported visible abdominal distension

**ROME I CRITERIA** abdominal pain or discomfort relieved with defecation or associated with a change in stool frequency or consistency for  $\geq$ 3 months, plus  $\geq$ 2 of the following on at least 25% of occasions or days: (1) altered stool frequency, (2) altered stool form, (3) altered stool passage, (4) passage of mucus per rectum, (5) bloating or distension

**KRUIS MODEL** a computer model based on a number of signs and symptoms to rule in and rule out IBD. Symptoms include (1) abdominal pain, flatulence, or bowel irregularity for >2 years; (2) description of abdominal pain as "burning, cutting, very strong, terrible, feeling of pressure, dull, boring, or not so bad"; and (3) alternating constipation and diarrhea. Signs include (1) abnormal physical findings and/or history pathognomonic for any diagnosis other than IBS, (2) ESR >10 mm/h, (3) leukocytosis  $>10\times10^9$ /L, (4) hemoglobin <120 g/L [<12 g/dL] for females or <140 g/L [<14 g/dL] for males, (5) impression by the physician that the patient's history suggests blood in the stool

	Sens	Spc	LR+	LR
Symptoms		•		
Lower abd pain	90%	32%	1.3	0.29
Passage of mucus	45%	65%	1.2	0.88
Feeling of incomplete evacuation	74%	45%	1.3	0.62
Looser stools at onset of pain	59%	73%	2.1	0.59
More frequent stools at onset of pain	53%	72%	1.9	0.67
Pain relieved by defecation	60%	66%	1.8	0.62
Patient reported visible abdominal distension	39%	77%	1.7	0.79
Diagnostic criteria				
Manning criteria	78%	72%	2.9	0.29
Rome I criteria	71%	85%	4.8	0.34
Kruis system	77%	89%	8.6	0.26

**APPROACH** "absence of abdominal pain reduced the likelihood of IBS. Overall, individual symptoms have limited accuracy for diagnosing IBS in patients referred with lower GI symptoms. The accuracy of the Manning criteria, Rome I criteria and Kruis scoring system were only modest'

JAMA 2008 300:15

# **Related Topics**

Acute Abdominal Pain (p. 115) Constipation in the Palliative Setting (p. 396) Nausea and Vomiting (p. 111) Opioid Use (p. 391)

#### SPECIFIC ENTITIES (CONT'D)

 ASSOCIATIONS patients with IBS are more likely to have functional dyspepsia, urinary symptoms, dysmenorrhea, dyspareunia, sexual dysfunction, a history of physical or sexual abuse, and fibromyalgia

# SPECIFIC ENTITIES (CONT'D)

- DIAGNOSIS IBS is a diagnosis of exclusion. Con sider flexible sigmoidoscopy/colonoscopy, evalua tion for celiac sprue (p. 124), and stool cultures to rule out other diseases
- TREATMENTS reassurance, stress reduction, fiber supplementation. Consider fibers, osmotic laxatives for constipation, loperamide 2 4 mg daily and alose tron 0.5 1 mg PO BID ×12 weeks (5HT3 antagonist) for diarrhea, and antispasmodics (hyoscyamine), TCAs (amitriptyline 10 75 mg qhs), desipramine 50 150 mg PO daily, and SSRIs for abdominal pain. Cognitive behavioral therapy may also be useful

NEJM 2008 358:16

128 Acute Liver Failure

# **Acute Liver Failure**

# DIFFERENTIAL DIAGNOSIS

# **HEPATOCELLULAR INJURY PATTERN** ( $\uparrow\uparrow$ AST/ALT $\pm\uparrow$ ALP/bili)

- INFECTIOUS HAV, HBV, HCV (rare), HDV, HEV, EBV, CMV, HSV, VZV, schistosomiasis, toxoplas mosis, bacterial cholangitis
- FATTY LIVER alcoholic, non alcoholic steatohe patitis (NASH)
- TOXIC acetaminophen, NSAIDs, amiodarone, labetalol, statins, phenytoin, valproic acid, fluoroquinolones, amoxicillin/clavulanate, sulfo namides, 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, che motherapy, OCP)
- **NEOPLASTIC** hepatoma
- AUTOIMMUNE autoimmune hepatitis
- HEREDITARY Wilson's, hemochromatosis, α1 antitrypsin deficiency, glycogen storage disease
- PREGNANCY acute fatty liver of pregnancy, HELLP
- OTHERS liver surgery, Reye's syndrome with viral illness, and ASA use
- NON-HEPATIC celiac sprue, adrenal insuffi ciency, myopathy, strenuous exercise

# **CHOLESTATIC PATTERN** ( $\uparrow\uparrow$ ALP/bilirubin $\pm\uparrow$ AST/ALT)

- BACTERIAL CHOLANGITIS
- BILIARY EPITHELIAL DAMAGE hepatitis, cirrhosis, biliary colic
- INTRAHEPATIC CHOLESTASIS sepsis, drugs (amox icillin clavulanate, erythromycin, trimetho prim sulfamethoxazole, indinavir, nevirapine, allopurinol, carbamazepine, captopril, chlorpro mazine, diltiazem, estrogens, fluphenazine, gold, imipramine), TPN, primary biliary cirrhosis
- BILIARY DUCTAL OBSTRUCTION choledocholithiasis, pancreatic cancer, cholangiocarcinoma, pancreati tis, primary sclerosing cholangitis

# **INFILTRATIVE PATTERN** ( $\uparrow\uparrow$ ALP with $\uparrow$ GGT $\pm\uparrow$ bili/AST/ALT)

- INFECTIOUS TB, histoplasmosis, abscess (bacter ial, 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 pro duct), albumin (synthesis), fibrinogen
- HEPATIC INJURY
   AST (intracellular; liver, heart, ske letal, kidneys, brain, pancreas, lungs, RBC, WBC),
   ALT (intracellular; specific for Liver), ALP (liver, gut, bone, placenta), GGT, 5'NT, LDH (bone, muscle, liver, lungs)

# COMPLICATIONS OF HEPATIC FAILURE ★SCREAM★

- **S**epsis
- Coagulopathy
- Renal failure
- Encephalopathy
- Ascites
- Metabolic changes (hypoglycemia, electrolyte abnormalities, acidosis)

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, peripheral smear, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HAV IgM, HAV IgG, HBsAg, HBsAb, HBclgM, HBclgG, lactate
- IMAGING U/S abd, CT abd

#### SPECIAL

 LABS EBV, CMV, HSV, ANA, antismooth muscle antibody (ASMA), antimitochondrial antibody (AMA), quantitative immunoglobulin, ferritin, Fe, Acute Liver Failure 129

## INVESTIGATIONS (CONT'D)

TIBC, % sat, ceruloplasmin, α1 antitrypsin, AFP, antitransglutaminase antibody, lipase, amylase, LDH, haptoglobin, acetaminophen, CK, TSH

- ERCP/MRCP
- GASTROSCOPY
- LIVER BIOPSY

# DIAGNOSTIC AND PROGNOSTIC ISSUES

↑ **AST/SGOT** do panel of liver function tests. If isolated rise, consider non hepatic causes. Otherwise, same as ALT workup. AST >ALT suggests alcoholic liver disease, fatty liver, or cirrhosis

↑ **ALT/SGPT** if symptomatic and presence of risk factors for liver disease, liver dysfunction (↓ albumin, ↑ INR, ↑ bili), ↑ ALT or AST > 3× upper limit of normal, or ↑ ALT > 6 months, consider basic workup including abdominal U/S with dopplers, viral serologies, ANA, ASMA, quantitative Ig, ceruloplasmin, iron studies, anti transglutaminase antibody, and possibly liver biopsy

↑ **ALP/BILI** ask about pain, symptoms of infiltrative disease, or IBD. To confirm liver involvement, perform bilirubin fractionation, GGT, 5'NT, abdominal U/S, AMA, and quantitative Ig. Consider MRCP/ERCP and liver biopsy

MONITORING INR and bilirubin are much more use ful to monitor liver function compared to transaminases SURVIVAL IN ACUTE HEPATIC FAILURE 35% in hyperacute, 7% in acute, and 14% subacute

# MANAGEMENT OF ACUTE LIVER FAILURE

#### SYMPTOM CONTROL

- ACUTE ABC, O<sub>2</sub>, IV hydration
- ELEVATED INTRACRANIAL PRESSURE for cerebral edema, consider prophylactic phenytoin, raise head of bed, hyperventilate, dexamethasone, mannitol, avoid excessive fluids
- **SEPSIS** antibiotics
- COAGULOPATHY vitamin K 10 mg IV/PO, FFP 2 4 U IV (only if active bleeding or invasive procedures, or difficult to follow INR afterward)
- ACUTE RENAL FAILURE supportive renal replace ment. Consider midodrine, octreotide, and albumin
- ENCEPHALOPATHY protein intake up to 1 g/kg/day.
   Lactulose 30 g PO QID PRN titrate to 2 4 bowel movements/day
- ACIDOSIS D10W with 1 2 amp NaHCO<sub>3</sub> 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
   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,

## MANAGEMENT OF ACUTE LIVER FAILURE (CONT'D)

followed by 70 mg/kg q4h for 17 doses. May con tinue 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 (pegy lated interferon ± ribavirin). Alcoholic hepatitis (abstinence, nutrition, prednisolone 40 mg PO ×28days but avoid if pancreatitis, Gl bleed, renal failure, or active infection; pentoxifylline 400 mg PO TID ×28 days, S adenosylmethionine 1200 mg PO daily ×2 years). Autoimmune hepatitis (steroid). Wilson's disease (D penicillamine)

**LIVER TRANSPLANT** patients with fulminant liver failure should be transferred to acute care centers with liver transplant expertise

# TREATMENT ISSUES

#### LIVER TRANSPLANT

- ALLOCATION based on ABO blood type, body size, wait designation, and degree of urgency
- KING'S COLLEGE CRITERIA FOR TYLENOL OVERDOSE
   ACUTE HEPATIC FAILURE (rule of 3's) either arterial
   pH <7.3 or grade III or IV encephalopathy, plus Cr
   >300 µmol/L [>3.3 mg/dL], plus INR >6
- KING'S COLLEGE CRITERIA FOR NON-TYLENOL ACUTE HEPATIC FAILURE INR >3 or any 3 of following: age <10 or >40, non A non B hepatitis, halothane hepatitis, idiosyncratic drug reactions, duration of jaundice before onset of encephalopathy >7 days, INR >1.5, bilirubin >308 μmol/L [179 mq/dL]
- CONTRAINDICATIONS malignancy (except hepato 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 alcohol related pyridoxal 5 phosphate deficiency), rare for AST to be >8× normal and for ALT to be >5× normal. GGT ↑, ALP ↑, bilirubin ↑
- TREATMENTS abstinence, nutrition, prednisolone 40 mg PO ×28 days, pentoxifylline 400 mg PO TID ×4 weeks, S adenosylmethionine 1200 mg PO daily ×2 years

130 Hepatitis B

#### SPECIFIC ENTITIES (CONT'D)

#### NON ALCOHOLIC STEATOHEPATITIS (NASH)

 ASSOCIATIONS obesity, hyperlipidemia, diabetes, Cushing's, TPN, high protein diets for weight loss, amiodarone, tamoxifen

#### SPECIFIC ENTITIES (CONT'D)

- DIAGNOSIS liver biopsy
- TREATMENTS weight loss, metformin (experimental)

# **Hepatitis B**

# NEJM 2004 350:11; NEJM 2008 359:14

#### PATHOPHYSIOLOGY

**NATURAL HISTORY** acute hepatitis  $\rightarrow$  chronic disease develops in >90% of neonates, in 10% if 12 years old, and in <1% if >12 years old  $\rightarrow$  12 20% with chronic hepatitis progress to cirrhosis in 5 years  $\rightarrow$  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 30 and 15% for 31% of 32% acute 15% of 33% and 15% for 33% and 15% for

ACUTE HEPATITIS B may range from subclinical/ anicteric hepatitis (70%) to icteric hepatitis (30%) and even fulminant hepatic failure (0.5 1%). Symptoms may include fever, anorexia, rash, nausea, jaundice, RUQ tenderness, arthralgia, and arthritis. ↑↑ ALT and AST

#### **CHRONIC HEPATITIS B**

- REPLICATIVE PHASE WITH IMMUNE TOLERANCE (only if vertical transmission) HBeAg positive, asympto matic 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 hypersplen ism or impaired synthetic function († INR, † bilir ubin, hypoalbuminemia)

**GENOTYPES** there are currently eight different genotypes (A to H)

**RISK FACTORS** vertical transmission, endemic areas, transfusions, dialysis, healthcare workers, IDU, high risk sex/homosexuals, body piercing, tattoos, organ transplantation

# Related Topics

Acute Liver Failure (p. 128) Chronic Liver Failure (p. 132) HBV/HIV Co infection (p. 261) Hepatitis C (p. 131) Hepatoma (p. 205)

## **CLINICAL FEATURES**

**HISTORY** symptoms of liver failure (jaundice, bleeding, infections, ascites, confusion), weight change, risk factors of hepatitis (family history, sexual activity, IDU, tattoos, piercing, healthcare worker, transfusions, dialysis), past medical history (alcohol, HCV, HIV), medication history

**PHYSICAL** liver examination, stigmata of chronic liver disease (see p. 132), weight

**EXTRAHEPATIC MANIFESTATIONS OF HBV** poly arteritis nodosa, membranous nephropathy, mem branoproliferative glomerulonephritis

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, HBV serology (HBsAb, HBsAg, HBclgM, HBclgG 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 anti gen. 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

Hepatitis C 131

## DIAGNOSTIC ISSUES (CONT'D)

injury. HBeAg negative infection is associated with fluctuating ALT and lower levels of HBV DNA. By definition. HBeAg seroconversion cannot occur

 HBEAB antibody against hepatitis B envelope protein. Suggests low/no viral replication, usually with low infectivity

# DIAGNOSTIC ISSUES (CONT'D)

 HBV DNA direct determination of hepatitis B virus DNA. HBV DNA level reflects viral replication activity and is associated with the risk of cirrhosis and hepatoma. HBV DNA determination is impor tant in both HBeAg+ and HBeAg individuals to determine need for antiviral therapy

Acute infection	HBsAg	HBclgM	HBsAb	HBclgG	HBeAg	HBeAb
Early	+				+	
Window		+			+	
Late		+/	+		+	
Immunity						
Vaccinated			+			
Cured			+/	+		+
Chronic infection						
Infectious/active	+			+	+	
Pre core mutant	+			+		
Low replicative	+			+		+

## MANAGEMENT

**LIFESTYLE CHANGES** avoid alcohol use, sexual education, HBV vaccination

**TREAT UNDERLYING CAUSE** interferon, pegylated interferon, lamivudine, adefovir, entecavir, telbivu dine, tenofovir

VACCINATION household and sexual contacts

# TREATMENT ISSUES

# TREATMENT DECISION FOR CHRONIC HEPATITIS B INFECTIONS

 HBEAG POSITIVE PATIENTS no spontaneous sero conversion after 6 months with recurrent flares,

## TREATMENT ISSUES (CONT'D)

significant fibrosis or inflammation, or polyarteritis nodosa with persistently high HBV DNA level, cir rhosis regardless of HBV DNA level

 HBEAG NEGATIVE PATIENTS (PRE-CORE OR CORE PRO-MOTER MUTATIONS) high HBV DNA level

Please see **NEJM 2008 359:14** and **Can J Gastro enterol 2007 21 Supp C** at www.hepatology.ca for consensus statement on management of hepati tis B

# **Hepatitis C**

NEJM 2001 345:1

## PATHOPHYSIOLOGY

**NATURAL HISTORY** acute infection  $\rightarrow$  55 85% of total will develop chronic infection  $\rightarrow$  50% of total will develop chronic hepatitis  $\rightarrow$  5 20% of total will develop cirrhosis  $\rightarrow$  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 ende mic regions
- Low perinatal transmission, transfusion before 1992, body piercing, long term dialysis, occupa tional exposure, intranasal drug use, multiple sex ual partners

## CLINICAL FEATURES

HISTORY symptoms of liver failure (jaundice, bleed ing, infections, ascites, confusion), weight change, risk factors of hepatitis (sexual activity, IDU, tattoos, pier cing, 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, cryo globulinemia, ITP
- VASCULAR necrotizing vasculitis, polyarteritis nodosa
- RHEUMATOLOGIC arthralgias, arthritis, myalgia, sicca
- NEUROLOGIC weakness, peripheral neuropathy
- ENDOCRINE diabetes, antithyroid antibodies
- DERMATOLOGIC psoriasis (20%), pruritus, Ray naud's, porphyria cutaneous tarda, lichen planus, cutaneous necrotizing vasculitis

## INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, albumin, anti HCV IgM and total (sens 92 97%), HCV RNA PCR (qualitative, quantitative), genotyping, βhCG (before treat ment), HAV serology, HBV serology, HDV serol ogy, iron, TIBC, HIV serology
- IMAGING U/S abd

#### **SPECIAL**

• LIVER BIOPSY not mandatory before starting treatments

# PROGNOSTIC ISSUES

**GOOD PREDICTIVE FACTORS** age <40, female, weight <75 kg [165 lbs], low titer, genotype 2/3, mild fibrosis

**POOR PROGNOSTIC FACTORS** age of infection >40, male, high BMI, alcohol, HIV co infection

# PROGNOSTIC ISSUES (CONT'D)

UNCERTAIN PROGNOSTIC FACTORS genotype viral load, route of transmission

# MANAGEMENT

**TREAT UNDERLYING CAUSE** pegylated interferon and ribavirin  $\times 48$  72 weeks if genotype 1 or 4 (response rate  $\sim 50\%$ ) or  $\times 12$  48 weeks if genotype 2 or 3 (response rate  $\sim 80\%$ ), orthotopic liver transplant

# TREATMENT ISSUES

**TREATMENT DECISION** complex decision depend ing 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 gui dance) acute HCV, HIV/HCV, HBV/HCV previous treatment failures, liver transplant, renal failure, current drug or alcohol use
- ABSOLUTE CONTRAINDICATION decompensated cirrhosis

Please see Can J Gastroenterol 2007 21 Supp C at www.hepatology.ca for consensus statement on management of hepatitis C

**MONITORING DURING HCV THERAPY** CBC weekly for 4 weeks, then CBC, AST, ALT, uric acid monthly, TSH and ANA every 3 months, and HCV RNA at 4, 12, and 24 weeks during treatment and 6 months after therapy. For significant anemia and neutropenia, give EPO and GCSF, respectively. Also monitor for depression

# **Chronic Liver Disease: Cirrhosis**

## **DIFFERENTIAL DIAGNOSIS**

**INFECTIONS** HBV, HCV, HDV, schistosomiasis, toxoplasmosis

**STEATOHEPATITIS** alcohol, non alcoholic stea tohepatitis (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 CHILD PUGH CLASSIFICATION OF LIVER CIRRHOSIS Encephalopathy Ascites Albumin Total bili INR 1 >35 g/L None <34 $\mu$ M <1.7 [>3.5 g/dL][<2 mg/dL]2 1 2 Slight 28 35 g/L $34 52 \mu M$ 1.7 2.3 [2.8 3.5 g/dL] [2 3 mg/dL] 3 3 4 < 28 a/LMod >52 $\mu$ M >2.3 [<2.8 g/dL] [>3 mg/dL]

# PATHOPHYSIOLOGY OF CHRONIC LIVER DISEASE (CONT'D)

The Child Pugh score is calculated as either encepha lopathy plus ascites plus INR, or albumin plus bilirubin plus INR. Patients with score >7 or any clinical signs of decompensation (variceal bleeding, ascites, ence phalopathy) should be considered for liver transplan tation. 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 elec tive TIPS procedure, now used as a tool for organ allocation in patients with chronic liver disease. The MELD score ranges from 6 to 40, with higher values indicating a worse prognosis

- ORIGINAL MELD =  $9.57 \times log_e(Cr in mg/dL) + 3.78 \times log_e(total bilirubin in mg/dL) + <math>11.2 \times log_e(INR) + 6.43$
- 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  $[0.025 \times MELD \times (140 \text{ Na})] + 140$

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, dia lysis), past medical history (alcohol, hereditary disor ders), medication history (acetaminophen/paraceta mol, 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 Fleischerrings (Wilson's disease)

#### DISTINGUISHING LIVER FROM RIGHT KIDNEY

 The liver has no palpable upper border and extends more laterally and medially

## CLINICAL FEATURES (CONT'D)

- 2. The liver is not usually ballotable, but the kidney is because of its retroperitoneal position
- 3. The percussion note is dull over the liver but is usually resonant over the kidney
- A friction rub may occasionally be heard over the liver, but never over the kidney because it is too posterior
- The liver has a shaper edge while kidney is usually more rounded

# DISTINGUISHING FEATURES BETWEEN PORTAL HYPERTENSION AND VENA CAVA OBSTRUCTION

- PORTAL HYPERTENSION caput medusa veins drain away from umbilicus. Stigmata of liver disease
- IVC OBSTRUCTION veins prominent in the abdo men 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 hepato megaly (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 nega tive, hepatomegaly is unlikely. If clinical suspicion is high, palpate and percuss. Overall, negative findings cannot rule out abnormal liver, and posi tive 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 patho logical 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, HBclgM, HBclgG, HCV serology
- IMAGING U/S abd, CT abd

## INVESTIGATIONS (CONT'D)

#### **SPECIAL**

- LABS ANA, antismooth muscle antibody, AMA, ferritin, ceruloplasmin, α1 antitrypsin, AFP, anti transglutaminase
- GASTROSCOPY to check for varices
- LIVER BIOPSY

## MANAGEMENT

**TREAT UNDERLYING CAUSE** consideration for liver transplantation

**SYMPTOM CONTROL** for variceal bleed prophy laxis, 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 cir rhosis, and those with HBV and hepatocellular carci noma 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 peri carditis, 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 cerulo plasmin, 24 h urine for copper
- TREATMENTS dietary restriction (avoid shellfish, organs, chocolate, nuts, and mushrooms), chelat ing agent (D 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, congeni tal diaphragmatic defect, ascitic fluid move to pleural space due to pressure gradient → transu dative pleural effusion → decreased lung volumes → V/Q mismatch → hypoxemia
- DIAGNOSIS diagnostic thoracentesis. U/S abd to assess liver and ascites. CT chest and abd to rule out other lesions. Intraperitoneal injection of <sup>99</sup>mTc labeled serum albumin may be helpful to confirm diagnosis
- TREATMENTS O<sub>2</sub>, therapeutic thoracentesis, salt restriction, diuretics, TIPSS. Chest tube is a last resort and only with small piqtail catheter

#### HEPATOPULMONARY SYNDROME

- PATHOPHYSIOLOGY portal hypertension → ↓ metabolism of vasodilating substance, or ↓ pro duction of vasoconstricting substance → pulmon ary capillary dilatation → diffusion perfusion imbalance → hypoxemia, dyspnea on exertion and/or at rest, orthodeoxia and platypnea, cynosis, clubbing and spider nevi
- DIAGNOSIS contrast echocardiogram/bubble study (presence of microbubbles in the left atrium 3 6 cardiac cycles after intravenous injection of normal saline suggests dilated pulmonary capil laries), lung perfusion scan, pulmonary angiogram (if severe hypoxemia)
- TREATMENTS O<sub>2</sub>, liver transplant

# NEJM 2007 358:22 PORTOPULMONARY HYPERTENSION

- PATHOPHYSIOLOGY portal hypertension → unknown substance reaches pulmonary vasculature causing vasoconstriction → findings similar to primary pul monary hypertension
- **DIAGNOSIS** echocardiogram, right heart cathe terization
- **TREATMENTS** O<sub>2</sub>, diuretics, sildenafil, prostaglan dins, calcium channel blockers, liver transplant

# **HEPATORENAL SYNDROME**

PATHOPHYSIOLOGY liver failure → dilated systemic circulation → ↑ renin aldosterone system with ↑ cardiac output but not enough to counter splanchnic vasodilatation → pre renal failure. Type I is more serious, defined as >50% reduction of CrCl to ≤20 mL/min in ≤2 weeks or >2× increase in creatinine to >220 μmol/L [>2.2 mg/dL]. Patients are usually oligouric or anuric. Type II includes patients not meeting criteria for type I and is characterized by ascites resistant to diuretics

Hepatic Encephalopathy 135

# 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 hyper tension → 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, her oine, ecstasy
- others salicylates

**INFECTIOUS** pneumonia, UTI, meningitis, ence phalitis, abscess, spontaneous bacterial peritonitis **METABOLIC** 

- ORGAN FAILURE hepatic, azotemia, hypothyroid ism, hypoxemia, CO<sub>2</sub> narcosis
- ELECTROLYTES ketoacidosis, hyponatremia, hypomagnesemia, hypercalcemia, glucose (hypo, hyper)

#### STRUCTURAL

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

## **NEUROPSYCHIATRIC**

## PATHOPHYSIOLOGY

# GRADING OF HEPATIC ENCEPHALOPATHY

- 1 reversed sleep cycle, mild confusion, tremor, incoordination
- 2 lethargy or irritability, disoriented to time, asterixis, ataxia
- 3 somnolence or agitation, disoriented to place, asterixis, hyperreflexia, positive Babinski
- 4 coma, decerebrate

#### PRECIPITANTS OF HEPATIC ENCEPHALOPATHY

 ↑ NH<sub>4</sub> PRODUCTION ↑ protein intake, constipation, Gl bleed, transfusion, infection (spontaneous bac terial peritonitis), azotemia, hypokalemia

# PATHOPHYSIOLOGY (CONT'D)

#### CLINICAL FEATURES

**HISTORY** characterize confusion (onset, duration, fluctuation), infectious symptoms, neurological symptoms, precipitants (diet, hydration, constipation, GI bleed, infection), past medical history (liver dis ease, alcohol and illicit drug use), medication history (sedatives, narcotics)

**PHYSICAL** vitals, signs of chronic liver disease, rec tal examination (if suspect Gl bleed), neurological examination, check for asterixis

# **INVESTIGATIONS**

# BASIC

- LABS CBCD, lytes, urea, Cr, glucose, TSH, AST, ALT, ALP, bilirubin, INR, PTT, NH<sub>4</sub>, Ca, Mg, PO<sub>4</sub>, 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

Ascites

Ascites

#### MANAGEMENT

## ACUTE HEPATIC ENCEPHALOPATHY

- WORKUP FOR SEPSIS
- SYMPTOM CONTROL consider sedation (haloperidol 1 2 mg PO/IV/SC q6h and q1h PRN) and ventila tion, 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

## MANAGEMENT (CONT'D)

300 mL lactulose mixed with 700 mL  $H_2O$  PR if NPO (also lactitol and lactose). **Neomycin** 500 2000 mg PO q8h or **metronidazole** 800 mg PO daily (alter natives to lactulose or use in combination). **Others** (*H. pylori* treatment, ornithine aspartate, branched amino acids)

• TREAT UNDERLYING CAUSE liver transplant

Related Topic

Delirium (p. 380)

# **Ascites** NEJM 2004 350:16

# DIFFERENTIAL DIAGNOSIS

## † HYDROSTATIC PRESSURE

- **CARDIAC** right heart failure, tricuspid regurgita tion, constrictive pericarditis
- HEPATIC pre sinusoidal (portal vein thrombo sis, schistosomiasis), sinusoidal (cirrhosis), post sinusoidal (Budd Chiari, veno occlusive)
- ↓ **ONCOTIC PRESSURE** malnutrition, liver dis ease, nephrotic, protein losing enteropathy

#### DIFFERENTIAL DIAGNOSIS (CONT'D)

# ↑ CAPILLARY PERMEABILITY/LYMPHATIC OBSTRUCTION

- INFECTIONS spontaneous bacterial peritonitis
- MALIGNANCY ovarian, peritoneal metastasis
- PANCREATITIS

OTHERS hypothyroidism

CLINICAL FEATURES					
RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE ASCITES?					
	Sens	Spc	LR+	LR	
History					
↑ abdominal girth	87%	77%	4.16	0.17	
Recent weight gain	67%	79%	3.2	0.42	
Ankle swelling	93%	68%	2.8	0.10	
Hepatitis	67%	79%	3.2	0.42	
Heart failure	47%	73%	2.04	0.73	
Alcoholism	60%	58%	1.44	0.69	
Hx of carcinoma	13%	85%	0.91	1.01	
Physical					
Bulging flanks	81%	59%	2.0	0.3	
Flank dullness	84%	59%	2.0	0.3	
Shifting dullness	77%	72%	2.7	0.3	
Fluid wave	62%	90%	6.0	0.4	
	C 11 C 11				

**APPROACH** "most useful findings for ruling out ascites are negative history of ankle swelling, ↑ abdominal girth, and negative for bulging flanks, flank dullness, or shifting dullness. Most powerful findings for making diagnosis of ascites are positive fluid wave, shifting dullness, or peripheral edema. Puddle sign and auscultatory percussion not recommended"

JAMA 1992 267:19

## INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bili rubin, 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, triglycer ide, cytology

# SPECIAL

LAPAROSCOPY WITH PERITONEAL BIOPSY

Ascites 137

#### 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 termina tion 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 thera peutic paracentesis with or without albumin or non albumin plasma expanders and found no consistent effect on morbidity or mortality

# FEATURES SUGGESTIVE OF SPONTANEOUS BACTERIAL PERITONITIS

	LR+	LR
Ascitic fluid WBC/PMN		
Ascitic fluid WBC $>$ 1000 cells/ $\mu$ L	9.1	0.25
Ascitic fluid WBC $>$ 500 cells/ $\mu$ L	5.9	0.21
Ascitic fluid WBC >250 cells/μL	0.9	1.1
Ascitic fluid PMN >500 cells/μL	10.6	0.16
Ascitic fluid PMN >250 cells/μL	6.4	0.20

#### Ascitic fluid pH and blood ascitic pH gradient Ascitic fluid pH <7.31 4.1 0.47 Ascitic fluid pH <7.32 4.8 0.65 Ascitic fluid pH <7.31 5.8 0.43 Ascitic fluid pH <7.35 9.0 0.31 Ascitic fluid pH < 7.40 2.5 0.23 Blood ascitic fluid pH gradient 4.6 0.47 >0.11 Blood ascitic fluid pH gradient 7.1 0.30 >0.10 Blood ascitic fluid pH gradient 0.12 11.3 >0.10

# FEATURES SUGGESTIVE OF PORTAL

HYPERTENSION		
	LR+	LR
Serum ascites albumin gradient (	(SAAG)	
Serum ascites albumin gradient	4.6	0.06
≥11 g/L		
ADDDOAGU # 101 (L.)		

**APPROACH** "ascitic fluid should be inoculated into blood culture bottles at the bedside. Sponta neous bacterial peritonitis is more likely at prede scribed 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 albu min gradient (<11 g/L [<1.1 g/dL])"

JAMA 2008 299:10

# DIAGNOSTIC ISSUES (CONT'D)

# PARACENTESIS PROCEDURE NEJM 2006 355:e21 SERUM ASCITES ALBUMIN GRADIENT (SAAG)

- PORTAL HYPERTENSION OR CONGESTIVE HEART FAILURE
   (serum albumin ascites albumin) ≥11 g/L
   [≥1.1 g/dL]. To distinguish between portal 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 albumin ascites albu min) <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 regurgita tion, 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 (dif fuse, continuous), diarrhea, confusion, or renal deterioration. Sepsis with hypotension and paraly tic 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

138 Jaundice

## SPECIFIC ENTITIES (CONT'D)

and incidence of hepato renal syndrome). **Sec ondary prophylaxis** include *ciprofloxacin* 

# SPECIFIC ENTITIES (CONT'D)

750 mg PO weekly or *trimethoprim sulfamethox* azole DS 1 tab PO daily

# **Jaundice**

# DIFFERENTIAL DIAGNOSIS OF JAUNDICE/ HYPERBILIRUBINEMIA

## PRE HEPATIC (hemolysis)

- RBC MEMBRANE spherocytosis, elliptocytosis
- **RBC ENZYMES** G6PD, pyruvate kinase deficiency
- RBC HEMOGLOBIN sickle cell
- BLOOD toxins, drugs (fludarabine), infections (malaria), immune
- VASCULAR abnormal valve, vasculitis, HUS/TTP/ DIC, HELLP, severe hypertension
- INEFFECTIVE ERYTHROPOIESIS megaloblastic anemia
- HEPATIC

   ↓ UPTAKE Gilbert's, drugs (rifampin, contrast)
- conjugation Gilbert's, Crigler Najjar I/II, hepa tocellular diseases, drugs (chloramphenicol)
- LEXCRETION (cholestasis) Dubin Johnson, Rotor, benign recurrent cholestasis, cholestasis of preg nancy, 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 excre tion 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, pre vious 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  $>70 \mu mol/L [>41 mg/dL]$ 

**PALE STOOL/PRURITUS** suggests conjugated hyperbilirubinemia pale stool/pruritus suggests cholestasis (bile cannot be secreted into the biliary system)

## CLINICAL FEATURES (CONT'D)

**PAIN** painful jaundice suggests acute obstruction (by stones, masses); investigate with U/S abd ERCP/MRCP/EUS. Painless jaundice suggests pancreatic cancer, infil tration, PSC, PBC, and drugs; investigate with biopsy

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, peripheral smear, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin (conjugated and unconjugated), INR, albumin, HAV IgM, HAV IgG, HBsAg, HBsAb, HBcIgM, anti HCV, ANA, antismooth muscle antibody (ASMA), anti mitochondrial antibody (AMA), ferritin, cer uloplasmin, α1 antitrypsin, AFP, LDH, haptoglo bin, 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 → inflamma tion and necrosis → cirrhosis
- CLINICAL FEATURES pruritus, fatigue, RUQ pain, xanthe lasmas, sicca syndrome, hyperlipidemia. With disease progression, symptoms of liver failure may be seen
- DIAGNOSIS antimitochondrial antibody (sens 95%), ANA (40%), ↑ bilirubin, ↑ ALP, ↓ C4, ↑ IgM, hyperli pidemia (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 pro gression (for stages I and II), delay time to transplant but does not treat pruritus. For pruritus, consider cholestyramine, rifampin, and naltrexone. Consider

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# SPECIFIC ENTITIES (CONT'D)

treating hyperlipidemia (despite hypercholestero lemia, risk of atherosclerotic death not increased). Prevent osteoporosis with calcium and vitamin D. Also provide supplement with fat soluble vitamins (KADE) which are not well absorbed in cholestasis. Consider liver transplant if rising bilirubin, liver decompensation, refractory pruritus, or severe bone disease

NEJM 2007 357:15

# SPECIFIC ENTITIES (CONT'D)

#### PRIMARY SCLEROSING CHOLANGITIS (PSC)

- PATHOPHYSIOLOGY cholangitis → fibrosis with intra and extrahepatic duct strictures → cirrhosis; 75% associated with ulcerative colitis, 10% with cholangiocarcinoma
- DIAGNOSIS ERCP (beading, strictures), biopsy
- TREATMENTS liver transplant

# **Acute Pancreatitis**

# NEJM 1994 330:17

#### CAUSES

# ★BAD HITS★ BILIARY STONES ALCOHOL

**DRUGS** thiazides, furosemide, sulfonamide, tet racycline, calcium, estrogen, vinca alkaloids, antire trovirals (didanosine, pentamidine)

**HYPER** hypercalcemia, hyperlipidemia (V, I, IV) **INFECTIOUS** *E. coli*, HIV, CMV, mumps, Ascariasis **IDIOPATHIC** 

INHERITED familial TRAUMA blunt

SURGERY ERCP, sphincter of Oddi dysfunction

## PATHOPHYSIOLOGY

# COMPLICATIONS OF ACUTE PANCREATITIS ★SCAR★

**S**epsis

Calcium (hypocalcemia)

Abdominal (necrotizing pancreatitis  $\pm$  hemorrhage, pancreatic pseudocyst  $\pm$  hemorrhage [10 20%], pancreatic abscess, splenic vein thrombosis, fistula, cholangitis

**R**espiratory failure and aspiration pneumonia **R**enal failure

#### CLINICAL FEATURES

**HISTORY** abdominal pain, nausea and vomiting, fever, anorexia, past medical history (previous pan creatitis, recent ERCP, biliary stones, alcohol use, HIV), medication history (diuretics, antibiotics)

**PHYSICAL** vitals, volume status, abdominal examina tion, Cullen's sign (periumbilical ecchymoses sugges tive of hemoperitoneum), Grey Turner's sign (ecchymoses of the flanks suggestive of retroperitoneal hemorrhage), Fox's sign (ecchymoses parallel and inferior to inguinal ligament along upper thighs suggesting retroperitoneal hemorrhage), Bryant's sign (blue scrotum suggesting retroperitoneal hemorrhage)

# INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, LDH, lipase, amylase, Ca, albumin, fasting lipid profile
- IMAGING U/S abd, CT abd (+ contrast for necro tic pancreatitis)
- ERCP both diagnostic and therapeutic

#### DIAGNOSTIC AND PROGNOSTIC ISSUES

# **TION** acute pancreatitis, pancreatic cancer, pan creatic duct obstruction, perforated peptic ulcer, bowel infarction, intestinal obstruction, renal failure

- ON ADMISSION age >55, WBC >16×10<sup>9</sup>/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</li>
   [<8 mg/dL], sequestration of fluid >6 L
- PROGNOSIS 0 2=2% mortality, 3 4=15%, 5 6= 50%, 7 8=100%

## MANAGEMENT

RANSON'S CRITERIA

**ACUTE** ABC, O<sub>2</sub>, **IV hydration**. NPO, NG if severe N&V or obstruction. *Morphine* 2.5 5 mg SC q4h PRN and 1 2 mg IV q1h PRN (for theoretical concern of morphine causing sphincter of Oddi spasm, some consider using Demerol instead). Antiemetics (*dimen hydrinate* 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 pancrea
titis (ERCP and biliary sphincterotomy within 72 h,
cholecystectomy). Necrotizing pancreatitis (ICU
admission, surgical debridement)

## SPECIFIC ENTITIES

## **ASCENDING CHOLANGITIS**

- PATHOPHYSIOLOGY biliary calculi (choledocho lithiasis), post ERCP, tumors, primary sclerosing cholangitis, or benign stricture → biliary obstruc tion and stasis → bacterial colonization and infection (E. coli, Klebsiella, Enterobacter, Enterococcus, anaerobes) → liver failure, sepsis
- CLINICAL FEATURES Charcot's triad consists of fever, right upper quadrant pain, and jaundice. Reynold's pentad is associated with the addition of hypotension and confusion

# SPECIFIC ENTITIES (CONT'D)

- DIAGNOSIS ↑ bilirubin, ALP, and potentially AST and ALT. Blood cultures essential. U/S abd to check for common bile duct dilatation and stones, ERCP, MRCP
- TREATMENTS antibiotics (imipenem 500 mg IV q6h, ampicillin plus gentamicin). Facilitate biliary drainage (ERCP with sphincterotomy, stone extraction, stent insertion, percutaneous drainage, surgical decompression)

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# Notes

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# Notes

# **6** HEMATOLOGY

Section Editor: Dr. Michael Kroll

# **Polycythemia**

#### DIFFERENTIAL DIAGNOSIS

**SPURIOUS** stress (Geisböck's syndrome), decrease intravascular volume

PRIMARY polycythemia rubra vera

#### SECONDARY ★HERA★

- HYPOXIA obstructive sleep apnea, COPD, smok ing, high altitude
- **EPO-SECRETING TUMORS** renal, hepatoma, cere bellar, pheochromocytoma
- RENAL polycystic kidney disease, hydronephro sis, post transplant
- ADRENAL Cushing's syndrome

#### PATHOPHYSIOLOGY

**DEFINITION OF POLYCYTHEMIA** hematocrit >0.6 in 3, hematocrit >0.5 in 9

# **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 (respira tory diseases, myeloproliferative disorders, myocar dial 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, hepato megaly, splenomegaly, excoriations, stigmata of a prior arterial or venous thrombotic event, gouty arthritis, and tophi

# INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, LAP, vitamin B12, RBC mass (total blood volume × Hct, to rule out spurious causes), carboxyhemoglobin level, cor tisol level, peripheral blood smear
- IMAGING CXR SPECIAL
- JAK2 MUTATION JAK2 is a cytoplasmic tyrosine kinase activated by EPO binding to its receptor; the V617F mutation activates JAK2 and thereby drives EPO independent erythropoiesis
- EPO LEVEL low in PRV, high if secondary causes
- HYPOXIA WORKUP oximetry, ABG, CO hemoglobin
- solid tumor workup CT abd, MRI head (if tumors)
- BONE MARROW BIOPSY rule out myelofibrosis and CML

# DIAGNOSTIC ISSUES

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

- ABSOLUTE ↑ RBC mass, no secondary cause (nor mal PaO<sub>2</sub>, EPO not elevated)
- MAJOR splenomegaly, JAKV617F
- MINOR WBC >12×10 $^3$ / $\mu$ L, platelet >400 ×10 $^3$ / $\mu$ L,
- LAP >100U/L and vitamin B12 >650pmol/L [>880 pg/mL]
- DIAGNOSIS need absolute criteria plus one major or two minor criteria for the diagnosis of poly cythemia rubra vera. See myeloproliferative disor ders (p. 165) for more details

# MANAGEMENT

**TREAT UNDERLYING CAUSE relative** (hydration), **CO hemoglobinemia** (smoking cessation. See p. 418), **sleep apnea** (CPAP. See p. 17), **polycythe mia vera** (cytoreduction with hydroxyurea is prefer able to phlebotomy to keep hematocrit <0.45 in ♂ and <0.42 in ♀, ASA 81 mg PO daily prevents thrombosis but watch out for bleeding)

# **Microcytic Anemia**

NEJM 2005 352:10

## DIFFERENTIAL DIAGNOSIS

#### **★TAILS**★

#### **THALASSEMIA**

ANEMIA OF CHRONIC DISEASE infection, malignancy, inflammatory disorders

**IRON DEFICIENCY** blood loss (GI, GU, vaginal, trauma), iron deficient diet, celiac disease, atrophic gastritis, renal failure on EPO, pulmonary hemosi derosis, intravascular hemolysis

LEAD POISONING SIDEROBLASTIC

# PATHOPHYSIOLOGY

**DEFINITION OF MICROCYTIC ANEMIA** Hb < 135 g/L [< 13.5 q/dL], MCV < 80 fL

**SEQUENCE OF IRON DEFICIENCY**  $\downarrow$  iron  $\rightarrow \uparrow$  TIBC

→ \( \) Hb → \( \) MCV → hypochromia **ANEMIA OF CHRONIC DISEASE** chronic inflamma tory states such as malignancy, infection and rheu matologic diseases → \( \) INF $_{\gamma}$ , TNF $_{\alpha}$ , IL 1, IL 6, IL 10 → \( \) hepatic expression of hepcidin which inhibits duo denal 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 (Gl, menstrual), pica (ice, dirt), diet history, fever, night sweats, weight loss, past medical history (malignancy, chronic infections, rheumatolo gic disorders), medications (NSAIDs, ASA, anticoagu lants), family history (thalassemia)

**PHYSICAL** vitals, koilonychia (spoon nails), alope cia, blue sclerae, conjunctival pallor, angular chloro sis, 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 (transfer rin), % sat, Hb electrophoresis, fecal occult blood (if suspect Gl bleed)

#### **SPECIAL**

- ENDOSCOPY gastroscopy and/or colonoscopy targeting symptoms in any man or post meno pausal woman with iron deficiency or in anyone with suspected GI bleeding
- SOLUBLE TRANSFERRIN RECEPTOR (sTfR) helps to distinguish between iron deficieny and anemia of chronic disease

## INVESTIGATIONS (CONT'D)

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

DIAGNOSTIC ISSUES					
IRON INDICES					
	Ferritin	Iron	TIBC	% sat	
Iron deficiency	1	$\downarrow$	1	$\downarrow$	
Anemia of	↑/N	$\downarrow$	N/↓	N/↓	
chronic					
disease					
Thalassemia	↑/N	1	$\downarrow$	1	
Sideroblastic	N/↑	N/.l.	N/. .	N/.l.	

# DISTINGUISHING FEATURES BETWEEN IRON DEFICIENCY AND THALASSEMIA

- RDW red cells in thalassemia tend to have a narrower distribution than in iron deficiency
- MCV red cells in thalassemia tend to be smaller than in iron deficiency
- RBC RBC high or normal if thalassemia but tend to decrease proportionally to Hb in iron deficiency
- THALASSEMIA INDEX MCV/RBC. Suggests thalasse mia if <13 and iron deficiency if >13
- MORPHOLOGY thalassemia causes microcytic tar qet cells

# CIENCY AND ANEMIA OF CHRONIC DISEASE fer ritin is indicative of marrow iron stores and is key to the diagnosis of iron deficiency anemia as serum iron and TIBC levels may change with other diseases

- <30 ng/ml iron deficiency anemia (PPV 92 98%)</p>
- 30 100 ng/ml combination of anemia of chronic disease and true iron deficiency if (sTfR/ log ferritin)>2. Anemia of chronic disease alone if (sTfR/log ferritin) <1</li>
- 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 145

# **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, myeloproli ferative disorders, lymphoma, metastasis, infec tions (esp. TB)
- DECREASED EPO renal failure
- ANEMIA OF CHRONIC DISEASE

# SEQUESTRATION splenomegaly

#### ↑ DESTRUCTION

- **IMMUNE** autoimmune hemolytic anemia (warm agglutinins, cold agglutinins)
- NON-IMMUNE
  - RBC MEMBRANE spherocytosis
  - RBC ENZYMES G6PD, pyruvate kinase defi ciency
  - RBC HEMOGLOBIN sickle cell anemia
  - MICROANGIOPATHIC DIC, HUS/TTP, prosthetic valve, hypertensive crisis
- BLOOD toxins, infections (malaria), immune
  MIXED PICTURE combined microcytic and macro
  cytic anemia (e.g. malnutrition causing iron defi
  ciency 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, myelodyspla sia), 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 periph eral 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 electrophor esis, fecal occult blood (if suspect Gl 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 caus ing 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 ane mia (acute hemolytic reaction)
  - NON-IMMUNE HEMOLYTIC ANEMIA (DAT nega tive) TTP/HUS, DIC, hemoglobinopathies, her editary 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 reticulo cyte count to evaluate if bone marrow response to anemia is appropriate or hypoproliferative

 RPI = [retic count × (hematocrit in %/45)]/ maturation factor

Maturation factor	Hematocrit
1.0%	45%
1.5%	35%
2.0%	25%
2.5%	20%

 INTERPRETATION RPI > 2% suggests adequate mar row response, < 2% suggests hypoproliferative (i.e. ↓ production)

# MANAGEMENT

#### TREAT UNDERLYING CAUSE

**SYMPTOM CONTROL transfusion** 2 U PRBC IV over 2 h. **Erythropoietin** (*epoetin alfa* 50 200 U/kg/week SC/IV div 2 3×/week, *darbepoetin alfa* 20 40 μg SC weekly) for anemia of chronic kidney disease or selected patients on active chemotherapy

146 Macrocytic Anemia

# SPECIFIC ENTITIES

# 

- CAUSES neoplasia (CLL, especially with fludarabine, pentostatin, cladribine), autoimmune (SLE), infections (viral), drugs (penicillins, fludarabine, methyldopa)
- CLINICAL FEATURES anemia, jaundice, splenome galy, anemia, smear (microspherocytosis), ↑ reticu locytes, ↑ bilirubin, ↑ LDH, ↓ haptoglobin, direct Coombs test (IqG±, C3±)
- TREATMENTS symptom control (transfusion with caution, difficult to cross match due to autoanti bodies reacting with antigens present on cells of almost all individuals). Steroids (prednisone 1 mg/ kg PO daily, taper after stable). Reduce effective ness of antibodies (IVIG, splenectomy). Immuno suppression (azathioprine 100 150 mg PO daily, cyclophosphamide 100 mg PO daily). Biological

## SPECIFIC ENTITIES (CONT'D)

agents (rituximab, alemtuzumab). **Treat under lying disease** (CLL, SLE, drugs)

# AUTOIMMUNE HEMOLYTIC ANEMIA: COLD AGGLUTININS IGM

- CAUSES neoplasia (CLL, lymphoma, Walden strom's macroglobulinemia, adenocarcinoma), infections (mycoplasma pneumonia, infectious mononucleosis, CMV, VZV)
- CLINICAL FEATURES anemia, agglutination, jaundice, splenomegaly. Anemia, smear (spherocytosis), ↑ reti culocytes, ↑ 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, cladri bine, capecitabine), **antiepileptics** (phenytoin, phenobarbital), **antibiotics/antivirals** (trimetho prim sulfamethoxazole, zidovudine)

VITAMIN B12 DEFICIENCY FROM PERNICIOUS ANEMIA

DIETARY FOLATE DEFICIENCY
MYELODYSPLASTIC SYNDROME
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA
HYPOTHYROIDISM
RETICULOCYTOSIS

## PATHOPHYSIOLOGY

**DEFINITION OF MACROCYTIC ANEMIA** Hb <135 g/L [>13.5 g/dL], MCV >100 fL

# **Related Topics**

Alcoholism (p. 105) Chronic Liver Disease (p. 132) Myelodysplastic Syndrome (p. 166) Vitamin B12 Deficiency (p. 405)

# CLINICAL FEATURES

**HISTORY** shortness of breath, chest pain, dizziness, fatigue, bleeding, fever, night sweats, weight loss, diet history, past medical history (liver disease,

#### CLINICAL FEATURES (CONT'D)

alcohol, hypothyroidism, myelodysplasia), medica tions (chemotherapy, antibiotics, antiepileptics)

PHYSICAL look for signs of hypothyroidism, vita min B12 deficiency and liver disease. Vitals (bradycar dia, hypoventilation, hypotension), leukonychia, club bing, 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, gyneco mastia, pericardial effusion, ascites, splenomegaly, caput medusa, hemorrhoids, testicular atrophy, prox imal muscle weakness, hyporeflexia, edema (non pit ting), 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

Sickle Cell Disease 147

## MANAGEMENT (CONT'D)

anemia. For patients with pernicious anemia, trans fuse fewer units and transfuse each unit slowly over 3 h since an expanded intravascular volume puts patients at risk for transfusion induced pulmonary edema

## MANAGEMENT (CONT'D)

TREAT UNDERLYING CAUSE folate deficiency (folate 0.4 mg PO/SC/IM daily  $\times 4$  5 d). Vitamin B12 deficiency (vitamin B12 1000 μg SC/IM daily  $\times 5$  10 days, then 1000 μg SC/IM qweek  $\times 4$  weeks, then every month). Hypothyroidism ( $\iota$  thyroxine start 12.5 50 μg PO daily, adjust every 2 weeks)

# **Sickle Cell Disease**

#### PATHOPHYSIOLOGY

 $\beta$  CHAIN MUTATION leads to formation of hemo globin S ( $\alpha 2\beta 52$ )  $\rightarrow$  polymerization of hemoglobin S  $\rightarrow$  elongated fibers that distort shape of RBC  $\rightarrow$  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 hapto globin). There may be associated folate/iron defi ciency from increased utilization
- ACUTE ANEMIA may be due to splenic sequestra tion crisis (venoocclusion of spleen leading to RBC pooling), aplastic crisis (transient arrest of erythro poiesis), 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 occlu sion, 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

**HEPATOSPLENIC** splenic infarction, acute hepatic ischemia, hepatic sequestration crisis, iron overload (transfusions)

**PULMONARY** restrictive lung disease (chronic interstitial fibrosis), obstructive lung disease, hypox emia, pulmonary hypertension, fat embolism

#### CLINICAL FEATURES (CONT'D)

**ANEMIA** remember that sickle cell disease is asso ciated with both acute and chronic anemia

**INFECTIONS** sepsis (particularly asplenic patients), meningitis, pneumonia, osteomyelitis

**NEUROLOGIC** ischemic stroke, intracerebral hemorrhage, septic emboli, spinal cord infarction or compression, vestibular dysfunction, sensory hearing loss, cognitive failure

# INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, LDH, haptoglobin, smear (sickled red cells, poly chromasia from reticulocytosis, Howell Jolly bodies from hyposplenia), reticulocytes, RBC folate, Fe, ferritin, % saturation, transferrin, hemoglobin elec trophoresis (identify subtypes), urinalysis
- MICROBIOLOGY blood C&S, sputum Gram stain/ AFB/C&S, urine C&S, stool C&S, O&P, C. diff toxin A/B

# MANAGEMENT

**ACUTE** ABC, O<sub>2</sub>, 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 infil trates, cough, progressive anemia, hypoxemia, with or without fever) treat precipitating factor, fluids, pain control, transfusions (simple or exchange)
- PRIAPISM hydration, analgesics, transfusions, urology consultation
- PREOPERATIVELY transfuse to Hb 100 g/L [10 g/dL]
   CHRONIC interprofessional team, immunizations
   (Streptococcus pneumoniae, Haemophilus influenzae, Niesseria meningitidis, hepatitis B virus, and influenza), exchange transfusion (goal HbS < 30%), hydroxyurea (increase levels of fetal Hb, decrease incidence of vasoocclusive pain), folic acid 1 mg PO daily</li>

## SPECIFIC ENTITIES

**ASPLENIC PATIENTS** particularly susceptible to encapsulated bacteria (*S. pneumoniae, H. influenzae,* and *N. meningitidis*), *Capnocytophaga canimorsus*, Gram negative enteric organisms, and babesiosis

 VACCINATIONS all patients should receive vaccina tions against H. influenzae, pneumococcus, and meningococcus. Flu shot should be given annually and other immunizations repeated every 5 years

# SPECIFIC ENTITIES (CONT'D)

- ANTIBIOTICS WITH FEVER any fever in an asplenic patient should prompt self administration of pre prescribed antibiotics (levofloxacin 750 mg PO daily, moxifloxacin 400 mg PO daily, or cefuroxime 1 g PO daily). Patients should then seek medical advice urgently
- MEDICAL ALERT BRACELET

# Neutropenia

## **DIFFERENTIAL DIAGNOSIS**

#### \*PANIC\*

POST INFECTIOUS sepsis

**AUTOIMMUNE** drug induced, SLE

**NEOPLASTIC** lymphoproliferative disorders, myelodysplasia, leukemias, myelophthisis

**INFECTIONS** sepsis, HIV

**INSUFFICIENCY** folate, vitamin B12

IATROGENIC chemotherapy, chloramphenicol, trimethoprim sulfamethoxazole, synthetic penicil lins, phenytoin, carbamazepine, NSAIDs, gold, antithyroid medications, phenothiazines, clozapine CONSUMPTION hypersplenism

#### **Related Topic**

Febrile Neutropenia (p. 236)

#### PATHOPHYSIOLOGY

**DEFINITION OF NEUTROPENIA** neutrophils  $< 1.5 \times 10^3 / \mu L$ 

#### INVESTIGATIONS

#### BASIC

• LABS CBCD, lytes, urea, Cr, peripheral smear, PTT, INR, AST, ALT, ALP

# INVESTIGATIONS (CONT'D)

#### **SPECIAL**

- FURTHER WORKUP bilirubin, fibrinogen, LDH, ANA, vitamin B12, RBC folate
- BONE MARROW BIOPSY

#### MANAGEMENT

#### TREAT UNDERLYING CAUSE

**GROWTH FACTORS** in some cases, the use of myeloid growth factors such as G CSF or GM CSF is appropriate

# TREATMENT ISSUES

**FEBRILE VS. NON FEBRILE NEUTROPENIA** the presence of fever (>38°C [>100.4°F]) in a neutropenic patient is considered an emergency, as overwhelming sepsis can develop quickly. Patients with febrile neu tropenia (see p. 236 for definition) require early eva luation, initiation of antibiotics, and potentially hospi talization. However, neutropenia alone without fever can usually be monitored on an outpatient basis. Iso lation is usually not required, although patients should avoid being in contact with people with active infections

# SPECIFIC ENTITIES

**ETHNIC NEUTROPENIA** neutrophil counts in blacks are generally lower. Neutrophil count may be down to  $1.5 \times 10^3 / \mu L$  and still be considered normal

# Eosinophilia

#### **DIFFERENTIAL DIAGNOSIS**

#### **★PAIN★**

## PRIMARILY ORGAN SPECIFIC DISORDERS

 PULMONARY interstitial lung disease, AIDS related pneumonia, idiopathic eosinophilic pneumonia, drug induced lung disease

#### DIFFERENTIAL DIAGNOSIS (CONT'D)

 GASTROINTESTINAL eosinophilic gastroenteritis, eosinophilic esophagitis, primary biliary cirrho sis, primary sclerosing cholangitits Eosinophilia 149

## 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, epi sodic angioedema with eosinophilia, Kimura disease and angiolymphoid hyperplasia with eosinophilia, eosinophilic fasciitis, eosinophilic cellulitis, eosinophilic pustular folliculitis, recurrent cutaneous necrotizing eosinophilic vasculitis, eosinophilic ulcers of the oral mucosa

#### **ALLERGIES**

NASAL allergic rhinitis, asthma, nasal polyposis
 MEDICATIONS cytokine mediated (GM CSF, IL
 2), pulmonary (NSAIDs), gastroenteritis
 (NSAIDs), interstitial nephritis (penicillins,
 cephalosporins), necrotizing myocarditis (rani
 tidine), 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 lym phoma, mastocytosis
- SOLID TUMOR large cell carcinoma (lung), squa mous 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 eosino philia include infections and allergies

## CLINICAL FEATURES

**HISTORY** dyspnea, chest pain, cough, sputum, diarrhea, rash, fever, lymphadenopathy, weight loss, night sweats, infectious contact, travel his tory, past medical history (allergic rhinitis,

## CLINICAL FEATURES (CONT'D)

asthma), medications (NSAIDs, antibiotics, pheny toin, 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 eosino phils are primarily tissue dwelling, they are likely several hundred fold more abundant in affected tis sues than represented in peripheral blood. Further more, the development of an intercurrent bacterial or viral infection may lead to suppression of blood eosi nophilia until the superimposed acute infection has resolved. Thus, elevated or even normal blood eosi nophil 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), **hydro xyurea**, **or imatinib** (for idiopathic hypereosinophilic syndrome)

#### SPECIFIC ENTITIES

#### **PULMONARY EOSINOPHILIA**

- PATHOPHYSIOLOGY defined as ↑ eosinophils in blood with evidence of lung involvement, radiolo gically, through bronchoalveolar lavage or lung biopsy
- CAUSES infectious (Loeffler's syndrome [Ascaris, hookworms, strongyloides], Paragonimus lung flukes, tropical pulmonary eosinophilia [Wucher eria bancrofti, Brugia malayi], coccidioidal), medications (NSAIDs, nitrofurantoin, ampicillin, mino cycline, phenytoin, ranitidine), idiopathic (acute eosinophilic pneumonia, chronic eosinophilic pneumonia), others (Churg Strauss, allergic bronchopulmonary aspergillosis)

150 Thrombocytosis

# **Thrombocytosis**

NEJM 2004 350:12

## DIFFERENTIAL DIAGNOSIS

**PRIMARY** (clonal thrombocytosis) essential thrombocythemia, chronic myelogenous leukemia, polycythemia rubra vera, myeloid metaplasia with or without myelofibrosis, prefibrotic myelofibrosis **SECONDARY** (reactive)

- MALIGNANCY
- INFECTIONS
- CONNECTIVE TISSUE DISEASE
- DRUG REACTIONS vincristine, all trans retinoic acid, cytokines, growth factors
- OTHERS iron deficiency, acute blood loss, hemolytic anemia, rebound from thrombocyto penia, splenectomy

## PATHOPHYSIOLOGY

**DEFINITION** platelets  $>450\times10^3/\mu$ L

## **Related Topic**

Myeloproliferative Disorders (p. 165)

## CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY THROMBOCYTOSIS					
	Primary	Secondary			
Underlying disease	N	Υ			
Digital ischemia/CVA	Υ	N			
Thrombosis	Υ	N			
Bleeding	Υ	N			
Splenomegaly	Y (40%)	N			
Peripheral smear	Giant platelets	Normal platelets			
Platelet function	Abnormal	Normal			

↑, giant

# INVESTIGATIONS

BM megakaryocytes

# BASIC

 LABS CBCD, peripheral smear, PTT, INR, Fe, fer ritin, 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  $>450 \times 10^3 / \mu L$ , use **ASA** 81 mg PO daily (low dose) plus **hydroxyurea** (or **anagrelide**) targeting normalization of the platelet count. When the platelets are  $>1500 \times 10^3 / \mu L$ , **plate letpheresis** 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

↑, normal

Thrombocytopenia 151

# **Thrombocytopenia**

## DIFFERENTIAL DIAGNOSIS

**PSEUDOTHROMBOCYTOPENIA** platelet clump ing (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, par vovirus, HCV, EBV
- APLASIA aplastic anemia, Fanconi anemia
- TOXINS chemotherapy, radiation, alcohol
- B12/FOLATE DEFICIENCY

**HYPERSPLENISM** congestive, reactive, infiltra tive (see SPLENOMEGALY p. 164)

#### **↑ DESTRUCTION**

- IMMUNE THROMBOCYTOPENIC PURPURA primary, secondary (lymphoma, CLL, HIV, SLE, Evans syndrome)
- ALLOIMMUNE post transfusion, post transplanta tion
- MICROANGIOPATHIC HEMOLYTIC ANEMIA dissemi nated intravascular coagulation (DIC), thrombo tic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), HELLP syndrome, anti phospholipid antibody syndrome
- INFECTIONS HIV, EBV, CMV
- MEDICATIONS heparin, GPIIb/Illa inhibitors, qui nine, quinidine, valproic acid, thiazides, sulfona mides, rifampin, indomethacin, vancomycin, linezolid

# PATHOPHYSIOLOGY

**DEFINITION** platelets  $< 150 \times 10^3 / \mu L$ . However, an acute drop of 50%, even if the platelet count remains in the normal range, requires close monitoring and potential investigations

**LIFE CYCLE** half life of platelets is 8 10 days. One third of the total body platelets is found in the spleen

# BLEEDING RISK IN UNDER PRODUCTION THROMBOCYTOPENIA

Platelet count
(×10³/μL)
>100
Minimal symptoms
50 100
Minor symptoms
10 50
Prone to bruises
< 10
Risk of spontaneous bleed
(intracranial bleed)

NOTE: in destruction or conjunctivation thrombos

**NOTE**: in destruction or sequestration thrombocy topenia, bleeding does not correlate with the mag nitude of thrombocytopenia

## CLINICAL FEATURES

HISTORY mucocutaneous bleeding (epistaxis, pete chiae, easy bruising), abdominal pain, bloody diarrhea, recent infections, fever, weight loss, past medical his tory (malignancy, HIV, ITP, alcohol), medications (heparin, GPIIb/Illa inhibitors, quinine, ASA, NSAIDs) PHYSICAL vitals. Look for intracranial bleed (fun doscopy), petechiae, and purpura. Check for lympha denopathy and hepatosplenomegaly

# **INV**ESTIGATIONS

# BASIC

 LABS CBCD, lytes, urea, Cr, peripheral smear, PTT, INR, AST, ALT, ALP, bilirubin, fibrinogen, LDH, ANA, vitamin B12, RBC folate, D dimer, HIV serology, hepatitis serology, Coombs test

## **SPECIAL**

- HITT ASSAY heparin induced platelet aggrega tion assay, heparin PF4 solid phase immunoas say, 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/seques tration/MDS

## MANAGEMENT

**SYMPTOM CONTROL** in under production throm bocytopenia, **transfuse** 5 U platelets if platelets  $<50\times10^3/\mu L$  and severe bleeding, platelets  $<10\times10^3/\mu L$  in afebrile non bleeding patient,  $<20\times10^3/\mu L$  in febrile non bleeding patient, and prior to certain procedures (expect platelet rise of  $\sim5/\text{unit}$ ). Note that platelet transfusions are not effective in ITP and may worsen TTP/HUS and HITT

**TREAT UNDERLYING CAUSE** discontinue medi cations that may cause thrombocytopenia (platelets may return to normal in 14 21 days). Please refer to specific disorders below for details regarding treat ment of each disease

#### SPECIFIC ENTITIES

MICROANGIOPATHIC HEMOLYTIC ANEMIA (MAHA) also called fragmentation hemolysis. Charac terized by non immune hemolytic anemia and schisto cytes. Causes include DIC, HELLP, TTP, HUS, malignancy, malignant hypertension, artificial heart valve, insertion of foreign bodies, and medications

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#### 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 com plications (hypoxia, dehydration, acidosis, acute renal failure). Replete coagulation factors if bleeding (FFP 2 U, cryoprecipitate 10 U). Antic oagulation 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 neurological deficit, sei zure, coma. Schistocytes on peripheral smear
- TREATMENTS full volume plasma exchange (plas mapheresis + FFP infusions), steroids, and sple nectomy if not resolving. Avoid platelet transfu sion, ASA and antimotility agents

# NEJM 2006 354:18

#### HEMOLYTIC UREMIC SYNDROME (HUS)

- PATHOPHYSIOLOGY exposure to Shiga toxin or defect in plasma factor H → arteriolar thrombi → predominantly renal involvement
- CAUSES E. coli O157:H7
- CLINICAL FEATURES microangiopathic hemolytic anemia (100%), thrombocytopenia (90%), renal dys function (90%). Schistocytes on peripheral smear
- **TREATMENTS** supportive care only. Does not respond to plasma exchange

# Related Topics

Anticoagulation Therapy (p. 160) Antiphospholipid Antibody Syndrome (p. 156) Thrombocytopenia in Pregnancy (p. 414)

# SPECIFIC ENTITIES (CONT'D)

# HEPARIN INDUCED THROMBOCYTOPENIA AND THROMBOSIS (HITT)

- PATHOPHYSIOLOGY type I (non immune) happens within 2 days, mild drop in platelets, and return to normal by itself. Type 2 (immune) starts between days 4 and 14. It is usually more severe (platelet drop >50%) and has great clinical significance. The pathogenesis is as follows: heparin complexes with PF4 (from platelets) → IgG against heparin PF4 complex → these megacomplexes bind to plate lets 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 >150×10<sup>3</sup>/μL 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 plate lets → isolated thrombocytopenia
- ASSOCIATIONS neoplasm (CLL, lymphoma), infections (HIV), autoimmune (SLE)
- **DIAGNOSIS** isolated thrombocytopenia with an otherwise normal CBC and no obvious causes
- TREATMENTS should be started if patient sympto matic and/or platelets  $< 20 \times 10^3 / \mu L$ . The goal of treatment is to support platelet counts until spon taneous 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

Bleeding Diathesis 153

# SPECIFIC ENTITIES (CONT'D)

- THIRD LINE for patients with chronic refractory ITP (platelets  $<50\times10^3/\mu\text{L}$  after 3 months) who failed or refused splenectomy, consider observation if no bleeding and platelets  $>20\times10^3/\mu\text{L}$ . Otherwise, treat with romiplostim or eltrombopag
- OTHER OPTIONS rituximab, chemotherapy (CVP), danazol. HAART for HIV associated ITP

NEJM 2002 346:13

# SPECIFIC ENTITIES (CONT'D)

**DRUG INDUCED IMMUNE THROMBOCYTOPE NIA** patients usually present with severe thrombo cytopenia (platelets  $< 20 \times 10^3/\mu L$ ). With the exception of platelet inhibitors, there is usually 5 7 days between initiation of drug therapy and platelet drop if patient is receiving the medication for the first time. Treatment consists of discontinuation of offending (or all) drugs and platelet transfusions

NEJM 2007 357:6

**EVANS SYNDROME** ITP and autoimmune hemoly tic anemia

# **Pancytopenia**

# **DIFFERENTIAL DIAGNOSIS**

#### \*PANIC\*

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA
(PNH) ↑ complement mediated red cell lysis
APLASTIC ANEMIA

- IDIOPATHIC (50%)
- INFECTIONS EBV, CMV, parvovirus, hepatitis
- FANCONI'S ANEMIA
- DRUG INDUCED chemotherapy, gold
- TOXINS alcohol

**NEOPLASTIC** leukemia (AML, CLL), MDS, bone marrow metastasis

INFECTIONS sepsis, TB, Parvovirus, fungal
INSUFFICIENCY folate, vitamin B12
IATROGENIC chemotherapy

**CONSUMPTION** hypersplenism, immune mediated destruction

## INVESTIGATIONS

#### BASIC

• LABS CBCD, peripheral smear, B12, RBC folate, HIV test, Coombs test

#### **SPECIAL**

- BONE MARROW BIOPSY if suspect aplastic anemia or malignancy
- FLOW CYTOMETRY if suspect PNH. Historically, sucrose hemolysis test used for screening, fol lowed by Ham acid hemolysis test for diagnosis. Currently flow cytometry is used to measure the

## INVESTIGATIONS (CONT'D)

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

#### DIAGNOSTIC ISSUES

**PRE MEDS FOR BONE MARROW BIOPSY** mor phine 2.5 5 mg IV, lorazepam 1 mg SL, Elma cream

#### MANAGEMENT

TREAT UNDERLYING CAUSE

#### SPECIFIC ENTITIES

- APLASTIC ANEMIA
- PATHOPHYSIOLOGY precipitants (e.g. Parvovirus, drugs) → T cell subsets produce local concentra tions of INFγ → ↑ Fas on CD34+ cells (maturing stem cells) → apoptosis → severe pancytopenia and hypocellular marrow. Complications include paroxysmal nocturnal hemoglobinuria, acute leu kemia, and MDS
- TREATMENTS antithymocyte globulin, cyclos porine, allogeneic stem cell transplant (if age < 50)</li>

**FANCONI'S ANEMIA** hereditary form of aplastic anemia that usually affects children but occasionally presents in adults. The main features include pancy topenia, hyperpigmentation, skeletal malformation, small stature, and hypogonadism

# **Bleeding Diathesis**

# DIFFERENTIAL DIAGNOSIS

- **★PVC★** platelets, vessels, coagulopathy EXTRINSIC PATHWAY (isolated PT ↑)
- FACTOR DEFICIENCY OR INHIBITOR VIIr

# DIFFERENTIAL DIAGNOSIS (CONT'D)

 VITAMIN K DEFICIENCY malnutrition, pancreatic insufficiency, recent antibiotic use, warfarin use (early stage) 154 Bleeding Diathesis

## DIFFERENTIAL DIAGNOSIS (CONT'D)

- LIVER DISEASE
- EARLY DIC

# INTRINSIC PATHWAY (isolated PTT 1)

- FACTOR DEFICIENCY X linked deficiency of factor VIII (hemophilia A) or factor IX (hemophilia B). Autosomal deficiency of factor XI, especially among Ashkenazi Jews (8% are carriers)
- VON WILLEBRAND DISEASE
- FACTOR INHIBITORS lupus anticoagulant due to APA; acquired hemophilia due to an inhibitor to factor VIII
- HEPARIN USE

# COMMON PATHWAY (PT ↑, PTT ↑)

- FACTOR DEFICIENCY X, V, II, I
- SEVERE VITAMIN K DEFICIENCY malnutrition, pancreatic insufficiency, recent antibiotic use, long term warfarin use
- SEVERE LIVER DISEASE
- SEVERE DIC

**PLATELET DYSFUNCTION** (normal PT and PTT, platelet  $>90\times10^3/\mu$ L, bleeding time  $\uparrow$ )

- INHERITED Bernard Soulier syndrome, Glanz mann's thrombasthenia, storage pool disease
- ACQUIRED renal failure, liver failure, myelopro liferative disorders, paraproteinemias, autoanti bodies, DIC, acquired storage pool disease

**VESSELS** collagen vascular disease, scurvy NOTE: INR=international normalized ratio, helps to standardize interpretation of PT

## PATHOPHYSIOLOGY

# **HEMOSTASIS**

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

#### PLATELET ACTIVATION PATHWAY

- Collagen binds to GPIa/IIa on platelet membrane, also binds to GPIb/IX via vWF
- Platelet becomes activated by agonist binding (thrombin, adenosine diphosphate, epinephrine, collagen)
- 3. Secretion of  $\delta$  granules (serotonin, ADP) and  $\alpha$  granules (vWF, growth factors, factor V, factor X, fibrinogen)
- Conformational change → phospholipids become available for factors V and VIII binding
- Platelet aggregation (unstable) by vWF and fibri nogen binding to the activated GPIIb/IIIa complex
- Platelet fibrin clot formation fibrin fibrin cross linked by factor XIII and platelet fibrin via GPIIb/IIIa

#### ANTICOAGULATION PATHWAYS

- 1. Antithrombin binds to thrombin and inhibits it
- Thrombin binds to thrombomodulin which acti vates protein C and S to cleave factors Va and VIIIa

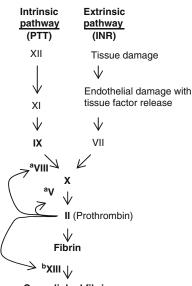
## PATHOPHYSIOLOGY (CONT'D)

3. Factor  $Xa \to tPA$  (by endothelial cells)  $\to$  plasmin  $\to$  fibrinolysis

# **COAGULATION FACTOR PEARLS**

- SYNTHESIZED IN LIVER factors I, II, V, VII, VIII, IX, X, XI, XII, protein C, S, AT III, plasminogen
- VITAMIN K DEPENDENT factors II, VII, IX, X, protein C. S. Z
- SYNTHESIZED IN ENDOTHELIAL CELLS AND MEGAKARYO-CYTES VWF

#### COAGULATION PATHWAY



**Cross linked fibrin** 

<sup>a</sup>Non enzymatic cofactors; <sup>b</sup>Factor XIII is called "fibrin stabilizing factor" because it covalently cross links fibrin polymers and strengthens the clot

# **FACTORS VII AND VIII ARE SPECIAL**

- FACTOR VII shortest half life (5 7 h). Decreased factor VII results in INR ↑. Thus, INR can help to detect early stages of liver failure, DIC, vitamin K deficiency, and warfarin use
- FACTOR VIII part of coagulation cascade and has von Willebrand factor (vWF, synthesized by endothelial cells) as carrier in plasma. Thus, von Willebrand disease (vWD) leads to ↓ factor VIII

## CLINICAL FEATURES

#### **BLEEDING SYNDROMES**

 PLATELET DYSFUNCTION skin/mucous membrane (petechiae, purpura, small/superficial ecchymosis, epistaxis, gingival bleed, menorrhagia), immediate bleed Bleeding Diathesis 155

## CLINICAL FEATURES (CONT'D)

 COAGULATION FACTORS joints/muscles (hemar throses, muscle hematomas, large/palpable ecchy mosis), delayed bleed

## INVESTIGATIONS

#### BASIC

- LABS CBCD, peripheral smear, AST, ALT, ALP, bilirubin, albumin, INR, PTT, D dimer, fibrinogen
   SPECIAL
- HEPZYME STUDY to remove heparin from blood samples to distinguish if isolated elevation of PTT is spurious
- **50:50 MIXING STUDY** to distinguish between factor deficiency (hemophilia) vs. inhibitors
- HEMOPHILIA WORKUP factor VII, factors VIII, IX, XI, factors X, V, II, I
- ANTIPHOSPHOLIPID ANTIBODY SYNDROME WORKUP lupus anticoagulant, anticardiolipin antibody, Russell's viper venom time
- VON WILLEBRAND DISEASE WORKUP von Willeb rand factor (vWF) antigen levels, factor VIII level,

# INVESTIGATIONS (CONT'D)

ristocetin cofactor activity, ristocetin induced platelet aggregation

- PLATELET DISORDER WORKUP bleeding time
  - MYELOMA WORKUP serum protein electrophoresis

## MANAGEMENT

ACUTE ABC, O<sub>2</sub>, IV, transfusion 2 U PRBC IV over 2 h, transfusion platelets 6 U, FFP 15 mL/kg, cryo precipitate 10 15 U q48h for fibrinogen deficiency TREAT UNDERLYING CAUSE avoid heparin, LMWH, warfarin. Vitamin K deficiency (vitamin K 10 mg PO/SC daily ×3 days). vWD type I (DDAVP 0.3 μg/kg SC, intermediate purity factor VIII)

#### SPECIFIC ENTITIES

#### **VON WILLEBRAND DISEASE (VWD)**

 PATHOPHYSIOLOGY vWF acts as a linker between platelets and endothelium and also serves as car rier for factor VIII. Thus, vWD deficiency may lead to decrease in factor VIII levels

ı	Inheritance Autosomal dominant	Pathophysiology Mild to moderate quantitative ↓ of all multimers
IIA	Autosomal dominant/ recessive	↓ activity of vWF due to decrease in large multimers of vWF (synthesis of active forms in platelet adhesion)
IIB	Autosomal dominant	Same as Ila except decrease due to large multimer vWF adherence to platelets
IIN III	Autosomal recessive Autosomal recessive	↓ vWF affinity for factor VIII, similar to hemophilia Complete absence of vWF

#### SPECIFIC ENTITIES (CONT'D)

- CLINICAL FEATURES platelet disorder with bruising, skin or mucosal bleeding, and heavy menstrual cycles for most subtypes, except type IIN which manifests as hemophilia with soft tissue, joint, and urinary bleeding
- DIAGNOSIS Ristocetin cofactor activity (RCo, assesses capacity of plasma vWF to support ristoce

#### SPECIFIC ENTITIES (CONT'D)

tin induced aggregation of control platelets), col lagen binding activity (assesses vWF binding to collagen), vWF antigen (non functional assay that quantifies vWF), vWF multimer assay (agarose gel to determine the size of multimers), ristocetin induced platelet aggregation (assesses vWF bind ing to platelets in patients' platelet rich plasma)

	vWFantigen vWF: RCo	vWF multimer	RIPA
1	<b>↓</b>	↓ all multimers	$\downarrow$
IIA	↓ or N	↓ large multimers	↓ or N
IIB	↓ or N	↓ large multimers	<b>↑</b>
IIN	Normal	Normal	Normal
III	<b>1</b> 1	↓↓ undetectable	$\downarrow \downarrow$

# SPECIFIC ENTITIES (CONT'D)

 TREATMENTS DDAVP 0.3 μg/kg by IV infusion or 300 μg one spray each nasal for all type I and most type II patients. vWF concentrates containing all vWF multimers may be used for type III and for bleeding or surgical management of type III/I

# SPECIFIC ENTITIES (CONT'D)

**BERNARD SOULIER SYNDROME** mutation of GPIb/IX (platelet receptor for vWF)

**GLANZMANN'S THROMBASTHENIA** mutation of GPIIb/IIIa (platelet receptor for fibrinogen)

**STORAGE POOL DISEASE** defect in releasing pla telet granules (especially ADP)

156 Hypercoagulable States

# 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 plas minogen activator)
- NEOPLASTIC solid tumors, myeloproliferative
- OTHERS immobilization, surgery, congestive heart failure, oral contraceptives, hormone repla cement therapy, pregnancy, nephrotic syndrome

# RISK FACTORS FOR ARTERIAL THROMBOEMBOLISM

- ATHEROSCLEROSIS hypertension, diabetes, smoking
- EMBOLIC AF, atrial myxoma, endocarditis, choles terol emboli, MI with ventricular thrombosis, para doxical 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, Wal denstrom's macroglobulinemia, cryoglobulinemia, sickle cell disease
- OTHERS antiphospholipid antibody syndrome, vasculitis, paradoxical embolism
- BIOPROSTHETIC HEART VALVE low level anticoagu lation (INR 2 3) in first 3 months following valve replacement

#### NEJM 2002 346:10

**FACTOR V LEIDEN** mutation that resists cleavage by activated protein C. Most common hereditary form of thrombophilia (3 4% general population)

**THROMBOPHILIC MUTATIONS** antithrombin III, homozygous factor V Leiden >protein S, protein C > heterozygous factor V Leiden in terms of risk of clots

## INVESTIGATIONS

#### BASIC

- LABS CBCD, PT, INR, activated protein C resis tance, factor V Leiden, prothrombin G20210A, anticardiolipin antibody, lupus anticoagulant, homocysteine, protein C, protein S, antithrombin III, fibrinogen, urinalysis
- IMAGING CXR

#### SPECIAL

• PREGNANCY TEST if female < 50

#### **Related Topics**

Anticoagulation Therapy (p. 160) DVT (p. 158)

Pulmonary Embolism (p. 8)

## **DIAGNOSTIC ISSUES**

**WARFARIN AND PROTEIN C** draw protein C and S prior to warfarin therapy as it reduces protein C before those of all other vitamin K dependent factors

#### MANAGEMENT

**ACUTE** ABC, O<sub>2</sub> to keep sat >94%, IV, consider thrombolysis

**ANTICOAGULATION heparin** (unfractionated heparin 5000U IV bolus, then 1000U/h and adjust to 1.5 2.5 × normal PTT) or **LMWH** (enoxaparin 1 mg/kg SC BID or 1.5 mg/kg SC daily). Start **warfarin** 5 mg PO daily within 72 h and continue heparin/LMWH until INR is between 2 and 3 for two consecutive days **IVC FILTER** if anticoagulation contraindicated

# TREATMENT ISSUES

#### WARFARIN USE AND PROTEIN C DEFICIENCY

patients with protein C deficiency given warfarin may be susceptible to transient hypercoagulable state (coumadin necrosis). This can be avoided by administering heparin along with warfarin

# PRIMARY PROPHYLAXIS OF THROMBOEMBOLISM IN HOSPITALIZED MEDICAL PATIENTS

- INDICATIONS patients on the medical service >40 year old have limited mobility for ≥3 days, and have at least 1 of following risk factors
  - CONDITIONS acute infectious disease, conges tive heart failure, acute myocardial infarction, acute respiratory disease, stroke, rheumatic dis ease, inflammatory bowel disease, cancer
  - CLINICAL CHARACTERISTIC previous venous thromboembolism, older age (especially >75),

Hypercoagulable States 157

## TREATMENT ISSUES (CONT'D)

recent surgery or trauma, immobility or paresis, BMI >30 kg/m<sup>2</sup>, central venous catheterization, inherited or acquired thrombophilic states, var icose 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 dalte parin 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</li>

**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 phospholi pids or cell surface proteins bound to anionic phospholipids. These include lupus anticoagulants, anticardiolipin antibody (false positive VDRL), and anti β2GP1 (β2 glycoprotein 1) antibody → may lead to hypercoagulable state and may rarely inhi bit 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 10<sup>th</sup> week of gestation, ≥1 premature births of morphologically normal neo nate at or before the 34<sup>th</sup> week of gestation, or ≥3 unexplained consecutive spontaneous abortions before the 10<sup>th</sup> week of gestation). **Laboratory criteria** include anticardiolipin antibodies (IgG or IgM at moderate or high levels on ≥2 occasions at least 6 weeks apart) or the presence of a lupus anticoagulant (≥2 occasions at least 6 weeks apart). Diagnosis requires at least one clinical and one laboratory criteria (sens 70%, spc 98%)
- CATASTROPHIC ANTIPHOSPHOLIPID SYNDROME acute and devastating syndrome with multiple simultaneous vascular occlusions throughout the body, affecting mainly small vessels of kidney, lungs, CNS, heart, and skin. May be associated with DIC, ARDS, cerebral and myocardial 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 dis covered antiphospholipid antibodies or lupus anticoagulants. Treatment of thromboses (both venous and arterial) is indefinite warfarin antic oagulation 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 (hepa tic 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**

NEJM 2004 351:3

# DIFFERENTIAL DIAGNOSIS OF UNILATERAL LEG SWELLING/DEEP VEIN THROMBOSIS

**VASCULAR** DVT, venous insufficiency, superficial thrombophlebitis (chronic)

LYMPHATIC lymphedema (chronic)

**DRUGS** drug induced edema (calcium channel blockers)

**OTHER** cellulitis, necrotizing fasciitis, knee injury, calf muscle tear, Baker cyst rupture

## PATHOPHYSIOLOGY

**LOCATION** DVT typically originates in the venous sinuses of the calf muscles and occasionally the proximal veins. While most calf vein thrombi lyse spontaneously, ~25% extend into proximal veins within a week

**COMPLICATIONS** clot extension, pulmonary embolism, recurrent thrombosis, post thrombotic syndrome, chronic pulmonary hypertension

# INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, PTT, INR, D dimer, fibrinogen, AST, ALT, ALP, bili
- **IMAGING** CXR, compression U/S (sens 95%, spc 95%), impedance plethysmography

# INVESTIGATIONS (CONT'D)

#### **SPECIAL**

- THROMBOPHILIA WORKUP if there is a family his tory of thrombosis, consider activated protein C resistance, factor V Leiden, prothrombin G20210A, antithrombin III, protein C, and protein S; check antiphospholipid antibodies if the VTE was unprovoked
- PREGNANCY TEST in female <50
- · VENOGRAM gold standard

#### DIAGNOSTIC ISSUES

COMPRESSION U/S high sensitivity (95%) and specificity (95%) for DVT. U/S of calf veins is not routinely performed because of lower sensitivity (70%). Rather, U/S of thigh (deep veins) is usually repeated in 1 week after a normal test to detect the possible extension of DVT from calf into proximal veins

### Related Topics

Anticoagulation Therapy (p. 160) Hypercoagulable States (p. 156) Pulmonary Embolism (p. 8)

## RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE DEEP VEIN THROMBOSIS?

**WELL'S CRITERIA FOR DVT** alternative diagnosis more or as likely (2), recent paralysis/paresis/plaster immobilization (+1), recent bedridden >3 days or major surgery <4 weeks (+1), localized tenderness along deep venous system (+1), calf swelling by more than 3 cm at 10 cm below tibial tuberosity (+1), pitting edema greater in symptomatic leq (+1), collateral non varicose superficial veins (+1), active cancer (+1)

# D DIMER UTILITY FOR DVT BASED ON WELL'S CRITERIA

	Sens	Spc	LR+	LR
Low risk	88%	72%	3.3	0.18
Moderate risk	90%	58%	2.1	0.19
High risk	92%	45%	1.6	0.16

- LOW RISK (0 or less points) <5% chance of DVT. If D dimer negative, can exclude DVT
- MODERATE RISK (1 2 points) 17% chance of DVT. Workup may or may not be needed
- HIGH RISK (3 or greater points) 53% chance of DVT. D dimer testing not useful. Proceed to compression U/S or impedance plethysmography → serial studies → venogram

**APPROACH** 'diagnostic accuracy for DVT improves when clinical probability is estimated before diagnostic tests. Patients with low clinical probability on the predictive rule have prevalence of DVT of <5%. In low probability patients with negative D dimer results, diagnosis of DVT can be excluded without ultrasound; in patients with high clinical suspicion for DVT, results should not affect clinical decisions'

JAMA 2006 295:2

# DISGNOSTIC ISSUES (CONT'D)

**THROMBOPHILIA WORKUP** should be done if sus pect a hereditary cause of thromboembolic disease. Alarm features include age < 45, unprovoked situation, family history (1 or more first degree relative), or

# DIAGNOSTIC ISSUES (CONT'D)

clot in unusual location (upper extremities, mesen teric vessels, brain)

**MALIGNANCY WORKUP** debatable when this should be done. Basic screening includes physical exam, CXR, U/S abd, mammogram, PSA

Notes 159

# DIAGNOSTIC ISSUES (CONT'D)

PROTEIN S AND PROTEIN C DEFICIENCY WHILE ANTICOAGULATED when anticoagulated, usually levels decrease by similar proportion. If sig nificant 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  $2.5 \times$  normal PTT) or **LMWH** (enoxaparin 1 mg/kg SC BID or 1.5 mg/kg SC daily). For long term antic oagulation, 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 hemodynami
cally unstable pulmonary embolism or massive iliofe
moral 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, antith rombin 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 intra cranial bleeding within the past 10 days, active bleeding, severe bleeding diathesis, or platelet < 20×10<sup>3</sup>/μL
- RELATIVE mild moderate bleeding diathesis or thrombocytopenia (20 100×10³/μL), brain metas tases from melanoma, renal cell carcinoma, chor iocarcinoma and thyroid cancers, recent major trauma, major abdominal surgery < 2 days, Gl or GU bleeding < 2 weeks, endocarditis, severe hypertension (>200/120 mmHg)

## SPECIFIC ENTITIES

**SUPERFICIAL THROMBOPHLEBITIS** characterized by painful, erythematous, palpable cord along a super ficial vein usually in the lower extremity, can be asso ciated with hypercoagulable states. Extension to deep vein system rarely occurs through perforating veins and is most likely when the proximal greater saphe nous vein or saphenous femoral junction is involved

**Notes** 

Approach	to Anticoagulatio	n Therapie	S	
Class/Drugs	Mechanism	Indications	Usual dose	Complications/
Warfarin	Inhibition of gamma carboxylation by inhibition of the vitamin K dependent epoxide reductase. Inhibits hepatic synthesis of vitamin K dependent factors (II, VII, IX, X, protein S, protein C)	DVT/PE Atrial fibrillation Prosthetic valves	Warfarin 5 mg PO daily ×3 days, then adjust based on INR	monitoring Complications—bleeding (may be reversed with vitamin K), coumadin induced skin necrosis Monitor—INR
Unfractionated	Indirect thrombin and	Acute DVT/PE	For acute clot,	Complications—bleeding
heparin	factor Xa inhibitor (non- selective). Binds to antithrombin (AT) and converts it from a slow form to fast acting form, which binds and inactivates thrombin and factors Xa, IXa, XIa, XIIa Heparin resistance is usually due to AT deficiency and could be treated with AT concentrates	Arterial embolism Prosthetic valves ACS DVT prophylaxis	unfractionated heparin 5000 U IV bolus, then 1000 U/h, and adjust to 1.5–2.5× normal PTT For DVT prophylaxis, unfractionated heparin 5000U SC 2 h before surgery, then 5000U SC BID	(may be reversed by protamine 1 mg/100 U UFH), HITT, osteoporosis Monitor—aPTT (1.5–2.5 × normal) and platelets Narrow therapeutic window and highly variable dose–response curve
Low molecular weight heparin: Enoxaparin Dalteparin Tinzaparin	Indirect factor Xa inhibitor (relatively selective).  Binds to AT and converts it from a slow form to fast acting form, which binds and inactivates factor Xa, and to a smaller extent, thrombin Inactivation of thrombin specifically requires heparin binding to both AT and thrombin. This complex only forms with heparin chains ≥18 saccharide long. Thus, LMWH is not as effective in inhibiting thrombin and does not prolong aPTT	Maintenance DVT/PE in cancer patients Arterial embolism Prosthetic valves ACS	For acute clots, enoxaparin  1 mg/kg SC BID or  1.5 mg/kg SC daily, dalteparin 200 U/kg SC daily, tinzaparin 175 U/kg SC daily For DVT prophylaxis, enoxaparin 40 mg SC daily ×7–14 days starting 12 h pre op, dalteparin 2500U SC 1 h pre op, then 2500 U SC 6 h after, then 5000 U SC daily ×5–14 days	Complications—bleeding (may be reversed partially with protamine sulfate 1 mg/100 anti Xa U of LMWH), HITT, avoid in spinal surgery Monitor—anti factor Xa activity and platelets. Anticoagulant response correlates well with body weight, allowing fixed dosing without monitoring usually. Less likely to induce HITT but still requires platelet monitoring
Heparinoids: Danaparoid (organon)	Indirect factor Xa inhibitors (selective). Mixture of heparin sulfate, dermatan sulfate, and chondroitin sulfate. Inhibits thrombin via a combination of AT (heparin cofactor II), heparin cofactor III, and some undefined mechanism  More selective factor Xa inhibitor than LMWH, with a ratio of antifactor Xa to AT activity of 28:1 compared to 3:1 with LMWH. aPTT not useful for monitoring	HITT Acute DVT	For HITT, danaparoid 2000 anti factor Xa U IV bolus, then 150–200 U/h, titrate to plasma anti Xa level of 0.5–0.8 U/mL	Complications—bleeding Monitor—anti factor Xa activity. Particularly important in renal failure 10% cross reactivity between danaparoid and the antibody responsible for HITT, but clinical significance is uncertain

Approach to Anticoagulation Therapies (cont'd)				
Class/Drugs	Mechanism	Indications	Usual dose	Complications/ monitoring
Fondaparinux	Indirect factor Xa inhibitor (highly selective). Similar to LMWH, but only a pentasaccharide that binds strongly to AT and inactivates factor Xa. Complex does not bind thrombin due to short length	DVT prophylaxis Acute DVT/PE Acute coronary syndrome HITT (no cross reactivity with heparin dependent anti platelet antibodies)	For DVT prophylaxis, fondaparinux 2.5 mg SC daily (start 6–8 h after surgical hemostasis) For acute clots, fondaparinux 5 mg SC daily for weight < 50 kg, 7.5 mg SC daily for weight 50–100 kg, 10 mg SC daily for weight >100 kg For UA/NSTEMI, fondaparinux 2.5 mg SC daily ×8 days or until discharge For STEMI, fondaparinux 2.5 mg SC daily ×8 days or until discharge	Complications—bleeding; avoid in spinal surgery Monitor—antifactor Xa activity
Rivaroxaban	Direct factor Xa inhibitors (highly selective). Similar to fondaparinux, but specifically inhibits factor Xa by binding to its active site without interacting with AT	DVT prophylaxis (phase II)		Complications—bleeding Monitor—antifactor Xa activity
Direct thrombin inhibitors: Dabigatran Desirudin Lepirudin Argatroban Ximelagatran	Direct thrombin inhibitors (highly selective). AT independent. In contrast to heparin, LMWH, and heparinoid, direct thrombin inhibitors can inhibit clot bound thrombin because their sites for binding (active site ± exosite I) are not masked by fibrin.  Does not depend on AT for action and thus unaffected by AT deficiency	HITT (lepirudin, argatroban) ACS (hirudin, argatroban) DVT prophylaxis (hirudin, dabigatran)	For HITT, <i>lepirudin</i> 0.1–0.4 mg/kg IV bolus, then 0.1–0.15 mg/kg/h; <i>argatroban</i> 2 μg/kg/min infusion	Complications—bleeding Monitor—aPTT

#### CONTRAINDICATIONS TO WARFARIN THERAPY

**ABSOLUTE** neurosurgery, ocular surgery or intra cranial bleeding within the past 10 days, active bleeding, severe bleeding diathesis, or platelet  $<20\times10^3/\mu L$ 

**RELATIVE** mild to moderate bleeding diathesis or thrombocytopenia  $(20\ 100\times10^3/\mu\text{L})$ , brain metas tases, recent major trauma, major abdominal surgery <2 days, GI or GU bleeding <2 weeks, endocarditis, severe hypertension (>200/120 mmHg)

#### **Related Topics**

DVT (p. 158)

Hypercoagulable States (p. 156) Pulmonary Embolism (p. 8)

#### WARFARIN INDUCED SKIN NECROSIS

**CLINICAL FEATURES** usually within first few days of warfarin therapy (especially large loading doses) $\rightarrow$  significantly decreases protein C levels  $\rightarrow$  transient hypercoagulable  $\rightarrow$  erythematous macule  $\rightarrow$  purpuric zone  $\rightarrow$  necrotic lesion. Occurs over extremities, breast, trunk, and penis

**TREATMENTS** immediately stop warfarin, give vitamin K, heparin IV, consider FFP or protein C con centrate. 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

162 Transfusion Reactions

### CORRECTION OF SUPRATHERAPEUTIC INR DUE TO WARFARIN USE (CONT'D)

INR 5 9 if no significant bleeding, hold the next 1 2 doses of warfarin or omit the next dose of warfarin and administer *vitamin K1* 2.5 mg PO. If rapid reversal required (e.g. bleeding or urgent surgery), *FFP* 10 20 mL/kg + *vitamin K1* 2 4 mg PO (↓ INR within 24 h), if INR remains high at 24 h, give additional *vitamin K1* 1 2 mg PO. May also consider prothromin complex concentrate in selected cases

**INR** >**9** if no significant bleeding, hold warfarin and administer *vitamin K1* 5 10 mg PO. Use additional

### CORRECTION OF SUPRATHERAPEUTIC INR DUE TO WARFARIN USE (CONT'D)

vitamin K1 if indicated by frequent INR monitoring. If serious bleeding, hold warfarin, administer *FFP* 20 30 mL/kg + vitamin K1 10 mg by slow IV infusion. Also can use prothrombin complex concentrate or recombinant factor VIIa, depending on volume status and urgency. If life threatening bleeding, hold warfarin therapy and administer recombinant factor VIIa, FFP, and vitamin K1 10 mg by slow IV infusion. Monitor INR and repeat as necessary. May also consider prothromin complex concentrate in selected cases

Transfusion Reactions			
COMPLICATIONS O	F TRANSFUSIONS		
Adverse Effect	Pathophysiology	Onset and Symptoms	Treatments
ABO incompatibility	Recipient Ab against donor RBC major antigen, 1/40,000	Immediate. Fever, ↓ BP, CP, lumbar pain, hemoglobinuria, and bleed	Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis
Acute hemolytic reaction	Recipient Ab against donor RBC minor antigen, 1/600,000	Acute/delay. Milder form of above	Stop transfusion and check blood. Fluids, diuretics, FFP, dialysis
Febrile reaction	Recipient Ab against donor WBC PRBC, 1/300; or platelets (5U), 1/10	End of transfusion. Fever, chills	Antihistamine ( <i>diphenhydramine</i> 50 mg IV ×1 dose), acetaminophen
Anaphylaxis	Recipient Ab against donor IgA, 1/40,000	Immediate. ↓ BP, bronchospasm, no fever	Stop transfusion, epinephrine, corticosteroids
Urticaria	Recipient IgE against donor antigens, 1/100 plasma containing products	Acute. Pruritic rash	Antihistamine (diphenhydramine 50 mg IV ×1 dose)
Post transfusion purpura (PTP)	Recipient Ab against donor platelet	7 10 days after. Consumptive thrombocytopenia and purpura	Steroids, plasmapheresis
Transfusion associated circulatory overload (TACO)	Hypervolemia 1/700	Acute/delay. Pulmonary edema	Epinephrine, corticosteroids
Septic transfusion	Platelets (5 U) 1/10,000 risk of symptomatic sepsis and 1/40,000 chance of death PRBC (1 U), 1/100,000 risk of symptomatic sepsis and 1/500,000 chance of death	Acute. Fever, ↓ BP	Stop transfusion, empiric antibiotics
Air embolism TRALI	Donor Ab against recipient WBC, 1/5000 plasma containing products	Acute. SOB, ↓ BP Acute. Hypoxemic, pulmonary edema	Supportive measures Supportive measures
GVHD	Donor lymphocytes against recipient tissue	Delay. Rash, hepatitis, diarrhea	
Infection risk	HIV 1/10 million, HCV 1/3 million < 1/1 million	n, HBV 1/72,000, HTLV1 1/2 r	million, West Nile virus

#### INVESTIGATIONS

**BLOOD TESTS** CBCD, peripheral smear, urea, Cr, PTT, INR, fibrinogen, blood C&S, send blood pro duct 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

### INDICATIONS FOR SPECIALLY PREPARED BLOOD PRODUCTS (CONT'D)

reactions or TRALI, prevention of HLA alloimmuniza tion (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, Hodqkin'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, thalas semia, and lead poisoning

**ANISOCHROMIA** two cell populations circulating simultaneously. One population is microcytic and hypochromic and the other is normocytic and nor mochromic. Causes include treated iron deficiency anemia, post transfusion of a hypochromic patient, sideroblastic anemia

#### RBC INTRACELLULAR INCLUSIONS

**BASOPHILIC STIPPLING**  $\beta$  thalassemia, lead, or arsenic poisoning

**PAPPENHEIMER BODIES** non nucleated RBC con taining such inclusions are called siderocytes, due to hyposplenism, thalassemia, and sideroblastic disor ders. Nucleated RBC are termed sideroblasts

**NUCLEATED RBC** acute systemic hypoxia, intense erythropoietin stimulation, infiltrative narrow pro cesses, 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 ellipto cytosis, megaloblastosis

**STOMATOCYTES** acute alcoholism, chronic liver disease, artifact

**ROULEAUX** stacking of RBC suggestive of high ESR or hypergammaglobulinemia. Causes include malig nancies (myeloma), infections, and connective tissue disease

164 Splenomegaly

#### **Splenomegaly**

#### DIFFERENTIAL DIAGNOSIS

**CONGESTIVE** right heart failure, constrictive pericarditis, tricuspid regurgitation, IVC obstruc tion, hepatic/splenic vein obstruction, cirrhosis with portal hypertension

#### INFILTRATIVE

- MALIGNANCY lymphoma (Hodgkin's, non Hodg kin'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 retro peritoneal 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?

< 250 g [ < 0.55 lb] or 250 cm<sup>3</sup>, 12 cm by 7 cm [4.7 in. by 2.8 in.]. anatomically, the spleen lies below the left diaphragm. It follows the curvature of left 10<sup>th</sup> rib and points anteriorly toward, the left colic flexure

Sens Spc Inspection

Bulging mass over left costal margin

Percussion

Castell's method (percuss lowest intercostal space in the left anterior axillary line during both 82% 83% expiration and full inspiration; dullness suggests splenomegaly

Nixon's method (right lateral decubitus position; percuss from lower level of pulmonary resonance 59% 94% in posterior axillary line downward obliquely to lower midanterior costal margin; >8 cm suggests splenomegaly)

Traube's space (percuss space 6<sup>th</sup> rib superiorly, mid axillary line laterally and costal margin 62% 72% inferiorly; dullness suggests splenomegaly

#### **Palpation**

Two handed palpation with patient in right lateral decubitus position 71% 90% One handed palpation with patient supine

APPROACH "given the low sensitivity of the clinical examination, routine examination for splenomegaly cannot definitively rule in or rule out splenomegaly in normal, asymptomatic patients where the prevalence is < 10% and additional imaging tests will be required. Rather, the examination for splenomegaly is most useful to rule in the diagnosis of splenomegaly among patients in whom there is a clinical suspicion of at least 10%. The examination should always start with percussion. If no dullness is detected on percussion, there is no need to palpate as the results of palpation will not effectively rule in or rule out splenic enlargement. If the possibility of missing splenic enlargement remains an important clinical concern, then ultrasound or scintigraphy is indicated. In the presence of percussion dullness, palpation should follow. If both tests are positive, the diagnosis of splenomegaly is established (providing the clinical suspicion of splenomegaly was at least 10% before examination). If palpation is negative, diagnostic imaging will be required to confidently rule in or rule out splenomegaly"

JAMA 1993 270:18

Low

#### INVESTIGATIONS

#### BASIC

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

#### SPECIAL

- CT ABD weight = 0.43×Length×Width ×Thickness
- SCINTIGRAPHY
- MALIGNANCY WORKUP bone marrow biopsy, lymph node biopsy, laparoscopy/laparotomy

#### MANAGEMENT

#### TREAT UNDERLYING CAUSE

SPLENECTOMY see p. 147 for more details

#### SPECIFIC ENTITIES

**CAUSES OF MASSIVE SPLENOMEGALY** lym phoma, hairy cell leukemia, CML, myelofibrosis, malaria, MAC in HIV, thalassemia major, sarcoidosis, Gaucher's disease

#### **Myeloproliferative Disorders**

NEJM 2007 357:3

#### DIFFERENTIAL DIAGNOSIS

ESSENTIAL THROMBOCYTOSIS (ET)
POLYCYTHEMIA RUBRA VERA (PRV)
CHRONIC MYELOGENOUS LEUKEMIA (CML)
MYELOFIBROSIS (MF)

**OTHERS** chronic eosinophilic leukemia, chronic myelomonocytic leukemia (CMML), chronic neutro philic leukemia, systemic mastocytosis

#### PATHOPHYSIOLOGY

MYELOPROLIFERATIVE DISORDERS associated with increased red blood cells (especially PRV), white blood cells (especially CML), and/or platelets (especially ET). MPS should not be confused with myelodysplastic syndrome (MDS), which is assoicated with a decreased production of blood cells. Both MPS and MDS can eventually lead to AML

**POLYCYTHEMIA RUBRA VERA** see POLYCYTHEMIA (p. 143)

**CHRONIC MYELOGENOUS LEUKEMIA** (CML) a stem cell disease with Philadelphia chromosome t(9;22) leading to fusion gene bcr abl, found in ery throblasts, megakaryocytes, granulocytes, monocytes, and most lymphocytes. ↓ LAP. Chronic phase → accel erated 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,  $\geq$  20% basophils,  $\geq$  30% blasts+ promyelocytes or platelets < 100  $\times$  10<sup>3</sup>/ $\mu$ 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 >1.0×10³/µL for at least 6 months), anemia, thrombocytopenia, and splenomegaly

#### PATHOPHYSIOLOGY (CONT'D)

**ESSENTIAL THROMBOCYTOSIS** see THROMBOCY TOSIS (p. 150)

**MYELOFIBROSIS** ↑ fibroblasts, marked ↑ spleen, teardrop RBC, nucleated RBC, large platelets

#### **Related Topics**

Polycythemia (p. 143) Thrombocytosis (p. 150)

#### CLINICAL FEATURES

HISTORY B symptoms (fever, night sweats, weight loss, pruritus), hyperviscosity symptoms (facial plethora, headache, visual or mental status changes, stroke, or another ischemic/thrombotic event)

PHYSICAL splenomegaly

INVESTIGATIONS

#### BASIC

- LABS CBCD, peripheral smear, reticulocyte count, uric acid
- BONE MARROW BIOPSY not useful for PRV. Consider cytogenetic studies of blood/bone marrow (FISH) or quantitative PCR to look for Ph chromosome

#### SPECIAL

- GENETIC TESTING JAK2 mutation (sensitivity ~100% for PRV and highly specific for other mye loproliferative disorders), bcr abl testing (CML)
- LEUKOCYTE ALKALINE PHOSPHATASE (LAP) ↑ in PRV, MF, ET, and leukemoid reactions; can be ↓ in CML and CMML
- VITAMIN B12 ↑ in CML due to granulocyte transcobalamin | levels
- EPO ↓ in PRV

#### DIAGNOSTIC AND PROGNOSTIC ISSUES

**LEUKOCYTE ALKALINE PHOSPHATASE** elevated in PRV, MF, and ET, but decreased in CML and CMML

#### DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

POLYCYTHEMIA RUBRA VERA median survival 10 15 years, ∼1/100 transforms to CML, MF, AML CHRONIC MYELOGENOUS LEUKEMIA median survival 3 4 years, ∼1/2 transforms to AML

**ESSENTIAL THROMBOCYTOSIS** median survival 10 15 years, ~1/1000 transforms to AML

**MYELOFIBROSIS** median survival 5 years,  $\sim 1/10$  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%, dasati nib and nilotinib may be used for imatinibresistant disease. Allogeneic stem cell transplant is asso ciated with 60 70% cure rate
- ACCELERATED PHASE imatinib mesylate 600 800 mg PO daily. Allogeneic stem cell trans plant is associated with 30 45% cure rate
- BLAST CRISIS imatinib mesylate 800 mg PO daily, plasmapheresis. Allogeneic stem cell transplant is associated with 10 15% cure rate
- IMATINIB-RESISTANT CML dasitinib, nilotinib, and stem cell transplantation

**ESSENTIAL THROMBOCYTOSIS** aspirin, anagre lide (↓ platelet via stabilizing membrane), hydro xyurea, alkylating agents, <sup>32</sup>P

**MYELOFIBROSIS** splenectomy, interferon  $\alpha$ , thalidomide

#### TREATMENT ISSUES

#### RESPONSE CRITERIA FOR CML

- HEMATOLOGICAL RESPONSE
  - **COMPLETE RESPONSE** WBC  $< 10 \times 10^3 / \mu L$  with no immature granulocytes and < 5% basophils, pla telet  $< 450 \times 10^3 / \mu L$ , and non palpable spleen

#### TREATMENT ISSUES (CONT'D)

- PARTIAL RESPONSE persistence of immature cells in peripheral blood, platelets >450×10<sup>3</sup>/μL but <50% of pre treatment levels, or persistent sple nomegaly but <50% of pre treatment size</li>
- **CYTOGENIC RESPONSE** (FISH detection of the Phila delphia chromosome)
  - COMPLETE 0% Ph+ cells
  - PARTIAL 1 35% Ph+ cells
  - MAJOR complete and partial cytogenetic response
    - MINOR 36 65% Ph+ cells
    - MINIMAL 66 95% Ph+ cells
- MOLECULAR RESPONSE (bcr abl transcript detection by RT PCR)
  - **COMPLETE** negative
  - MAJOR bcr abl to control gene ratio <0.1 (3 log decrease in bcr abl transcript in peripheral blood)

### DEFINITION OF TREATMENT FAILURE FOR CML PATIENTS ON IMATINIB THERAPY

Months	Suboptimal	Failure
3	< CHR	No HR
6	< PCGR	< CHR, no CGR
12	< CCGR	< PCGR
18	< MMR	< CCGR
Anytime	ACA, loss of	Loss of CHR or
	MMR	CCGR

where HR=hematologic response, CHR=complete hematologic response, CGR=cytogenetic response, PCGR=partial cytogenetic response, CCGR=complete cytogenetic response, MMR=major molecular response, ACA=additional chromosomal abnormality MONITORING FOR CHRONIC MYELOGENOUS LEUKE MIA 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

NEJM 1999 341:14

#### HEMATOLOGIC MALIGNANCIES OVERVIEW

MYELO bone marrow. Myeloproliferative disor ders (PRV, CML, ET, and MF) involve cell accumula tion, while myelodysplastic disorders involve abnor mal bone marrow cell growth. Both disorders have risk of transformation to acute myeloid leukemia MYELOID neutrophils, monocytes, macro phages, eosinophils, basophils, mast cells, erythro cytes, platelets, and their precursors. Myeloid malignancies include AML and CML

#### HEMATOLOGIC MALIGNANCIES OVERVIEW (CONT'D)

**LYMPHOID** B cells, T cells, natural killer cells. Lymphoid malignancies include ALL, CLL, and all lymphomas

**LEUKEMIA** malignant cells in blood and/or bone marrow. May be myeloid (AML, CML) or lymphoid\* (LL/ALL, SLL/CLL) in origin. Myeloid leukemia sel dom presents in lymph nodes

ACUTE LEUKEMIA involves immature blast cells.
 More aggressive course

#### HEMATOLOGIC MALIGNANCIES OVERVIEW (CONT'D)

• CHRONIC LEUKEMIA involves mature differen tiated cells. More indolent course

**LYMPHOMA** malignancy of lymphoid origin and presents more in lymphoid organs

- HODGKIN'S LYMPHOMA B cell (Reed Sternberg cell)
- NON-HODGKIN'S LYMPHOMA B, T, or NK cells \*lymphoblastic lymphoma (LL) = acute lympho blastic leukemia (ALL). Small lymphocytic lymphoma (SLL) = chronic lymphocytic leukemia (CLL)

#### PATHOPHYSIOLOGY

#### **EPIDEMIOLOGY**

- **INCIDENCE** 1 2% of all cancers, 90% of all acute leukemias in adulthood, mean age 65
- MORTALITY 1.5% of all cancers

#### **RISK FACTORS FOR AML**

- FAMILY HISTORY family history (3×), Down's, Kli nefelter, Fanconi syndrome, Bloom's, ataxia telan giectasia, neurofibromatosis
- ENVIRONMENTAL previous chemotherapy (alkylat ing agents [melphalan, cyclophosphamide, chlor ambucil, temozolomide], topoisomerase II inhibitors [anthracyclines, etoposide]), radiation, benzene
- DISEASES MDS, MPS (PRV, CML, ET, MF), PNH, aplastic anemia

### DISTINGUISHING FEATURES BETWEEN TREAT MENT INDUCED AMLS

	Alkylating agents	Topoisomerase II inhibitors
Latency	5 7 years	2 3 years
MDS pre AML	Yes	No
AML types	All, M1 2	M4 5
Karyotype	5, 7	11q23, 21q22, inv16
Prognosis	Worse	Poor except for
		Inv16 karyotype

#### CLINICAL FEATURES

PANCYTOPENIA weakness, fatigue, infections, gingival bleed, ecchymosis, epistaxis, menorrhagia BONE PAIN ribs, sternum, long bones CUTANEOUS LESIONS leukemic cutis (especially M4, M5), chloromas (skin local collection of blasts, granulo cytic sarcoma especially M2), gum hypertrophy (M5) CNS LEUKEMIA (especially M4, M4EO, and M5) DIC associated with M3 subtype

**NOTE**: lymphadenopathy, hepatosplenomegaly not

#### INVESTIGATIONS

#### BASIC

 LABS CBCD, smear (Auer rods), lytes, urea, Cr, Ca, PO<sub>4</sub>, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibrinogen

#### INVESTIGATIONS (CONT'D)

 BONE MARROW BIOPSY (>20% BLASTS) WITH CYTO-GENETIC 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 MO 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 microgranu lar subtypes (M3v)
- FAB M4 acute myelomonocytic leukemia (AMML), including the variant AMML with abnor mal 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 cytoge netics or trisomy 8
- POOR RISK (15% 5 year survival, 78% relapse)
   adverse karyotypes include monosomy chromo
   some 5 or chromosome 7, del(5q), abn(3q26),
   t(6;9), 11q23 aberrations except for t(9;11), or mul
   tiple 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, radia tion, 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 survi val) or NOVE (mitoxantrone plus etoposide)

#### MANAGEMENT (CONT'D)

- CONSOLIDATION TREATMENT
  - COMPLETE REMISSION POST-INDUCTION
    - GOOD RISK chemotherapy IDAC or HDAC  $\times 3$
    - INTERMEDIATE RISK sibling donor allogeneic stem cell transplant (SCT) if available; other wise, consolidation chemotherapy
    - POOR RISK allogeneic SCT if matched donor avail able; 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. Other wise, palliation only
- RELAPSE allogeneic SCT if matched donor avail able (preferred); otherwise, salvage chemotherapy with cytarabine/carboplatin, clinical trials, or palliation

**AGE** >**60** individualized treatment. If unable to tol erate aggressive therapy, consider IDAC with attenu ated 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 com plete remission with induction chemotherapy, especially those with monoblastic phenotype. After induction, the remission rate in younger patients (<55 years) is 70 85%, but only 40 50% in older patients **ALLOGENEIC SCT** if HLA matched, may opt for consolidation chemotherapy while waiting for match donor. Allogeneic SCT has resulted in cure rates of 50 60% for recipients in 1st remission

#### SPECIFIC ENTITIES

**MYELODYSPLASTIC SYNDROME** (MDS) opposite of myeloproliferative disorders, decreased cell counts

SUBTYPES refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with multilineage dysplasia, refractory anemia with multilineage dysplasia and ringed sideroblasts, refractory anemia with excess blasts (RAEB) 5 10% blasts, refractory anemia with excess blasts in transformation (RAEB t) 10 19% blasts, MDS unclassified. RA and RARS are at low risk of transforming to AML (i.e. >20% blasts), while the rest are at high risk

#### SPECIFIC ENTITIES (CONT'D)

 DIAGNOSIS peripheral blood smear (RBC with abnormal morphologic features, dysgranulopoi esis with Pelger Huët deformity, nuclear atypia and hypogranulation, relative monocytosis), bone marrow biopsy

# INTERNATIONAL PROGNOSTIC SCORING SYSTEM FOR MYELODYSPLASTIC SYNDROMES Score 0 0.5 1 1.5 2 % blasts in <5 5 10 11 20 21 30 BM

Karyotype Good Med. Poor Cytopenia 0/1 2/3

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

Risk group	Score	Median survival
Low	0	5.7 years
Intermediate 1	0.5 1.0	3.5 years
Intermediate 2	1.5 2.0	1.2 years
High	≥2.5	0.4 year

• TREATMENTS transfusions, EPO, treat infections early, 5 azacytidine, lenalidomide, decitabine, allo geneic stem cell transplant (IPSS  $\geq$ 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 mainte nance 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 pulmon ary 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**

#### NEJM 2006 354:2

#### PATHOPHYSIOLOGY

#### HISTOLOGIC TYPE

- FAB L1 small, uniform lymphoblasts with indis tinct nucleoli
- FAB L2 larger, pleomorphic lymphoblasts with low nucleus to cytoplasm ratio and clear nucleoli
- FAB L3 large, pleomorphic lymphoblasts with basophilic cytoplasm, large nucleoli, vacuoles

#### WHO CLASSIFICATION

- PRECURSOR B CELL (L1, L2)
  - PRO-B ALL resembles an early stage of B cell
  - PRE-B-CELL ALL intracytoplasmic immunoglobulin
  - B-CELL ALL express surface immunoglobulin
- PRECURSOR T CELL (L1, L2)
- BURKITT-LIKE ALL (L3)

**RISK FACTORS FOR ALL** old age, previous che motherapy or radiation, Down's syndrome

#### CLINICAL FEATURES

**PANCYTOPENIA** weakness, fatigue, infections, gin gival bleed, ecchymosis, petechiae, epistaxis, menorrhaqia

**ORGAN INVOLVEMENT** lymphadenopathy, hepa tomegaly, splenomegaly, bone pain, cranial nerve palsies, headaches

**NOTE:** precursor B lymphoblastic lymphoma is asso ciated with lymphadenopathy/extranodal involve ment and < 25% blasts, while precursor T LBL is associated mediastinal mass and < 25% blasts

### DISTINGUISHING FEATURES BETWEEN AML AND ALL

	AML	Precursor ALL
Blasts	Larger	Small
Auer rods	+	
TdT		+
MPO	+	

#### INVESTIGATIONS

#### **BASIC**

- LABS CBCD, smear, lytes, urea, Cr, Ca, PO<sub>4</sub>, Mg, uric acid, albumin, urinalysis, LDH, INR, PTT, fibri nogen, flow cytometry of peripheral blood (immunophenotyping)
- BONE MARROW BIOPSY >25% blast, flow cyto metry for immunophenotyping, cytogenetic analysis (detection of BCR ABL fusion and chro mosomal abnormalities with pulsed field gel electrophoresis and/or RT PCR)
- 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 prog nosis, with a 5 year survival of 35%. Factors asso ciated with poorer survival include the following:

- CLINICAL lack of response to induction therapy (most important), old age, leukocyte count, CNS involvement
- CYTOGENETICS BCR ABL fusion or t(9;22) (also known as the Philadelphia chromosome, in 20 50% of adults), MLL AF4 fusion or t(4;11) (in 5 6% of adults), t(8;14), t(1;19), hypodiploidy ( < 45 chromosomes/cell), del(7), trisomy
- FAVORABLE PROGNOSIS hyperdiploidy, del(9), TEL AML1 fusion or t(12;21) (in 10% of adults)

#### RISK CATEGORIES

- HIGH RISK any of age >60, t(9;22) or bcr abl, t(4;11), t(1;19); WBC  $>30\times10^3/\mu L$  in B ALL or  $>100\times10^3/\mu L$  in T ALL or pro B ALL
- STANDARD RISK none of high risk features

  RISK FACTORS FOR CNS RELAPSE high risk
  genetic features, T ALL, large tumor burden, CSF
  positivity

#### MANAGEMENT

**REMISSION INDUCTION THERAPY** combination chemotherapy with prednisone, vincristine, an anthracycline  $\pm$  asparaginase, and cyclophospha mide. 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 con taining 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 mercaptopur ine daily, methotrexate weekly, vincristine and pre dnisone monthly) or dexamethasone for 2 3 years, except for patients who received allogeneic SCT

#### TREATMENT ISSUES

**SURVIVORSHIP ISSUES** risk of secondary malig nancies, neurologic sequelae, cardiotoxicity, inferti lity, depression, anxiety, and fatigue

#### **Related Topics**

Febrile Neutropenia (p. 236) Tumor Lysis Syndrome (p. 228)

#### **Chronic Lymphocytic Leukemia**

#### NEJM 2005 352:8

#### DIFFERENTIAL DIAGNOSIS OF LYMPHOCYTOSIS

#### NEOPLASTIC

- CHRONIC LYMPHOCYTIC LEUKEMIA (CLL, most com mon cause)
- PROLYMPHOCYTIC LEUKEMIA
- LEUKEMIC PHASE OF LYMPHOMAS mantle cell lym phoma, lymphoplasmacytic lymphoma, follicular lymphoma, marginal zone lymphoma, hairy cell leukemia
- LARGE GRANULAR CELL LYMPHOCYTE LEUKEMIA INFECTIONS pertussis, infectious mononucleo sis, 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 leu kemia 10%, diffuse large B cell lymphoma (Richter's transformation) 3 10%, Hodgkin's disease 0.5%, mul tiple 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, hypo gammaglobulinemia, monoclonal gammopathy

**SECOND MALIGNANCIES** non melanoma skin cancer 4.7%, sarcomas 3.3%, kidney 2.8%, lung 2%, prostate 1.5%

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, smear (smudge cells), lytes, urea, Cr, Ca, PO<sub>4</sub>, Mg, uric acid, LDH, β2 microglo bulin, albumin, quantitative immunoglobulin, serum protein electrophoresis, urinary protein electrophoresis
- PERIPHERAL BLOOD FLOW CYTOMETRY FOR SURFACE MARKERS

#### SPECIAL

- BONE MARROW BIOPSY
- LYMPH NODE BIOPSY
- MICROBIOLOGY monospot test, hepatitis serol ogy if need to rule out other causes

#### DIAGNOSTIC AND PROGNOSTIC ISSUES

#### NCI WORKING GROUP DIAGNOSTIC CRITERIA

- PERIPHERAL BLOOD absolute lymphocyte count in the >5×10<sup>3</sup>/µL, with ≥1 B cell marker (CD19, CD20, CD23) and CD5; >55% atypical cells
- BONE MARROW a normocellular to hypercellular marrow with >30% lymphocytes. Interstitial/nod ular pattern (70%) has a better prognosis than diffuse/extensive pattern (30%)
- IMMUNOPHENOTYPE CD5+, CD19+, CD20+, CD23+, CD43+, CD10 , Slq+
- NOTE for patients with lymphocyte count 5 10×10<sup>3</sup>/μL, lymphocyte phenotyping is required

#### **RAI STAGING**

- 0 lymphocytosis in blood or bone marrow. Median survival >150 months
- lymphocytosis + lymphadenopathy. Median survival 101 months
- II lymphocytosis + organomegaly. Median survival 71 months
- III lymphocytosis + anemia ( <110 g/L [ <11 g/dL]). Median survival 19 months
- IV lymphocytosis + thrombocytopenia (<100 ×10<sup>3</sup>/mL). Median survival 19 months

Hodgkin's Lymphoma 171

#### 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 $\times$ 10 $^3$ / $\mu$ L). Median survival 2 years

**ADVERSE PROGNOSTIC FACTORS OF CLL** higher Rai stage, high Binet stage, diffuse pattern on bone marrow biopsy, lymphocyte doubling time <1 year (5 year survival vs. 12 year survival), CD38+, unmu tated IgV<sub>H</sub> genes, ZAP70 positive, P2X7 receptor, p53 mutation, gene 1513A/A genotype, 17p deletion, 11q deletion, trisomy 12

**FEATURES SUGGESTIVE OF TRANSFORMA TION** *new onset* localized lymph node enlarge ment, 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 + allo geneic 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** (chlor ambucil, 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 (weak ness, painful lymphadenopathy, B symptoms, sympto matic splenomegaly), anemia (Hb < 110 g/L [<11 g/ thrombocytopenia (platelets  $< 100 \times 10^3 / \mu L$ ), autoimmune hemolytic anemia/thrombocytopenia that failed steroids, progressive disease (increasing lym phocytosis with doubling time <6 months  $\pm$  rapidly enlarging lymph nodes, spleen, and liver). If evidence of

#### MANAGEMENT (CONT'D)

Richter's transformation, treat as aggressive lym phoma with CHOPR

**NOTE** while traditionally SLL has been managed as a low grade non Hodgkin's lymphoma, it is identical to CLL and should be treated as such

#### TREATMENT ISSUES

### NCI WORKING GROUP DIAGNOSTIC CRITERIA FOR TREATMENT RESPONSE

- COMPLETE RESPONSE normal physical examination and no symptoms. Lymphocytes ≤4 ×10³/μL, neutrophils ≥1.5×10³/μL, platelets >100×10³/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 ≥1.5×10<sup>3</sup>/μL, platelets >100×10<sup>3</sup>/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 cyto plasmic projections giving a hairy appearance.
   Secretes fibronectin, cytokines, and TNF causing bone marrow fibrosis
- CLINICAL FEATURES splenomegaly (90%), cytope nia (fatigue, recurrent infections, thrombocytope nia), and leukocytosis. Lymphadenopathy is uncommon
- TREATMENTS treat only if symptomatic (cytope nia, 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 lym phoma characterized by the presence of Reed Sternberg cells. CD15 and CD30 positive. Spreads in orderly fashion to contiquous nodal regions

#### PATHOPHYSIOLOGY (CONT'D)

 NODULAR SCLEROSIS (70%) more common in females, above diaphragm involvement (mediastinal mass). Three grades include lymphocyte predominant (G1), mixed (G2), and syncytial (G3) 172 Hodgkin's Lymphoma

#### 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 LYM-PHOMA (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, hepatosplenome galy, mediastinal/abdominal/pelvic masses may cause local destruction, obstruction, and compression
- **HEMATOLOGIC** anemia, thrombocytopenia, lym phocytosis, 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 (paraneoplas tic cerebellar degeneration, chorea, limbic ence phalitis, subacute sensory neuropathy, subacute lower motor neuropathy, stiff man syndrome), renal (minimal change disease, FSGS), hypercalcemia

### DISTINGUISHING FEATURES BETWEEN MALIGNANT AND NON MALIGNANT LYMPHADENOPATHY

	Malignancy	Benign
Size	Larger, grows	Smaller
Consistency	Rubbery, firm	Soft
Mobility	Immobile	Mobile
Matted	Yes	No
Tenderness	No	Yes

#### STAGING

### COTSWOLDS STAGING (MODIFIED FROM ANN ARBOR STAGING)

- I Single node region or lymphoid structure (spleen, thymus, Waldeyer's ring)
- II Two or more node regions on the same side of diaphragm. All nodal disease within the mediastinum is considered to be a single lymph node region and hilar involvement constitutes an additional site of involvement. The number of anatomic regions should be indicated by a subscript (e.g. II 2)
- III Involvement on both sides of diaphragm.

  III 1 indicates involvement of the spleen or splenic hilar, celiac, or portal nodes. Stage III 2 indicates involvement of the paraaortic, iliac, inguinal, or mesenteric nodes
- IV Diffuse or disseminated foci of involvement of one or more extralymphatic sites (e.g. bone marrow, extranodal sites that cannot be included in one radiation field)

#### DESIGNATIONS

- E extralymphatic site (i.e. involvement outside of lymph nodes, spleen, thymus, and Waldeyer's ring) or involvement by direct extension
- X bulky disease defined as mediastinal mass >1/3
   of internal transverse diameter of the thorax at the
   level of T5/6 interspace or >10 cm [>3.9 in.] 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 $\times$ 10<sup>3</sup>/ $\mu$ L, platelets <125 $\times$ 10<sup>3</sup>/ $\mu$ L
- ENT EXAMINATION stage IA or IIA with upper cervical lymph node involvement
- MRI SPINE if suspect spinal cord compression
- **MUGA SCAN** evaluate cardiac function prior to anthracycline therapy
- GALLIUM SCAN stage IA or IIA without intrathor acic involvement

#### PROGNOSTIC ISSUES

PROGNOSTIC FACTORS FOR EARLY STAGE DIS EASE age >50, bulky disease, ESR >50 mm/h without B symptoms or ESR >30 mm/h with B symptoms, anemia

#### INTERNATIONAL PROGNOSTIC FACTOR PROJECT SCORE FOR ADVANCED HODGKIN'S LYMPHOMA (HASENCLEVER SCORE)

- FACTORS age >45, male gender, Ann Arbor clin ical stage IV, albumin <40 g/L [<4 g/dL], hemoglobin <105 g/L [<10.5 g/dL], WBC >15 $\times$ 10<sup>3</sup>/ $\mu$ L, lymphocyte <0.6 $\times$ 10<sup>3</sup>/ $\mu$ L, or <8% of total WBC count
- **scoring** 1 point per factor, with a score of 0 7
- UTILITY the 5 year progression free survival was 84, 77, 67, 60, 51, 42% for scores of 0, 1, 2, 3, 4, and 5 7, respectively

#### MANAGEMENT

LIMITED STAGE (stage IA, IIA, and IB in some institutions, 30%) ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) x2 cycles. PET scan afterward, if complete remission, 2 more cycles; otherwise, give involved field radiation. If stage IA low bulk high neck (above hyoid) or epitrochlear nodular lymphocyte predominant disease, involved field radiation only ADVANCED STAGE (70%) ABVD ×6 cycles. Reas

sess with CT and/or PET scan. If residual disease, con

sider involved field irradiation. Alternative regimens

#### MANAGEMENT (CONT'D)

include BEACOPP (bleomycin, etoposide, doxorubi cin, cyclophosphamide, vincristine, procarbazine, pre dnisone) combined with involved field radiotherapy or Stanford V regimen (doxorubicin, vinblastine, mechlorethamine, vincristine, bleomycin, etoposide, prednisone) combined with involved field radiotherapy

**REFRACTORY OR RELAPSED DISEASE** high dose chemotherapy with CBV (cyclophosphamide, BCNU, etoposide) or BEAM (BCNU, etoposide, cytarabine, melphalan) and irradiation plus autologous stem cell transplant. Overall, 40 50% of refractory disease and 60 70% of first relapse can be cured

#### TREATMENT ISSUES

**INDICATIONS** FOR AUTOLOGOUS STEM CELL TRANSPLANT progression during first line che motherapy, relapse <1 year after completion of che motherapy, relapse with B symptoms or extranodal sites. Patients with relapse >1 year or only in pre viously unirradiated lymph nodes may or may not require transplant

**FOLLOW UP** every 3 months for the first 2 years, every 6 months for the next 3 years, then annually. Pay particular attention to relapse (10 30%), hypothyroidism (50%), dental caries, and second malignancies (breast, lung, esophageal, stomach, thyroid, melanoma, cervical, AML)

#### Non-Hodgkin's Lymphoma

#### DIFFERENTIAL DIAGNOSIS OF LYMPHADENOPATHY

#### INFECTIONS

- BACTERIAL local infections, brucellosis, leptospiro sis, 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, autoim mune lymphoproliferative disease

INFLAMMATORY RA, SLE, dermatomyositis, Still's disease, Churg Strauss syndrome
INFILTRATIVE sarcoidosis, amyloidosis, histiocy tosis, 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 centro blasts/high power field), IIIA (>15 centroblasts/high power field, centrocytes present)
  - MARGINAL ZONE LYMPHOMA (MZL, 5%) MALT, nodal, splenic
  - MANTLE CELL LYMPHOMA (MCL, 7%) mantle zone, nodular, diffuse, blastoid variant
  - SMALL LYMPHOCYTIC LYMPHOMA (SLL, 5 10%) identical to chronic lymphocytic leukemia in pathologic characteristics, but treated as low grade B cell lymphoma

#### PATHOPHYSIOLOGY (CONT'D)

- HAIRY CELL LEUKEMIA (HCL)
- LYMPHOPLASMACYTIC LYMPHOMA (LPL, 2 3%) previously Waldenstrom's macroglobulinemia
- PLASMA CELL MYELOMA/PLASMACYTOMA (MM)
- AGGRESSIVE B-CELL LYMPHOMAS
  - FOLLICULAR LYMPHOMA (FL) grade IIIB (sheets of centroblasts)
  - DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL, 30 40%) clinical subtypes include primary mediastinal B cell lymphoma, primary effusion lymphoma (HHV8), and intravascular B cell lymphoma. Pathologic subtypes include T cell rich B cell lymphoma, anaplastic large cell lymphoma, centroblastic, and immunoblastic
  - DOUBLE-HIT DLBCL (both c myc and bcl2 translocations)
- LEUKEMIC B-CELL LYMPHOMAS
  - BURKITT'S LYMPHOMA (BL)
  - PRECURSOR B LYMPHOBLASTIC LYMPHOMA (ALL)
- INDOLENT T-CELL LYMPHOMAS
  - MYCOSIS FUNGOIDES (mf)
  - PRIMARY CUTANEOUS ANAPLASTIC LARGE CELL (PCALC)
  - LYMPHOPROLIFERATIVE DISEASE OF LARGE GRANU-LAR LYMPHOCYTES (LGL)
- INDOLENT NATURAL KILLER CELL LYMPHOMAS
  - NATURAL KILLER CELL LARGE GRANULAR LYMPHO-CYTE LEUKEMIA (NK LGL)
- AGGRESSIVE T-CELL LYMPHOMAS
  - PERIPHERAL T-CELL LYMPHOMA, NOT OTHERWISE SPECIFIED (PTCL NOS)
  - PERIPHERAL T-CELL LYMPHOMA, SPECIFIED
    angioimmunoblastic (AlLD++ type), nasal
    T/NK cell type, subcutaneous panniculitic,
    intestinal enteropathy associated, hepatosple
    nic, anaplastic large cell including null cell
- LEUKEMIC T-CELL LYMPHOMAS
  - ADULT T-CELL LYMPHOMA/LEUKEMIA (HTLV)
  - PRECURSOR T LYMPHOBLASTIC
  - LEUKEMIA/LYMPHOMA

#### RISK FACTORS

- FAMILY HISTORY
- ENVIRONMENTAL previous immunosuppressive therapy, radiation, allogeneic stem cell transplant, pesticides, agricultural chemicals, smoking, hair dyes, geography (e.g. risk of Burkitt's lymphoma is 50× higher in Africa than in the USA)
- DISEASES infections (HIV, EBV, HHV8, HCV, HTLV, Helicobacter pylori), inflammatory disorders (RA, SLE, Sjogren's syndrome, mixed cryoglobulinemia, inflammatory bowel disease), inherited immune defects

#### PATHOPHYSIOLOGY (CONT'D)

#### CLASSIC TRANSLOCATIONS IN LYMPHOMA

- MANTLE CELL LYMPHOMA t(11;14) in 95%, cyclin D1 (bcl1)
- FOLLICULAR LYMPHOMA t(14;18) in 85%, anti apoptotic protein (bcl2)
- DIFFUSE LARGE CELL LYMPHOMA t(3;14) in 40%, zinc finger transcription factor (bcl6)
- MALT t(1;14) in < 5%, bcl10
- **BURKITT'S LYMPHOMA** t(8;14), t(2;8), or t(8;22) in 100%, c myc

#### INFECTIONS AND LYMPHOMA

- EBV Hodgkin's lymphoma, Burkitt lymphoma, post transplant lymphoproliferative disorders, pri mary CNS lymphoma
- HCV splenic marginal zone lymphoma
- HHV8 Castleman disease, primary effusion lymphoma
- HIV primary CNS lymphoma
- HTLV adult T cell leukemia/lymphoma
- BORRELIA BURGDORFERI cutaneous marginal zone lymphoma
- CAMPYLOBACTER JEJUNI small bowel marginal zone lymphoma
- CHLAMYDIA PSITACCI eye marginal zone lymphoma
- H. PYLORI gastric MALT

#### TRANSFORMATION OF INDOLENT LYMPHOMA

10% of SLL, MZL, and LPL and 60% of FL eventually transform into aggressive DLBCL. Features suggestive of transformation include rapid local progression, progression at unusual extranodal sites (CNS, lungs, soft tissue), acute rise in LDH, hypercalcemia, and new onset B symptoms

#### CLINICAL FEATURES

#### SYMPTOMS

- MASS EFFECT lymphadenopathy (occipital, posterior auricular, preauricular, mandibular, submental, cervical, supra and infraclavicular, Waldeyer's ring (tonsils, base of tongue, nasopharynx), epitrochlear, axillary, inguinal, popliteal), hepatosplenomegaly, mediastinal/abdominal/pelvic/testicular/CNS masses may cause local destruction, obstruction, and compression
- HEMATOLOGIC anemia, thrombocytopenia, lympho cytosis
- 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 lym phoma, particularly if B symptoms or multisystem involvement

#### STAGING

**TUMOR BURDEN** a combination of stage, bulki ness (>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
- 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 Wal deyer's ring) or involvement by direct extension
- **S** splenic involvement
- A no B symptoms
- **B** weight loss >10% over 6 months, fever >38°C [100.4°F], drenching night sweats

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, peripheral smear, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, PO<sub>4</sub>, 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

#### 

#### INTERNATIONAL PROGNOSTIC INDEX (IPI)

FACTORS age >60, serum LDH >normal, ECOG performance status ≥2, Ann Arbor clinical stage III or IV, extranodal disease sites ≥2 (defined as involvement of organs other than lymph nodes, spleen, thymus, and Waldeyer's ring)

#### DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- **SCORING** 1 point per factor, with a score of 0 5
- UTILITY 5 year overall survival approximately 73%, 51%, 43%, and 26% for IPI of 0 1, 2, 3, and 4 5. With the new revised IPI (post rituximab era), 5 year overall survival 94%, 79%, and 55% for IPI of 0, 1 2, and 3 5, respectively

### FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI)

- FACTORS age >60, serum LDH >normal, hemo globin <120 g/L [<12 g/dL], Ann Arbor clinical stage III or IV, involved nodal sites >4
- **scoring** 1 point per factor, with a score of 0 5
- UTILITY for follicular lymphoma patients specifically; 5 year survival approximately 91%, 78%, and 52% for FLIPI of 0 1, 2 and 3 5, respectively

#### MANAGEMENT

#### INDOLENT LYMPHOMAS

- LIMITED STAGE (IA or IIA, 10%) radiation (10 year survival 50%)
- ADVANCED STAGE (IB, IIB, III, IV, or any bulky disease, 90%) if asymptomatic (40%), watchful waiting. If symptomatic or threatening disease (60%), CVPR ×8 cycles (cyclophosphamide, vincristine, predni sone, 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<sup>131</sup> tositumomab, and Y<sup>90</sup> ibritumomab. Stem cell transplant in fit individuals

#### AGGRESSIVE LYMPHOMAS

- LIMITED STAGE (IA or IIA, 30%) CHOPR (cyclopho sphamide, doxorubicin, vincristine, prednisone, rituximab) ×3 cycles. PET scan afterwards, if com plete remission, one more cycle; otherwise, give involved field radiation
- ADVANCED STAGE (IB, IIB, III, IV, or any bulky disease, 70%) CHOPR ×6. PET scan afterwards, if local residual disease, give involved field radiation; if diffuse residual disease, consider salvage therapy (see below). For patients with bone marrow/per ipheral blood involvement, intrathecal che motherapy 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 | or ||, non bulky | <5 cm, no bone marrow/blood/CNS

#### MANAGEMENT (CONT'D)

disease and normal LDH), give CODOX MR (cyclo phosphamide, doxorubicin, vincristine, metho trexate, 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 treat ment. 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 (hydra tion, 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/cytara bine regimen. All patients should receive tumor lysis syndrome prophylaxis (hydration, allopurinol)

#### TREATMENT ISSUES

#### INTERNATIONAL WORKSHOP CRITERIA FOR TREATMENT RESPONSE FOR HODGKIN'S AND NON HODGKIN'S LYMPHOMA

**COMPLETE REMISSION** (CR) disappearance of all evidence of disease

- Nodal masses: if FDG avid or PET positive prior to therapy, mass of any size permitted if PET negative. If variably FDG avid or PET negative, regression to normal size on CT required
- **Liver and spleen:** not palpable, nodules disappeared
- Bone marrow: infiltrate cleared on repeat biopsy; if indeterminate by morphology, immu nohistochemistry should be negative

**PARTIAL REMISSION** (PR) regression of measur able disease and no new sites

- Nodal masses: ≥50% decrease in sum of the product of the diameter (SPD) of up to 6 largest dominant masses; no increase in size of other nodes. If FDG avid or PET positive prior to ther apy, one or more PET positive at previously involved site; or if variably FDG avid or PET negative, regression on CT ≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter)
- Liver and spleen: no increase in size

#### TREATMENT ISSUES (CONT'D)

• **Bone marrow:** irrelevant if positive prior to therapy; cell type should be specified

STABLE DISEASE (SD) failure to attain CR/PR or PD

 Nodal masses: if FDG avid or PET positive prior to therapy, PET positive at prior sites of disease and no new sites on CT or PET. If variably FDG avid or PET negative, no change in size of pre vious lesions on CT

#### RELAPSED DISEASE (RD) OR PROGRESSIVE DIS

**EASE** (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, ≥50% increase in SPD of more
  than one node, or ≥50% increase in longest dia
  meter of a previously identified node >1 cm in short
  axis. Lesions PET positive if FDG avid lymphoma or
  PET positive prior to therapy
- Liver and spleen: >50% increase from nadir in the SPD of any previous lesions
- Bone marrow: new or recurrent involvement

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#### SPECIFIC ENTITIES

### EYE LYMPHOMA • PATHOPHYSIOLOGY periorbital in

- 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 con fined to CNS. May have leptomeningeal or intrao cular involvement. Frequently aggressive B cell lymphoma
- CLINICAL FEATURES focal neurological deficit, per sonality change, mild dementia, persistent headache
- DIAGNOSIS CT or MRI head, lumbar puncture, slit lamp examination. If CNS lymphoma in the differ ential, try to avoid giving steroids before biopsy
- TREATMENTS high dose corticosteroid with high dose methotrexate is preferred. Whole brain radia tion represents an alternative. Prognosis is 60% 2 year survival and 30% 5 year survival

#### LEPTOMENINGEAL MENINGITIS

 RISK FACTORS aggressive lymphomas (lympho blastic lymphoma, DLBCL, Burkitt's lymphoma, MCL), extranodal sites involvement (bone marrow, testicular, paranasal, retroperitoneal lymph nodes), any of the five IPI prognostic factors

#### SPECIFIC ENTITIES (CONT'D)

- CLINICAL FEATURES jaw pain and numbness, radi cular pain, back pain, neck pain/rigidity, confusion, cranial nerve deficits (especially II, III, V, VI, VII), focal weakness, sensory changes, headaches
- DIAGNOSIS lumbar puncture with positive cytol ogy (sens 60% with single attempt, 3 attempts for increased yield), gadolinium enhanced MRI show ing enhancement and enlargement of one or more cranial nerves due to tumor infiltration
- TREATMENTS high dose steroid (dexamethasone 12 20 mg PO/IV daily), radiation to the site of disease, intrathecal methotrexate, or cytarabine. Important to treat underlying systemic disease. Highly selected patients may benefit from high dose chemotherapy with stem cell transplantation with better outcomes. Median survival after CNS recurrence is 3 months

#### LOCALIZED PARANASAL SINUS LYMPHOMA

- PATHOPHYSIOLOGY usually DLBCL type. May involve CNS if invade through the base of skull
- CLINICAL FEATURES local pain, rhinorrhea, nasal or upper airway obstruction, facial swelling, epistaxis, diplopia, visual loss
- **TREATMENTS** CHOPR×3 + involved field radiation + intrathecal chemotherapy×6

#### MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT)

- PATHOPHYSIOLOGY extranodal marginal zone B cell lymphomas that present with localized disease involving the GI tract, salivary glands, thyroid, orbit, conjunctiva, breast, and lung. Note that diffuse large cell lymphoma and mantle cell lymphoma also commonly involve GI mucosa
- ASSOCIATIONS H. pylori associated chronic gastri tis, celiac disease, crohn's disease, gastrointestinal nodular lymphoid hyperplasia
- **DIAGNOSIS** for gastric MALT, need to determine presence of  $\it{H. pylori}$  by biopsy (gastroscopy)  $\pm$  urea breath test
- TREATMENTS for H. pylori positive gastric MALT, triple therapy may be adequate. Need to confirm eradication of H. pylori. Follow closely with gastro scopy. If MALT persists for over 8 12 months, should consider single agent chemotherapy (cyclophosphamide, chlorambucil) or involved field radiation. Partial gastrectomy may be needed for hemorrhage or perforation

#### ACUTE LYMPHOBLASTIC LYMPHOMA

- PATHOPHYSIOLOGY continuum of presentation with acute lymphoblastic leukemia. Considered lymphoma if < 5% blasts in bone marrow; other wise, considered leukemia
- CLINICAL FEATURES usually mediastinal mass in young males

#### SPECIFIC ENTITIES (CONT'D)

#### BURKITT'S LYMPHOMA

- PATHOPHYSIOLOGY t(8;14) leading to c myc overexpression
- CLINICAL FEATURES usually advanced stage (80 90%). Abdominal mass, CNS, breast/ovarian involvement, and nodal sites but mediastinum usually spared

#### **TESTICULAR LYMPHOMA**

- PATHOPHYSIOLOGY 60% primary testicular lym phoma, 40% spread from other sites. Frequently DLBCL or immunoblastic subtype
- CLINICAL FEATURES painless testicular mass in older man. High risk for recurrence, particularly CNS relapse
- DIAGNOSIS scrotal U/S
- TREATMENTS unilateral orchiectomy + CHOPR + involved field radiation to scrotum + intrathecal chemotherapy if stage III/IV disease

### POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

- PATHOPHYSIOLOGY mostly of host origin and usually EBV positive (LMP 1 oncogene). EBV nega tive PTLD present later and are more aggressive than EBV positive PTLD. Mostly B cell non Hodg kin's lymphoma and very rarely T cell or NK cell lymphomas
- RISK FACTORS high degree of immunosuppres sion, pre transplant EBV negativity. Risk highest in the first year, then reduces by 80%
- CLINICAL FEATURES clinical spectrum includes reactive plasmacytic hyperplasia (55%, infectious mononucleosis like illness with no malignant trans formation), polymorphic B cell hyperplasia (30%, polyclonal cytogenetic abnormalities, immunoglo bulin gene rearrangements, and disruption of underlying tissue architecture), and B or T cell lymphomas (15%, monoclonal malignancy)
- TREATMENTS reduction in immunosuppression (may be sufficient for hyperplasia without mono clonal component), rituximab, chemotherapy (CHOP), antiviral agents, IVIG, surgical resection, radiation, interferon α. Overall survival 25 35%. Prognostic factors include advanced age, perfor mance status >1, involved site >1

#### MYCOSIS FUNGOIDES

- PATHOPHYSIOLOGY indolent cutaneous T cell lym phoma. Stages include premycotic, plaque, and tumor stage. Sezary syndrome is a variant of myco sis fungoides with a triad of erythroderma, lym phadenopathy, and leukemia
- CLINICAL FEATURES localized patches or plaques evolving into nodules and diffuse exfoliative ery throderma associated with abnormal circulating cells. Poor prognostic factors include extensive

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#### SPECIFIC ENTITIES (CONT'D)

cutaneous disease (erythroderma), nodal spread, and extracutaneous involvement (liver, spleen, lung, GI tract)

 TREATMENTS topical corticosteroids, topical nitro gen 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, clus terin 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

#### SPECIFIC ENTITIES (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

#### **CASTLEMAN'S DISEASE**

- PATHOPHYSIOLOGY lymphoid proliferation asso ciated with POEMS syndrome, lymphomas (Hodg kin's, non Hodgkin's), and Kaposi's sarcoma. HIV and HHV8 common in multicentric subtype
- CLINICAL FEATURES unicentric (isolated lymphadeno pathy, 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. Sur vival 8 14 months)

#### **Multiple Myeloma**

NEJM 1997 336:23 NEJM 2004 351:18

#### TYPES OF PLASMA CELL DYSCRASIAS

**MULTIPLE MYELOMA** (75%) malignant clone extends from pre B cell to plasma cell stage of differentiation. May produce IgG (60%), IgA (20%), or light chains (15%)

WALDENSTROM'S MACROGLOBULEMIA (20%) proliferation of plasmacytoid lymphocytes (cell type that occurs earlier than plasma cell). Produces IgM. Now classified as lymphoplasmacytic lymphoma

**HEAVY CHAIN DEPOSITION DISEASE** IgA, IgG, or IgM heavy chain

**LIGHT CHAIN DEPOSITION DISEASE**  $\kappa$  or  $\lambda$  light chain

**AL (PRIMARY) AMYLOIDOSIS**  $\lambda$  or  $\kappa$  light chain

#### light Chain

#### PATHOPHYSIOLOGY EPIDEMIOLOGY

- INCIDENCE 1%
- MORTALITY 1%

#### **RISK FACTORS**

- PERSONAL old age, black race
- DISEASES chronic polyclonal hypergamma globulinemia
- TREATMENT radiation

#### CLINICAL FEATURES

#### **SYMPTOMS**

 PANCYTOPENIA weakness, fatigue, infections, gin gival bleed, ecchymosis, epistaxis, menorrhagia

#### CLINICAL FEATURES (CONT'D)

- LYTIC BONE LESIONS pain, fractures
- HYPERCALCEMIA weakness, nausea, abdominal pain, polyuria, altered mental status
- NEUROLOGIC peripheral neuropathy from amyloi dosis, plasma cell infiltration of the meninges, cord compression, or radiculopathy from vertebral osteolytic lesions ± plasmacytoma
- RENAL FAILURE
  - PRE-RENAL N&V, renal vein thrombosis, Ca induced vasospasm
  - RENAL myeloma kidney (tubulointerstitial damage from increased light chain absorption at proximal tubule), plasma cell infiltration, Bence Jones/cast nephropathy, amyloidosis (λ), light chain deposition disease (κ), hypercalcemia (nephrogenic DI), cryo globulinemia, pyelonephritis, sepsis
  - POST-RENAL renal stones (uric acid), neuro genic bladder
- constitutional anorexia, fatigue, weight loss

#### INVESTIGATIONS

#### **BASIC**

 LABS CBCD, peripheral smear, lytes, urea, Cr, Ca, β2 microglobulin, serum viscosity, quantita tive immunoglobulin, albumin, serum protein electrophoresis (reciprocal depression), urinary Multiple Myeloma 179

#### INVESTIGATIONS (CONT'D)

protein electrophoresis, 24 h urinary collection for Bence Jones protein

- IMAGING skeletal survey
- BONE MARROW BIOPSY
- NOTE: light chain myeloma (20%) may have nor mal serum protein electrophoresis. Urinary Bence Jones protein (urine protein electrophor esis) is required to detect paraproteinemia; non secretatory myeloma (3%) requires bone mar row biopsy for diagnosis

#### **Related Topics**

Amyloidosis (p. 420) Renal Failure (p. 68)

#### DIAGNOSTIC AND PROGNOSTIC ISSUES

### INTERNATIONAL MYELOMA WORKING GROUP CRITERIA

- MULTIPLE MYELOMA
  - BONE MARROW PLASMA CELLS/PLASMACYTOMA no percent specified, but usually >10%
  - M-PROTEIN in serum and/or urine, no concentration specified, but >30 g/L [>3 g/dL] in serum if overt myeloma
  - TISSUE IMPAIRMENT ★CRAB★ increased calcium (>2.75 mmol/L [>11 mg/dL]), renal insufficiency (Cr >173 mmol/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 neces sary if bone marrow plasma cells>10%)
  - TISSUE IMPAIRMENT no symptoms
- MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIF-ICANCE (MGUS)
  - BONE MARROW PLASMA CELLS <10% (bone marrow biopsy is not required for suspected MGUS if M protein ≤15 g/L [≤1.5 g/dL], IgG subtype, and patient asymptomatic)
  - M-PROTEIN < 30 g/L[<3g/dL]
  - TISSUE IMPAIRMENT no symptoms
  - COURSE occurs in 2% of population over age 50 and 3% over age 70. Rate of transformation to malignant plasma cell disorder (multiple mye loma, Waldenstrom's macroglobulinemia, pri mary amyloidosis, B cell lymphoma, or chronic lymphocytic leukemia) is about 1% per year

NEJM 2006 355:26

#### DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

#### **DIAGNOSTIC CLUES**

- SYMPTOMS the presence of tissue impairment suggests either multiple myeloma (usually high M protein) or amyloidosis (usually low M protein). AL amyloidosis is characterized by insoluble, toxic amyloid precursor (light chains) aggregates that deposit in tissues in antiparallel β pleated sheet configuration. The absence of symptoms suggests MGUS or SMM
- QUANTITATIVE IG typically decreased serum levels of normal polyclonal immunoglobulins in multiple myeloma. However, this may also occur in MGUS
- BENCE JONES PROTEINURIA the presence of monoclonal light chains (especially >1 g/day) in the urine suggests multiple myeloma. However, small amounts (<50 mg/day) may also occur in MGUS
- SERUM M PROTEIN LEVEL the higher the level, the higher the likelihood of multiple myeloma. Some define 35 g/L [3.5 g/dL] for IgG and 20 g/L [2 g/dL] for IgA as cutoff, others define 30 g/L [3 g/dL] regardless of Ig subtype as cutoff

#### **DURIE SALMON STAGING FOR MULTIPLE MYELOMA**

- STAGE I (low tumor burden,  $<0.6\times10^{12}/\text{m}^2$ ) all of Hb >100 g/L [>10 g/dL],  $\text{Ca}^{2+}\leq 2.6$  mmol/L [ $\leq 10.4$  mg/dL], bones normal or solitary bone plasmacytoma only,  $\log < 50$  g/L [< 5 g/dL],  $\log < 30$  g/L [< 3 g/dL], and urinary  $\lambda$  or  $\kappa$  chains < 4 g/day. Median survival  $\sim 60$  months
- STAGE II (intermediate burden, 0.6 1.2×10<sup>12</sup>/ m<sup>2</sup>) between stages I and III. Median survival ~30 months
- STAGE III (high tumor burden, >1.2×10<sup>12</sup>/m²) any of Hb <85 g/L [<8.5 g/dL],  $Ca^{2+}$  >2.6 mmol/L [>10.4 mg/dL], >3 lytic lesions, plus one of IgG >70 g/L [>7 g/dL], IgA >50 g/L [>5 g/dL], or urinary  $\lambda$  or  $\kappa$  chains >12 g/day. Median survival ~15 months
- SUBSTAGES A (Cr  $<175~\mu mol/L~[<1.9~mg/dL])$  and B (renal failure with Cr  $>175~\mu mol/L~[>1.9~mg/dL])$

## PROGNOSTIC FACTORS FOR MULTIPLE MYE LOMA β2 microglobulin, albumin, platelet, creati nine, 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
- **STAGE III** β2 microglobulin ≥5.5 mg/L. Median survival 29 months

JCO 2005 23:15

#### MANAGEMENT

#### MULTIPLE MYELOMA

- AGE < 65 AND OTHERWISE HEALTHY (curative) induction chemotherapy with thalidomide plus dexamethasone (first choice), lenalidomide plus dexamethasone, pulse dexamethasone, or VAD (vincristine, doxorubicin, dexamethasone) × 3 4 months. If good response, then proceed to high dose melphalan followed by autologous stem cell transplant. This regimen prolongs survival by 12 months, but is not curative. Consider tandem transplantation if less than a good partial response (i.e. ≤90% reduction of monoclonal protein)
- AGE >65 OR COMORBIDITIES (palliative) MP (mel phalan + prednisone) ± thalidomide. Addition of interferon to MP provides small benefit. If bony disease, add bisphosphonate (alendronate, zole dronate). Second line options include thalido mide (response ~30%) + dexamethasone, lena lidomide + dexamethasone, bortezomib (response ~30%), dexamethasone alone, and infusional VAD
- SUPPORTIVE MEASURES hydration (>3 l/day), hypercalcemia (hydration, prednisone 25 mg PO QID, pamidronate), renal insufficiency (treat underlying cause), infections (antibiotics, consider IVIG as last resort if recurrent infections despite prophylactic antibiotics), skeletal lesions (pami dronate 90 mg IV over 2 h q3 4weeks, radiation, vertebroplasty), anemia Hb < 90 g/L [<9 g/dL] (transfusions, usually respond to an erythropoiesis stimulating agent, although one should exercise great caution given the increased risk of throm boembolism and death), hyperviscosity syn drome (Ostwald viscosimeter >5, plasmapheresis), anticoagulation (if on thalidomide/lenalidomide and chemotherapy)

#### MANAGEMENT (CONT'D)

**SMM** no treatment. Follow clinically **MGUS** no treatment. Follow clinically

#### TREATMENT ISSUES

INDICATIONS FOR TREATING MULTIPLE MYE LOMA >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 mono clonal 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 (hyperpig mentation, hypertrichosis, acrocyanosis, plethora, hemangioma/telangiectasia). Polyneuropathy and monoclonal plasma cell disorder most important

**HYPERVISCOSITY SYNDROME** IgG >70 g/L [>7 g/dL] or IgA >50 g/L [>5 g/dL]. Symptoms include fatigue, changes in mental status, focal or non focal neurologic changes, visual changes along with reti nopathy, angina pectoris, bleeding disorder, cryoglo bulin, Raynaud's phenomenon, or purpuric eruptions on exposure to the cold

#### Febrile Neutropenia

See FEBRILE NEUTROPENIA (p. 236)

#### Hematopoietic Stem Cell Transplant

CMAJ 2004 170:10 NEJM 2006 354:17

#### TERMINOLOGIES

**ALLOGENEIC TRANSPLANTATION** (40%) stem cells from HLA matched sibling donor (25%) or unre lated donor (75%). The main advantage is graft vs. leukemia effect (GVL), while the main disadvantage is graft vs. host effect (GVHD)

#### TERMINOLOGIES (CONT'D)

**AUTOLOGOUS TRANSPLANTATION** (60%) stem cells from self. The main advantage is lesser toxicity compared to allogeneic transplant, while the main disadvantage is possible contamination of the graft with malignant cells

#### TERMINOLOGIES (CONT'D)

**DONOR SOURCE peripheral blood** (10 20 L of blood, mobilization with GCSF, venipuncture, leuka pheresis (up to 3 times for autologous stem cell trans plant), faster engraftment, and improved overall survival (for autologous stem cell transplant and matched sibling allogeneic transplant), **bone marrow, umbilical cord blood** (unlimited supply of donors, although limited amount of cord blood. More tolerant for mis matches in allogeneic transplant)

#### COMMON INDICATIONS

**DECIDING BETWEEN ALLOGENEIC AND AUTOLO GOUS 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 proviscing 10 200% cure if many proviscing 10 200% cure if first proviscing 10 200% cure if many proviscing 10 200% cu

Active leukerilla (30 70% cure il lifst 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 regimens include cyclophosphamide plus total body irra 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 regimen more tolerable for older patients (e.g.

#### ALLOGENEIC TRANSPLANTATION (CONT'D)

fludarabine plus cyclophosphamide, melphalan). Monitor toxicities closely during this time

- **HEMATOLOGIC** pancytopenia, febrile neutropenia
- EARLY NON-HEMATOLOGIC alopecia, N&V, orophar yngeal mucositis, diarrhea, sinusoidal obstruction syndrome (previously known as hepatic veno occlusive disease with tender hepatomegaly, jaun dicem and ascites), seizures, parotitis, pericarditis, cardiomyopathy, interstitial pneumonitis, hemor rhaqic 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  $\pm 10$  and  $\pm 20$ . Defined as ANC  $\pm 20.5 \times 10^3 / \mu L$ , with platelet and RBC engraftment following. GCSF may be used in non leukemic patients to accelerate engraftment by up to 1 week. Patient is supported with blood products and antimicrobial prophylaxis (e.g. ciprofloxacin for Gram negatives, trimethoprim sulfamethoxazole for PCP, acyclovir for HSV, 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 ( $\pm 20.5$ ). 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. Immu nosuppressive treatment can usually be stopped within 1 3 years post allogeneic transplant. Graft vs. host disease (GVHD) is a donor T cell mediated process. Overall transplant related mortality is approximately 20 25%

#### **GRAFT VS. HOST DISEASE**

 ACUTE GVHD (<100 days) occurs in 40% of matched sibling and 80% of unrelated donor 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 cor ticosteroids, cyclosporine, mycophenolate mofetil, tacrolimus, and antithymocyte globulin

#### ALLOGENEIC TRANSPLANTATION (CONT'D)

 CHRONIC GVHD (>100 days) an autoimmune syn drome 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, cuta neous scleroderma, and bronchiolitis obliterans. Treatments include corticosteroids and cyclospor ine or tacrolimus for at least 6 months

#### INFECTIONS

- **PRE-GRAFTMENT** ( < 30 days) HSV, Gram negative bacteria, Gram positive *Streptococcus*, fungal, cen tral line infections (*S. epidermis*)
- EARLY INFECTIONS (30 100 days) CMV, some fun gal, 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

#### AUTOLOGOUS TRANSPLANTATION (CONT'D)

irradiation, and BEAM (BCNU, etoposide, cytosine arabinoside, melphalan)

**TRANSPLANTATION** similar to allogeneic trans plant, 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)

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#### Notes

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### Notes

### **7** ONCOLOGY

Section Editor: Dr. Sharlene Gill

Lung Cancer NEJM 2004 350:4

#### PATHOPHYSIOLOGY

#### CLASSIFICATION BY HISTOLOGY

- SMALL CELL (SCLC, 15%) smokers, central lesions, early metastasis compared to NSCLC
- NON-SMALL CELL (NSCLC, 85%)
  - ADENOCARCINOMA (50 60%) women, non smokers, peripheral lesions. Bronchoalveolar (BAC) subtype may originate distal to grossly recognizable bronchi. BAC tends to be well differentiated, grows along intact alveolar spe tra, and has a propensity for aerogenous and lymphatic spread. May present as diffuse infil tration on chest X ray
  - **squamous** (25%) smokers, central, cavitary lesions
  - LARGE CELL (15%) peripheral lesions with pro minent 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 devel oping lung cancer. 85 90% of all lung cancers are

#### PATHOPHYSIOLOGY (CONT'D)

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  $(2\times)$  and second hand smoke  $(1.3\times)$  are also risk factors

- ENVIRONMENTAL asbestos (7×), arsenic, silica, chromium, nickel, polycyclic hydrocarbons, radon (10×), β carotene supplements (in heavy smokers, 2 3×)
- DISEASES tuberculosis, COPD, pulmonary fibrosis, previous radiation
- FAMILY HISTORY

#### CLINICAL FEATURES

**LOCOREGIONAL** cough, sputum (salty suggests bronchoalveolar), hemoptysis, dyspnea, chest pain, wheezing, dysphagia, brachial plexus, hoarseness, Horner's syndrome, superior vena cava syndrome **METASTATIC** bone pain, jaundice, seizures, head

CONSTITUTIONAL weight loss, anorexia, fatigue

aches, adrenal lesions, skin lesions

PARANEOPLASTIC SYNDROMES				
	SCLC	Squamous	Adenocarcinoma	Large cell
SIADH	$\checkmark$			
Ectopic Cushing's	$\checkmark$			
Neurological syndromes <sup>a</sup>	$\checkmark$			
Hypercalcemia		$\checkmark$	$\checkmark$	
Clubbing or hypertrophic osteoarthropathy		$\checkmark$	$\checkmark$	
Hypercoagulable state	$\checkmark$	$\checkmark$	$\checkmark$	✓
Gynecomastia				✓

<sup>a</sup>Neurological syndromes associated with SCLC include dementia, cerebellar degeneration, limbic encep halopathy, optic neuritis and retinopathy, paraneoplastic sensory neuropathy (anti Hu antibodies), and Eaton Lambert syndrome

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#### STAGING

### TNM STAGING FOR NON SMALL CELL LUNG CANCER (7<sup>TH</sup> 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; invol ving the visceral pleura; associated with atelec tasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
  - T2a >3 <5 cm
  - T2b >5 7 cm
- T3 >7 cm or invades chest wall, diaphragm, mediastinal pleura, parietal pericardium or main bronchus <2 cm to carina; atelectasis/ obstructive pneumonitis of entire lung; separate tumor nodule(s) within the same lobe
- T4=invasion of mediastinum, heart, great vessels, carina, trachea, esophagus, or vertebral body; ipsilateral tumor nodule(s) in different lobes

#### N stage

- N1=ipsilateral peribronchial and hilar LN
- N2=ipsilateral mediastinal and subcarinal LN
- N3=ipsilateral supraclavicular and scalene or any contralateral LN

**M stage** (typically involves pleural fluid, lungs, brain, liver, adrenals, bones, and skin)

- M1a=malignant pleural effusion, pericardial effusion, separate tumor nodule(s) in contralat eral lobe
- M1b=distant metastasis

### STAGE GROUPINGS FOR NON SMALL CELL LUNG CANCER

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

#### STAGING FOR SMALL CELL LUNG CANCER

 LIMITED STAGE (40%) tumor confined to the hemi thorax, 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, bilir ubin, LDH, INR, PTT, Ca, albumin, CEA
- IMAGING CXR (compared to old) and CT chest
- BIOPSY bronchoscopy with lavage/wash/ brushings/biopsy, endoscopic U/S with biopsy, thoracentesis (if pleural effusion), CT guided transthoracic needle aspiration (if peripheral lesion), mediastinoscopy (if any nodes on CT and potentially resectable disease, sens 90%, spc 100%), thoracotomy

#### SPECIAL

0%

Dead

- PET/CT sens 88%, spc 85%. Usually used for sta ging 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

KARNO	OFSKY PERFORMANCE STATUS Function
100%	Normal, no complaints, no evidence of disease
90%	Able to carry on normal activity: minor symptoms of disease
80%	Normal activity with effort: some symptoms of disease
70%	Cares for self: unable to carry on normal activity or active work
60%	Requires occasional assistance but is able to care for needs
50%	Requires considerable assistance and frequent medical care
40%	Disabled: requires special care and assistance
30%	Severely disabled: hospitalization is indicated, death not imminent
20%	Very sick, hospitalization necessary: active treatment necessary
10%	Moribund, fatal processes progressing rapidly

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#### DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

### EASTERN CO OPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

- 0 normal. KPS 100%
- 1 limited activity, otherwise ambulatory. KPS 80 90%
- 2 resting <50% of day. KPS 60 70%
- **3** resting >50% of day. KPS 40 50%
- 4 bed bound. KPS 10 30%
- 5 dead. KPS 0%

#### ADVERSE PROGNOSTIC FACTORS

- GENERAL poor performance status (ECOG >1), involuntary weight loss (>5%), advanced stage, SCLC
- POOR OUTCOME AFTER SURGERY poor performance status, weight loss (>5%), low FEV1, low P<sub>a</sub>O<sub>2</sub>, recent history of smoking

**PROGNOSIS OF SMALL CELL LUNG CANCER** lim ited stage 20 40% 2 year survival, 16 24 months median survival, extensive stage <5% 2 year survival, 6 12 months median survival. Median survival post relapse 4 months

#### MANAGEMENT

#### NON SMALL CELL LUNG CANCER

- STAGE IA lobectomy/pneumonectomy
- STAGE IB lobectomy/pneumonectomy. Con sider adjuvant chemotherapy (cisplatin vinorel bine ×4) if high risk features (e.g. >4 cm, high grade)
- STAGE II lobectomy/pneumonectomy + adju vant chemotherapy (cisplatin vinorelbine ×4)
- STAGE IIIA (N2 disease) concurrent chemoradia tion (cisplatin etoposide ×4), followed by either pneumonectomy/lobectomy or radiation boost
- STAGE IIIA (unresectable) AND IIIB no surgery.
   Concurrent chemoradiation (cisplatin etopo side ×4) with potential chance of cure. Can con sider sequential chemo radiation but may have reduced chance of cure
- STAGE IV palliative radiation should be administered before chemotherapy if patients present with hemoptysis, SVC syndrome, severe bone pain, or obstructive pneumonia. Palliative chemother apy (cisplatin pemetrexed ×4 (for non squamous histologies), cisplatin gemcitabine ×4 (for squamous histology), cisplatin vinorelbine ×4, or car boplatin paclitaxel ×4) ± bevacizumab. For patients who have not progressed after 4 cycles of platinum based induction chemotherapy, consider maintenance pemetrexed until disease progres sion. For recurrent disease after platinum based therapy, consider docetaxel (for squamous cell

#### MANAGEMENT (CONT'D)

histology), pemetrexed, or erlotinib (for adenocar cinoma histology)

#### SMALL CELL LUNG CANCER

- LIMITED STAGE radiation + concurrent che motherapy (cisplatin + etoposide ×4) + prophy lactic cranial irradiation if good partial/complete response
- EXTENSIVE STAGE palliative chemotherapy (cisplatin + etoposide ×4, cisplatin + irinotecan ×4, etoposide ×4) + prophylactic cranial irradiation if partial/complete response. For recurrent disease after platinum based therapy, consider topotecan, cisplatin + irinotecan ± ifosfamide, gemcitabine + irinotecan, gemcitabine + paclitaxel

#### TREATMENT ISSUES

**SMOKING CESSATION** for smokers of <20 pack year, the risk of developing lung cancer decreases significantly after 15 years of abstinence, but still slightly higher than non smokers

NON RESECTABLE DISEASE CRITERIA (stage IIIB or greater) distant metastasis, mediastinal LN metastasis, trachea/contralateral main bronchi involve ment, SVC obstruction, malignant pleural effusion, recurrent laryngeal nerve paralysis, SCLC (unless very early)

#### CONTRAINDICATIONS TO CHEST RADIATION

significant pre existing lung disease, cardiomyopa thy, connective tissue disease (SLE, scleroderma), prior radiation to same body region, pregnancy

**CONTRAINDICATIONS TO BEVACIZUMAB** squa mous cell carcinoma, hemoptysis, uncontrolled cere bral 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 predic tive factors include EGFR mutation and high EGFR qene copy number

#### **Related Topics**

Dyspnea (p. 3)

Horner's Syndrome (p. 13)

SVC Syndrome (p. 228)

Solitary Pulmonary Nodule (p. 13)

Smoking Cessation (p. 418)

Superior Vena Cava Syndrome (p. 228)

Pre Operative Assessment (p. 422)

188 Mesothelioma

Mesothelioma NEJM 2005 353:15

#### PATHOPHYSIOLOGY

#### CLASSIFICATION BY HISTOLOGY

- **EPITHELIOID** tubulopapillary, glandular, or solid. 50 60%
- SARCOMATOID spindle cells
- BIPHASIC mixed with both epithelioid and sarco matoid features

ASBESTOS AND MESOTHELIOMA accounts for approximately 80% of mesothelioma. Risk of mesothelioma is higher with amphiboles/blue asbes tos 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 phos phorylate 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), pericar dial (pericardial effusion, tamponade)

**METASTATIC** miliary spread, liver, lung, bone, and/ or adrenal lesions

CONSTITUTIONAL weight loss, anorexia, fatigue

#### STAGING

#### TNM STAGING

#### T stage

- T1=invasion limited to ipsilateral pleura (T1a=parietal pleura, T1b=parietal pleura with focal visceral pleura involvement)
- T2=invades ipsilateral visceral pleura diffusely, lung, or diaphragm
- T3=invades ipsilateral endothoracic fascia, med iastinal 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 multi focal), 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 mam mary, supraclavicular, or scalene LN

#### STAGING (CONT'D)

#### M stage

M1=distant metastasis

#### STAGE GROUPINGS

Stage	TNM @=any
IA	T1aN0M0
IB	T1bN0M0
II	T2N0M0
III	T1 2N1 2M0, T3N0 2M0
IV	T4N@M0, T@N3M1, T@N@M1

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bili
- IMAGING CXR, CT chest/abd, or MRI chest
- BIOPSY thoracentesis (sens 33 84%, cytology is usually inadequate), thoracoscopy with pleural biopsy

#### SPECIAL

- SERUM MESOTHELIN-RELATED PROTEIN (SMRP) sens 75 84%
- PET scan if surgical candidate

#### PROGNOSTIC ISSUES

**ADVERSE PROGNOSTIC FACTORS** male, poor per formance 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 controver sial and of questionable benefit. It should be con sidered 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 unresect able disease

**STAGE III, IV** (unresectable disease) palliative **chemotherapy** (cisplatin pemetrexed with vita min B12 and folic acid supplementation or cispla tin gemcitabine). Second line options include repeating cisplatin gemcitabine, cisplatin pemetrexed, and vinor elbine. **Pleurodesis** should be considered

#### **Thymoma and Thymic Carcinoma**

#### PATHOPHYSIOLOGY

#### CLASSIFICATION BY HISTOLOGY

- EPITHELIAL
- NEUROFNDOCRINE
- GERM CELL
- LYMPHOID
- STROMAL

#### CLINICAL FEATURES

**LOCOREGIONAL** dyspnea, cough, chest pain, hoar seness, dysphagia, superior vena cava obstruction **METASTATIC** 

CONSTITUTIONAL weight loss, anorexia, fatigue PARANEOPLASTIC myasthenia gravis (30 50%, diplopia, ptosis, dysphagia, weakness, fatigue), pure red cell aplasia (5 15%), pure white cell aplasia, pancytopenia, hypogammaglobulinemia (recurrent infections, diarrhea), rheumatologic diseases, and endocrinopathies. Note that remission of thymoma does not necessarily correlate with improvement of paraneoplastic syndromes

#### **STAGING**

#### YAMAKAWA MASAOKA TNM STAGING T stage

- T1=intact capsule
- T2=macroscopically invades surrounding fatty tissue or mediastinal pleura, microscopically invades capsule
- T3=invades pericardium, great vessels, lung
- T4=pleural or pericardial dissemination

#### N stage

- N1=anterior mediastinal LN
- N2=other intrathoracic LN
- N3=extrathoracic LN

M stage (drop metastasis in pleural space)

• M1=distant metastasis

#### STAGING (CONT'D)

STAGE GROUPINGS				
Stage	TNM @=any	5 year survival		
1	T1N0M0	95%		
II	T2N0M0	85%		
III	T3N0M0	70%		
IVA	T4N0M0	- 50%		
IVB	T@N1 3M0, T@N@M1	JU70		

#### Related Topic

Myasthenia Gravis (p. 318)

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bili
- IMAGING CXR, CT chest
- BIOPSY

#### MANAGEMENT

**STAGE I, II, III** (resectable disease) **resection** (usually including adjacent lung parenchyma and pericardium)  $\pm$  **adjuvant radiation**  $\pm$  (**neo**) **adjuvant chemotherapy** (cisplatin etoposide, cisplatin doxorubicin cyclophosphamide)

**STAGE IV** (unresectable disease) **palliative radia tion**  $\pm$  **palliative chemotherapy** (cisplatin etopo side, cisplatin doxorubicin cyclophosphamide)

#### TREATMENT ISSUES

**INDICATIONS FOR RADIOTHERAPY** locally ad vanced or metastatic unresectable disease, residual disease post resection, and complete resection of invasive thymoma or thymic carcinoma

#### **Breast Cancer**

NEJM 2004 350:14

#### DIFFERENTIAL DIAGNOSIS OF BREAST MASS

**BENIGN** cysts (obstructed collecting ducts), fibroa denoma (overgrowth of periductal stromal connec tive tissue within the lobules), mammary duct ectasia, intraductal papilloma, mastitis, fat necrosis

**ATYPICAL HYPERPLASIA** 3  $5 \times$  increased risk of breast cancer

**CARCINOMA IN SITU** ductal (DCIS), lobular (LCIS) **MALIGNANT** breast cancer (see below for details)

#### PATHOPHYSIOLOGY

#### CLASSIFICATION OF PRE MALIGNANT LESIONS

- DUCTAL CARCINOMA IN SITU (DCIS) precursor lesion to invasive cancer
- LOBULAR CARCINOMA IN SITU (LCIS) diffuse and can be bilateral (risk of contralateral invasive breast cancer may be as high as ipsilateral disease). Marker for increased risk of development of invasive cancer (1% 1 year of development of invasive cancer)

#### PATHOPHYSIOLOGY (CONT'D)

#### **CLASSIFICATION OF MALIGNANT LESIONS**

- DUCTAL ADENOCARCINOMA 80%
- LOBULAR ADENOCARCINOMA
   10%, more likely to be bilateral and multicentric. Tends to metastasize later than ductal carcinoma and spreads to unusual sites such as Gl tract, peritoneum, and meninges. Most are ER+ and 20 30% have E cadherin muta tions (associated with hereditary diffuse type gas tric cancer). Clinically, more difficult to detect by palpation and by mammography
- TUBULAR, MEDULLARY, PAPILLARY, COLLOID, SPINDLE CELL, MUCINOUS 10%, better prognosis
- SARCOMA LIKE phylloides, post radiation RISK FACTORS
- PERSONAL female, increased age, early age of menarche, late age of first parity, lack of breast feeding, late age of menopause, oral contracep tives († risk if >4 years of use), hormone replace ment, 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 Demon stration 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 asso ciated with luminal subtype. Phase II data have shown that these tumors are particularly sensitive to plati num based chemotherapy and poly(ADP ribose) poly merase (PARP) inhibitors due to defects in DNA homo logous recombination repair from BRCA mutation

#### CLINICAL FEATURES

### RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE BREAST CANCER?

**PHYSICAL** the value of inspection is unproved. Pal pation with clinical breast examination (CBE) includes proper positioning of the patient, use of a vertical strip pattern, proper position and movement of the fingers (pads of 2<sup>nd</sup> 4<sup>th</sup> fingers rolling motion), thoroughness of search, and spending at least 3 min per breast (sens 54%, spc 94%, LR+ 10.6, LR 0.47)

**APPROACH** "screening by both clinical breast examination and mammography is associated with decreased breast cancer mortality. Clinical

#### **CLINICAL FEATURES (CONT'D)**

breast examination alone detected between 3 45% of breast cancers that were missed by screening mammography. While clinical breast examination alone cannot rule out disease, the high specificity of certain abnormal findings significantly increases the probability of breast cancer"

#### JAMA 1996 282:13

**LOCOREGIONAL** breast lump (with or without pain), nipple discharge, eczema or retraction, skin erosion, erythema or edema, change in breast size, axillary adenopathy

**METASTATIC** bone pain, seizure, headache, dys pnea, jaundice

CONSTITUTIONAL fatigue, weight loss, anorexia

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, 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 cytol ogy only and cannot differentiate between inva sive 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=in flammatory carcinoma)

N stage (axillary, internal mammary, supraclavicular)

- N1
  - cN1=ipsilateral mobile axillary lymph node(s)
  - pN1mi=micrometastasis 0.2 2 mm
  - pN1a=1 3 axillary lymph node(s)
  - pN1b=internal mammary lymph nodes with microscopic disease detected by SLND but not clinically apparent
  - pN1c=N1a and N1b
  - N2
    - cN2a=ipsilateral fixed/matted axillary lymph node(s)

#### TNM STAGING (CONT'D)

- cN2b=ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node
- pN2a=4 9 axillary lymph nodes
- pN2b=ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node

#### N3

- **cN3a**=ipsilateral infraclavicular lymph node(s)
- cN3b=ipsilateral internal mammary and axil lary 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 ipsi lateral 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 micro scopic 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

JIAGE	ditooi iitas	
Stage	TNM @=any	5 Year survival
1	T1N0M0	100%
IIA	T0 1N1M0, T2N0M0	90%
IIB	T2N1M0, T3N0M0	80%
IIIA	T0 2N2M0, T3N1 2M0	70%
IIIB	T4N0 2M0	50%
IIIC	T@N3M0	40%
IV	T@N@M1	20%

#### DIAGNOSTIC AND PROGNOSTIC ISSUES

MAMMOGRAPHIC FINDINGS OF BREAST CAN

**CER** spiculated, crab like, puckering lesions, architectural distortion, clustered microcalcifications

**SCREENING** monthly self breast examination, annual clinical breast examination, annual mammo gram 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  $\leq$ 15 mm, 2=16 40 mm, 3 >40 mm
- MARGIN WIDTH 1 >10 mm, 2=1 10 mm, 3 <1 mm

#### DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

- GRADE 1=non high grade, no comedo necrosis, 2=non high grade with comedo necrosis, 3=high grade with or without comedo necrosis
- AGE 1 >60, 2=40 60, 3 <40 years old
- INTERPRETATION add up the four factors

VNPI score	Risk of relapse	Treatment recommendation
≤6	Low	Lumpectomy only
7 9	Mod	Lumpectomy plus radiation
≥10	High	Consider mastectomy

#### MANAGEMENT

#### DCIS

- RESECTION breast conserving surgery, plus adju vant 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 consid ered 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

- RESECTION breast conserving surgery or mastect omy, plus sentinel biopsy or axillary lymph node dissection. If sentinel lymph node positive, pro ceed to axillary dissection
- 2. ADJUVANT SYSTEMIC THERAPY anthracycline  $\pm$  tax ane (see below for details)  $\pm$  trastuzumab
- 3. ADJUVANT RADIATION always give adjuvant radia tion after breast conserving surgery. Adjuvant radiation should be considered after mastectomy if large tumor, skin involvement, muscle involve ment, positive node, positive margins, or lympho vascular invasion
- ADJUVANT HORMONAL give if ER/PR positive (see below for details)

#### STAGE III

- 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 mastect omy, plus axillary lymph node dissection
- ADJUVANT RADIATION almost always given for stage III disease
- 4. **ADJUVANT HORMONAL** give if ER/PR positive (see below for details)

#### MANAGEMENT (CONT'D)

#### STAGE IV

- 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
- PALLIATIVE CHEMOTHERAPY for visceral or ER/PR negative disease. Choices include anthracyclines, taxanes, gemcitabine, capecitabine, and vinorelbine
- 3. BIOLOGICAL THERAPY for Her2+ disease, add tras tuzumab to chemotherapy and continue mainte nance trastuzumab until disease progression. The role of newer targeted therapies including lapati nib (dual tyrosine kinase inhibitor of EGFR and HER2) and bevacizumab (anti VEGF) is expanding in pre treated patients
- 4. PALLIATIVE RADIATION for symptom control
- BISPHOSPHONATES if bone metastasis, pamidro nate 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 mas tectomy  $\pm$  radiation. Hormonal and/or chemother apy may also be considered

#### **Related Topics**

BRCA Mutations (p. 224) Cancer Screening (p. 222)

#### BREAST SURGERY OVERVIEW

**COMPLETE SURGERY** modified radical mastect omy, 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, quadran tectomy, wide local excision

**SURGICAL MARGIN** positive margin is defined as tumor touching ink and would require either re exci sion (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. Contraindica tions include locally advanced breast cancer, multi focal 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) oophor ectomy, 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 (preme nopausal 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
- women or premenopausal women after ovarian ablation as suppress peripheral estrone production only) inhibit aromatase, an enzyme in skin, adi pose tissue, and breast that converts androstene dione (from the adrenals) to estrone and estradiol. 
  Steroidal (exemestane 25 mg PO daily), non ster oidal (letrozole 2.5 mg PO daily, anastrozole 1 mg PO daily). Side effects include hot flashes, mood swings, vaginal dryness, myalgia/arthralgia, head ache, 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 THER APY 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 pre menopausal 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 tamox ifen ×5 years followed by letrozole ×5 years. Con sider 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 invariant and minimum to the control of the control

patients with slowly progressive disease, no visceral involvement, and minimal symptoms may be best served with a trial of endocrine therapy. For preme nopausal women, consider ovarian ablation + tamox ifen  $\rightarrow$  aromatase inhibitor 1  $\rightarrow$  aromatase inhibitor 2  $\rightarrow$  fulvestrant  $\rightarrow$  megestrol. For postmenopausal women, aromatase inhibitor 1  $\rightarrow$  tamoxifen  $\rightarrow$  aromatase inhibitor 2  $\rightarrow$  fulvestrant  $\rightarrow$  megestrol. Time

#### HORMONAL THERAPY OVERVIEW (CONT'D)

to progression is 8 months with tamoxifen and 10 months with aromatase inhibitors

#### ADJUVANT CHEMOTHERAPY OVERVIEW

### WHO SHOULD GET ADJUVANT CHEMOTHERAPY: THE ST. GALLEN GUIDELINE

- LOW RISK node negative and age ≥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)

APPROACH TO SYSTEMIC THERAPY FOR BREAST CANCER			
	ER/PR +ve	ER/PR unknown	ER/PR ve
Low risk	H or nil	H or nil	N/A
Intermediate risk	H or $Cx \rightarrow H$	Cx→H	Cx
High risk	Cx→H	Cx→H	Cx
where Cx=chemo, H=hormonal therapy			

### ADJUVANT CHEMOTHERAPY OVERVIEW (CONT'D) WHO SHOULD GET ADJUVANT CHEMOTHERAPY: THE NCCN GUIDELINE

- ALL HISTOLOGIC SUBTYPES EXCEPT TUBULAR OR COLLOID
   CANCERS adjuvant chemotherapy should be given if ≥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 che motherapy should be given if  $\geq 3$  cm or node positive. Consider chemotherapy if 1 2.9 cm

#### **ADJUVANT REGIMENS**

- FIRST GENERATION CMF PO, AC×4, FEC50×6
- SECOND GENERATION CAF $\times$ 6, FAC $\times$ 6, CEF $\times$ 6, FEC100 $\times$ 6, AC $\times$ 4+D $\times$ 4, DC $\times$ 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			
	Postmenopausal	Premenopausal	
1 <sup>st</sup> gen.	8% ER+, 15% ER	30%	
2 <sup>nd</sup> gen.	26% ER+, 32% ER	44%	
3 <sup>rd</sup> gen.	40% ER+, 45% ER	55%	

#### ADJUVANT CHEMOTHERAPY OVERVIEW (CONT'D)

RELATIVE RISK REDUCTION FOR RECURRENCE			
	Postmenopausal	Premenopausal	
1 <sup>st</sup> gen.	12% ER+, 23% ER	37%	
2 <sup>nd</sup> gen.	30% ER+, 38% ER	50%	
3 <sup>rd</sup> gen.	43% ER+, 50% ER	59%	

#### ADVERSE EFFECTS OF ADJUVANT CHEMOTHERAPY

- ALOPECIA anthracycline or taxane regimens (100%), CMF (50%)
- FEBRILE NEUTROPENIA DAC (40%) and dose dense regimens require GCSF. CEF >FEC; FAC >FEC; ACT >AC/CMF
- NAUSEA AND VOMITING CMF > anthracyclines
- OTHER ACUTE SIDE EFFECTS fatigue and weight gain. With taxanes, may experience myalgia, arthralgia, and neuropathy (motor, sensory)
- PREMATURE OVARIAN FAILURE CMF >CEF/FEC >AC: DAC >FAC
- OTHER LONG-TERM SIDE EFFECTS cardiotoxicity (dose dependent and increases with age, ~1% with anthracycline doses used in adjuvant regi mens), secondary cancers (AML, MDS with alkylat ing agents, ~1 2% depending on regimen)

PREDICTIVE FACTORS FOR ADJUVANT CHE MOTHERAPY 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. Con sider anthracycline and docetaxel for node positive breast cancer, anthracycline  $\pm$  paclitaxel + traustu zumab 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?

ER

#### FOR NODE NEGATIVE WOMEN

Premenopausal	Postmenopausal
ddACT	ddACT

ER+ FEC, CEF If G3 or large T,
FAC, FEC, AC, DC
Lower risk AC No chemo

#### ADJUVANT CHEMOTHERAPY OVERVIEW (CONT'D)

FOR NODE	POSITIVE WOMEN	
	Premenopausal	Postmenopausal
ER	FECD (DAC), ddACT	FECD, ddACT
ER+	FECD (DAC), FEC, CEF	FAC, FECD, FEC, AC
Lower risk	AC, DC, or no chemo	AC, DC or no chemo

#### NEOADJUVANT CHEMOTHERAPY FOR LOCALLY ADVANCED BREAST CANCER

- DEFINITION T3N1, T4, N2, or N3 disease
- NEOADJUVANT REGIMENS anthracycline plus doce taxel regimens (ACD, DAC, FECD), ACDH or DCH (docetaxel, carboplatin, and trastuzumab) for Her2 positive disease

### ADVANTAGES AND DISADVANTAGES OF NEOADJUVANT AND ADJUVANT THERAPY Neoadjuvant Adjuvant

Clinical staging is less accurate Pathological confirmation of chemotherapy efficacy Definitive treatment delayed

Reduced tumor improves local control

Surgery refusal in patients with complete response Timely application of chemotherapy

Better performance status allowing aggressive therapy

Intact blood/lymph vessels allowing optimal drug concentrations

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

Impaired blood/lymph vessel supply in pelvis

#### PALLIATIVE CHEMOTHERAPY OVERVIEW

PALLIATIVE REGIMENS doublet regimens include doxorubicin plus paclitaxel, capecitabine plus docetaxel, docetaxel plus gemcitabine, paclitaxel plus gemcitabine, and weekly paclitaxel plus bevacizumab. Single agents include capecitabine, vinorelbine, and taxane

APPROACH IN THE METASTATIC SETTING patients with rapidly growing disease, especially involvement of visceral organs such as lung or liver may benefit more from chemotherapy compared to hormonal therapy due to a more rapid response. Choice depends on prior adjuvant chemotherapy, disease free interval, patient's performance status, and willingness/ability to tolerate side effects. Doublet regimens are associated with higher response rate and modest gains in overall survival but more toxicities. Single agents are tolerated better with limited alopecia and are particularly appro priate for patients who are elderly or have poor perfor mance status. At eventual progressive disease, change

#### PALLIATIVE CHEMOTHERAPY OVERVIEW (CONT'D)

chemotherapy to non cross resistance drugs. Use sin gle agent only as no evidence for enhanced overall survival with doublets beyond first line

#### BIOLOGICAL THERAPY OVERVIEW

**HER2/NEU STATUS** 15 20% positive. Her2 positivity is a poor prognostic factor, but predicts response to trastuzumab and anthracycline chemotherapy

**APPROACH** Her2 positive disease should be treated with chemotherapy plus trastuzumab in the adjuvant/neoadjuvant settings. Do not give concomitantly with anthracyclines. In the metastatic setting, give chemotherapy and then maintenance trastuzumab until progression

**ADVERSE EFFECTS** infusion reactions (40%, usually with first administration), cardiotoxicity, and pulmonary (rare)

Esophageal Cancer 195

#### BIOLOGICAL THERAPY OVERVIEW (CONT'D)

DISTINGUISHING FEATURES BETWEEN CARDIOTOXICITY DUE TO ANTHRACYCLINE AND TRASTUZUMAB Anthracycline Trastuzumab			
Mechanism	Lipid peroxidation and vacuolation → myocyte fibrosis	Unknown	
Structural damage	Present	Not seen	
Cardiomyopathy	Dilated	Dilated	
Dose dependent	Yes	No	
Prevention	Dexrazoxone	None	
	Weekly Treatment		
	Liposomal Doxorubicin		
	Limit dose		
Treatment	Stop therapy	Stop therapy	
	Cannot give more	May restart	
Course	Irreversible	Reversible	

#### MANAGEMENT OF BRAIN METASTASES

**APPROACH** steroids, resection plus radiation, or radiation alone if resection not possible. Principles are similar for CNS recurrence

 SURGERY consider resection if solitary lesion or primary lesion causing neurological complications.
 Surgery plus radiation is associated with better overall survival than radiation alone for eligible candidates (10 vs. 6 months)

#### MANAGEMENT OF BRAIN METASTASES (CONT'D)

- RADIATION may be re irradiated if over 1 year from first whole brain radiation
- STEREOTACTIC RADIATION less generalized toxicity.
   If <3 lesions and all <3 cm [<1.2 in.]</li>
- CHEMOTHERAPY limited role with high dose meth otrexate and possibly capecitabine

#### **Esophageal Cancer**

#### NEJM 2003 349:23

#### PATHOPHYSIOLOGY

#### CLASSIFICATION BY HISTOLOGY

- ADENOCARCINOMA 75% in distal esophagus
- SQUAMOUS evenly distributed between upper, middle, and lower third esophagus
- MELANOMA
- LEIOMYOSARCOMA
- LYMPHOMA
- CARCINOID

RISK FACTO	RS		
		Squamous	Adeno
Frequency		50%	50%
Barrett's eso	phagus		$>$ 8 $\times$
Reflux sympt	toms		4 8×
Obesity			2 4×
Smoking		4 8×	2 4×
Alcohol Use		4 8×	
Caustic injury	y to	>8×	
esophagu	S		
Achalasia		4 8×	
Poverty		2 4×	
History of H8	&N cancer	>8×	
History of br	east cancer	4 8×	4 8×
with radia	ntion		

# PATHOPHYSIOLOGY (CONT'D) Squamous Adeno Plummer Vinson >8× syndrome Non epidermolytic palmoplantar keratoderma

 $<2\times$ 

#### CLINICAL FEATURES

Frequent hot beverages

**LOCAL** dysphagia (74%), odynophagia (17%), upper Gl bleed, epigastric pain

**REGIONAL** dyspnea, cough, hoarseness, pain (ret rosternal, 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) 196 Esophageal Cancer

### 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, infraaortic, infracarinal and lower pos terior 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

5171CE C110 C1 111 C5			
Stage	TNM @=any	5 year survival	
0	TisN0M0	>95%	
1	T1N0M0	50 80%	
IIA	T2 3N0M0T	30 40%	
IIB	T1 2N1M0	10 30%	
III	T3N1M0 T4N0 1M0	10 15%	
IVA	T@N@M1a	<5%	
IVB	T@N@M1b	<1%	

### INVESTIGATIONS

### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, 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  $\pm$  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. Con sider 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 carci noma (difficult resection). Neoadjuvant chemother apy (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 preo perative 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 squa mous cell carcinomas are very sensitive to che moradiation, and thus surgery may not be needed

**METASTATIC, UNRESECTABLE** (M1, 15%, median survival 9 12 months)

- PALLIATIVE CHEMOTHERAPY similar to gastric can cer. Standard regimens include ECF, DCF (D=doc etaxel, 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 irinote can), or 5 fluorouracil or irinotecan alone. No standard for second line, which may include FOL FIRI, 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 endolum inal stent if obstruction, phototherapy, G tube insertion

### TREATMENT ISSUES

**FOLLOW UP** no agreed upon surveillance pro gram. 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

197 Gastric Cancer

### **Gastric Cancer**

### PATHOPHYSIOLOGY

### CLASSIFICATION BY HISTOLOGY

- ADENOCARCINOMA (95%) diffuse, intestinal, or mixed type
- LEIOMYOSARCOMA (5%)
- LYMPHOMA mucosal associated lymphoma
- CARCINOID GI STROMAL

### PATHOLOGIC SUBTYPES Diffuse type Intestinal type Location Proximal Distal Age of onset Younger Older Gender F > MM > FRisk factors Hereditary Endemic H. pylori 32% 89% Metastasis Peritoneal Hepatic Outcome Worse Better

LINITIS PLASTICA (15%) diffuse disease involving the entire stomach. Very poor prognosis; slightly better with superficial/expansive type (5 10%)

**LOCATION** 35% proximal, 25% body, 40% distal **RISK FACTORS** 

- PERSONAL Asian origin (Japanese and Chinese)
- FAMILY HISTORY affected relatives (L), HNPCC, FAP, Li Fraumeni, Peutz Jeghers syndrome, her editary 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), per nicious 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), dys pnea, sister Mary Joseph nodule (umbilicus), Kruken berg tumor (ovaries)

**CONSTITUTIONAL** anorexia, fatigue, weight loss PARANEOPLASTIC acanthosis nigricans, sebor rheic keratosis (Leser Trelat sign), inflammatory myo sitis, circinate erythema, cerebellar ataxia, throm boembolism, 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,pan creas, 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 supraclavicu lar LN, left axillary LN, umbilicus, ovary)

M1=distant metastasis

	GROUPINGS TNM @=any	Freq	5 year survival
IA	T1N0M0	10%	78%
IB	T2N0M0, T1N1M0	10%	58%
II	T3N0M0, T2N1M0, T1N2M0	20%	34%
IIIA	T4N0M0, T3N1M0, T2N2M0 }	40%	20% 8%
IIIB	T3N2M0 ∫	<b>40</b> /0	8%
IV	T4N@M0, T@N3M0,	30%	7%
	T@N@M1		

### INVESTIGATIONS

### **BASIC**

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, 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 popula tion 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

198 Colorectal Cancer

### **Related Topics**

Dyspepsia (p. 113) Leser Trelat Sign (p. 368) MALT (p. 177) Melena (p. 118)

### MANAGEMENT

STAGE IA gastrectomy (total or subtotal) with D1 dissection

### STAGE IB, II, III

- OPTION 1 neoadjuvant ECF×3 (epirubicin, cis platin, infusional 5 fluorouracil) + surgery + adju vant ECF×3; 43% of patients able to complete treatment
- **option 2 gastrectomy** (total or subtotal) with D1 dissection + **adjuvant chemoradiation** (5 fluorouracil)
- INSUFFICIENT EVIDENCE D2 dissection, adjuvant radiation alone, adjuvant chemotherapy alone, and neoadjuvant radiation

**STAGE IV (T1 4N1 3M0)** same treatment approach as stage III if resectable disease. Otherwise, same treatment approach as metastatic disease

### STAGE IV (M1, MEDIAN SURVIVAL 10 MONTHS)

 PALLIATIVE CHEMOTHERAPY standard regimens include ECF (E=epirubicin, C=cisplatin, F=infusional 5 fluorouracil), DCF (D=docetaxel, C=cisplatin, F=5 fluorouracil), ECX, EOX, EOF (X=capecitabine,

### MANAGEMENT (CONT'D)

O=oxaliplatin). For patients with poor performance status, consider CF, FOLFIRI (5 fluorouracil leucov orin irinotecan), 5 fluorouracil alone, or irinotecan alone. No standard for second line, which may include FOLFIRI, irinotecan alone, or taxane alone. Recent findings from the TOGA trial demonstrate improved survival with the addition of trastuzumab to chemotherapy in HER2 positive gastric cancer (positivity rate 15 20%)

- PALLIATIVE RADIATION for bony metastasis or bleeding tumors
- PALLIATIVE SURGERY gastrojejunostomy, partial gastrectomy to bypass obstruction

### TREATMENT ISSUES

**VITAMIN B12 DEFICIENCY** may develop after a few years in patients who received subtotal or total gastrectomy

### LYMPH NODE RESECTION

- D1 dissection removal of the stomach and less and greater omentum with the associated N1 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 pro gram. 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 quidelines)

### **Colorectal Cancer**

NEJM 2005 352:5

### PATHOPHYSIOLOGY

### **CLASSIFICATION BY HISTOLOGY**

- ADENOCARCINOMA mucinous subtype, signet ring cells, adenosquamous, medullary
- CARCINOID mostly involving appendix and rec tum, less malignant
- RARE squamous cell, small cell, undifferentiated
- ADENOMATOUS POLYP pre malignant

### **RISK FACTORS**

- PERSONAL age
- FAMILY HISTORY affected relatives (2×), HNPCC (mutation in MSH 2, MLH 1, PMS 1, PMS 2, or MSH 6 genes responsible for mismatch repair, 6% of all colon cancers), familial adenomatous polyposis (1% of all colon cancers related to mutation in APC gene, all affected will have colon cancer by age 40), Peutz Je ghers syndrome, juvenile polyposis, Gardner's syn drome, 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 coli tis (1%/year after 10 years), diabetes, obesity

**LOCATION** 50% rectosigmoid, 18% descending colon, 11% transverse colon, 20% in the ascending colon and cecum

# DISTINGUISHING FEATURES BETWEEN COLON AND RECTAL CANCER

	Colon cancer	Rectal cancer
Frequency	2/3	1/3
Location	>12 cm	<12 cm
	[>4.7 in.]	[<4.7 in.]
	from anal	from anal
	verge or	verge or
	above	below
	peritoneal	peritoneal
	reflection	reflection

PATHOPHYSIOLOGY (CONT'D)				
Colon cancer Rectal cancer				
Metastasis	Liver	Liver and lung		
Adjuvant	Chemo	RT and chemo		
treatments				

**MOLECULAR SEQUENCE FOR DEVELOPMENT OF COLON CANCER** the Vogelstein model of carcino genesis developed based on analysis of FAP lesions. Normal epithelium  $\rightarrow$  loss of 5q (e.g. APC,  $\beta$  catenin) over decades  $\rightarrow$  adenoma development  $\rightarrow$  loss of 18q (e.g. k ras) over 2 5 years  $\rightarrow$  late adenoma  $\rightarrow$  loss of 17p (e.g. p53) over 2 5 years  $\rightarrow$  early cancer  $\rightarrow$  loss of 8p  $\rightarrow$  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 prolif eration despite inhibition of EGFR

### CLINICAL FEATURES

**LOCOREGIONAL** bowel habit  $\Delta$ , hematochezia, paradoxical diarrhea, tenesmus, abdominal pain, iron deficiency anemia

METASTATIC RUQ pain, dyspnea

**CONSTITUTIONAL** weight loss, anorexia, fatigue **OTHER** Streptococcus bovis bacteremia and Clostri dium septicum sepsis; colorectal cancer in 16 32% of patients with S. bovis bacteremia

### STAGING

### TNM STAGING

### T stage

- T1=invades submucosa
- T2=invades muscularis propria
- T3=invades subserosa or non peritonealized pericolic tissues
- T4=perforation of visceral peritoneum or directly invades into adjacent structure (bowel, bladder, uterus, pelvic wall)

**N stage** (mesenteric → supraclavicular)

- N1=1 3 LN
- **N2**=>4 LN

M stage (liver, lung, bone, brain)

• M1=distant metastasis

STAGING (CONT'D)						
STAGE	STAGE GROUPINGS					
Stage	TNM @=any	Frequency	5 year			
			survival			
1	T1 2N0M0	15%	90%			
IIA	T3N0M0 \	20%	85%			
IIB	T4N0M0 ∫	2070	70%			
IIA	T1 2N1M0		80%			
IIIB	T3 4N1M0	40%	60%			
IIIC	T@N2M0		45%			
IV	T@N@M1	25%	5%			

### INVESTIGATIONS

### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin. INR, PTT, albumin, lipase, CEA, CA19 9
- IMAGING barium enema, CT abd, CXR, MRI, and endorectal U/S in rectal cancer
- BIOPSY colonoscopy with biopsy, laparoscopy, laparotomy

### MANAGEMENT OF COLON CANCER

STAGE I surgical resection only

STAGE II surgical resection. Adjuvant che motherapy (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 che motherapy (FOLFOX is the first choice. Other possi bilities include capecitabine, 5 fluorouracil leucov orin, infusional 5 fluorouracil if patient is not fit or has contraindications to oxaliplatin)

STAGE IV if metastasis limited to liver and poten tially resectable, consider liver resection plus perio perative 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. Ral titrexed if 5 fluorouracil intolerant. Cetuximab irino tecan or single agent panitumumab in third line if KRAS wild type)

### **Related Topics**

Cancer Screening (p. 222)

Chemotherapy Induced Diarrhea (p. 231)

Oral Mucositis (p. 230)

Hematochezia (p. 120)

Hereditary Cancers (p. 224)

200 Colorectal Cancer

### MANAGEMENT OF RECTAL CANCER

HIGHLY RESECTABLE (stage I) transanal excision only if <30% circumference, <3 cm [<1.2 in.], margins >0.3 cm [>0.12 in.] mobile, within 8 cm [3.1 in.] of anal verge, no lymphovascular or perineural invasion, well or moderately differentiated tumor. Otherwise, total mesorectal excision via low anterior resection or abdominoperineal resection

**RESECTABLE** (stage II and some stage III with no high risk feature (not fixed, not low <5 cm [2 in.], not bulky) **neoadjuvant radiation** (short course, 1 week) + **total mesorectal excision** + **adjuvant che motherapy** based on pathologic stage: FOLFOX $\times$ 12 if pathologic node positive (i.e. node positive); capecita bine  $\times$ 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 chemor adiation (long course, 5 weeks, 5040 cGy plus infu sional 5 fluorouracil or capecitabine) + total mesor ectal 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 oxa liplatin; FOLFIRI=5 fluorouracil, leucovorin, and iri notecan; 5 fluorouracil/LV=5 fluorouracil and leucovorin

### TREATMENT ISSUES

ESTIMATED BENEFITS OF ADJUVANT
CHEMOTHERAPY FOR STAGE III COLORECTAL
CANCER

# RELATIVE RISK REDUCTION FROM MAYO CLINIC DATABASE

Recurrence	Death
17%	14%
40%	34%
	.,,,

TREATMENT ISSUES (CONT'D)				
Recurrence Death				
FOLFOX vs. 5 FU	FOLFOX vs. 5 FU			
Node ve	18%	18%		
Node +ve	24%	24%		

RELATIVE RISK REDUCTION FROM ADJUVANT				
	Recurrence	Death		
5 FU benefit				
Node ve	20%	18%		
Node +ve	43%	38%		
FOLFOX benefit				
Node ve	39%	24%		
Node +ve	59%	48%		

**COLORECTAL CANCER SURVEILLANCE** for patients with stage II and III disease who would be candidate for salvage treatment if recurrence, ASCO suggests medical visit with history and physical examination every 3 6 months ×3 years, then every 6 months for the next 2 years, and then yearly after. Perform CEA every 3 months for at least 3 years. CT chest/abd (+ CT pelvis for rectal cancer) yearly ×3 years. Colono scopy 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 tern ary complex with thymidylate synthetase, permit ting 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 ves sels 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 201

### **Carcinoid Tumors**

NEJM 1999 340:11

### PATHOPHYSIOLOGY

### CLASSIFICATION OF NEUROENDOCRINE TUMORS

- HIGH GRADE poorly differentiated neuroendo crine carcinomas, small cell like tumors
- LOW GRADE carcinoid tumors, pancreatic islet tumors (VIPoma, glucagonoma, gastrinoma, insulinoma, somatostatinoma), paragangliomas, pheochromocy tomas, medullary thyroid carcinomas

### CLASSIFICATION BY LOCATION

- FOREGUT CARCINOID lungs, bronchi, stomach
- MIDGUT CARCINOID small intestine, appendix, proximal large bowel
- HINDGUT CARCINOID distal colon, rectum, geni tourinary tract

### SPECIFIC DETAILS BY LOCATION

- LUNGS AND BRONCHI derived from epithelial endo crine cells
  - WELL-DIFFERENTIATED NEUROENDOCRINE TUMOR (typi cal 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-ASSO-CIATED CARCINOID TUMOR (75%) indolent, usually multiple, not associated with carcinoid syndrome
  - TYPE 2: CARCINOID TUMOR ASSOCIATED WITH ZOL-LINGER-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 metas
    tases. Contain a variety of endocrine cells. May
    be associated with atypical carcinoid syndrome
- SMALL BOWEL derived from intraepithelial endo crine cells. Often multiple, usually in ileum. Asso ciated 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 sube pithelial endocrine cells. Usually indolent
- colon derived from epithelial endocrine cells.
   Usually right sided, often presents at late stage
- RECTUM derived from epithelial endocrine cells.
   Carcinoid syndrome rare

### **Related Topics**

Wheezing (p. 1) Chronic Diarrhea (p. 124) MEN syndrome (p. 348)

### PATHOPHYSIOLOGY (CONT'D)

**FUNCTIONALITY** carcinoid tumors arise from neu roendocrine cells. Contain membrane bound neurosecre tory granules such as serotonin, histamine, dopamine, substance P, neurotensin, prostaglandins, kallikrein, ACTH, calcitonin, gastrin. Release of these vasoactive agents leads to episodic symptoms. However, about 50% of tumors are non secretory and thus non functional **SEROTONIN SYNTHESIS** 5 hydroxytryptophan (with aromatic acid decarboxylase) → serotonin (with monoamine oxidase) → 5 hydroxyindoleacetic acid (5 HIAA) → excreted in urine

**METASTASIS** liver and sometimes bones (osteoblastic)

### CLINICAL FEATURES

**GENERAL** the majority of patients are asymptomatic (10% of small intestine in the presence of liver metas tases, < 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 (abdom inal), bleeding

**NEUROENDOCRINE SYNDROMES** (30 40% of tumors active) serotonin mainly (episodic purplish flushing, diarrhea, wheezing, hypotension and even tually right sided valvular heart disease), fibrosing mesenteritis, Cushing's, acromegaly (rare). Attacks may be spontaneous or precipitated by stress, exer cise, 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 dia betes mellitus (insulin release impaired), cholelithia sis (reduced gallbladder contractility), and diarrhea/ steatorrhea (pancreatic insufficiency)

**NIACIN DEFICIENCY** pellagra as tryptophan directed to production of serotonin

METASTASIS jaundice, liver failure, bone pain CARCINOID HEART DISEASE occurs in 1/2 of patients with carcinoid syndrome. Factors (e.g. seroto nin) secreted by liver metastases into hepatic vein → plaque like, fibrous endocardial thickening involving the right side of the heart → tricuspid regurgitation most common. Tricuspid stenosis, pulmonary regurgitation, and pulmonary stenosis may also occur. Pulmonary carcinoids may produce left sided valvular disease

### INVESTIGATIONS

### BASIC

 LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, INR, PTT, albumin, serum chromogranin A, 24 h urine 5 HIAA (sens 73%, spc 100%)

### INVESTIGATIONS (CONT'D)

- IMAGING CT chest/abd/pelvis, somatostatin scintigraphy (sens 89%), MIBG scan (useful if somatostatin scan negative). Echocardiogram
- BIOPSY ensure pathology includes Ki67 immunohistochemistry

### **SPECIAL**

- PANCREATIC NEUROENDOCRINE TUMOR WORKUP pan creatic polypeptide, α hCG, chromogranin A, gas trin, 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, lanreo tide, loperamide 4 mg × 1 dose, then 2 mg q4h PRN, maximum 16 mg/day, atropine diphenoxylate 1 2 tabs q6 8h, cyproheptadine, methysergide, ondan setron 8 mg PO TID. Gastric carcinoid can respond to a histamine blocker
- HYPOTENSION pure α adrenergic medications such as methoxamine and angiotensin. Corticos teroids may be useful for prophylaxis. Strictly avoid β adrenergic agonists such as epinephrine and dopamine as they may aggravate hypotension
- FLUSHING octreotide, prochlorperazine 10 mg PO QID (foregut), phenoxybenzamine 10 20 mg PO BID, prednisone 20 40 mg PO daily (foregut)
- **BRONCHOSPASM** salbutamol 2 puffs INH q4h PRN, ipratropium, theophylline
- CARCINOID HEART DISEASE medical management of heart failure, valvular replacement may be considered but patients are usually high risk surgical candidates

### LOCALIZED DISEASE resection

### ADVANCED/METASTATIC DISEASE

 PALLIATIVE RESECTION for debulking, prevention of mesenteric fibrosis by mid gut carcinoids, and treatment of obstruction and extraintestinal pri mary tumors such as bronchial and ovarian

### MANAGEMENT (CONT'D)

- 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 SOMATOS-TATIN ANALOGUES difficult to access as only few institutions offer this therapy
- HEPATIC METASTASES resection, radiofrequency ablation and cryoablation, hepatic artery embo lization

### TREATMENT ISSUES

**SOMATOSTATIN ANALOGUES** octreotide is a long acting somatostatin analogue that binds to somatos tatin 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 perio peratively to prevent carcinoid crisis. Controversial indications include post surgery, post embolization or radiofrequency ablation, and post adjuvant treat ment with no evidence of disease
- DOSING give 50 μg as test dose (may cause gas tric 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, abdom inal cramps, diarrhea/constipation, gallstones, impaired glucose tolerance, hypothyroidism, dys pnea, arrhythmia, HTN, fatigue, headache, dizzi ness, fever, flu like symptoms

**FOLLOW UP** clinical assessment along with chro mogranin 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, mesentery, and retroperitoneum

### PATHOPHYSIOLOGY (CONT'D)

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

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

Anal Cancer 203

### CLINICAL FEATURES

LOCOREGIONAL GI bleed, abdominal mass, abdominal pain

METASTATIC RUQ pain, jaundice

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

### INVESTIGATIONS

### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, INR, PTT, albumin
- IMAGING CT abd/pelvis ± MRI, U/S abd, chest imaging, PET/CT in selected patients
- BIOPSY endoscopy, laparotomy. Consider KIT and PDGRA mutational testing for KIT negative tumors

### PROGNOSTIC ISSUES

**ADVERSE PROGNOSTIC FACTORS** size, mitotic rate, tumor site (small intestine worse), incomplete resection (<35% vs. 50 65% 5 year survival)

**PREDICTIVE FACTORS** exon 11 KIT mutation is predictive of response to imatinib compared to exon 9 KIT mutation or wild type

### MANAGEMENT

**RESECTABLE DISEASE** segmental resection without regional lymphadenectomy. Adjuvant *imatinib* 400 mg PO daily is recommended for at least 12 months for patients with intermediate to high risk GIST

UNRESECTABLE, RECURRENT, OR METASTATIC DISEASE imatinib 400 mg/day (until disease progression) is recommended, except for exon 9 mutation in which imatinib 800 mg/day is appro priate. For patients with non-metastatic but unresectable disease, consider neoadjuvant ima tinib 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 pro gression on imatinib, increase dose to 800 mg/ day. With further disease progression, sunitinib should be considered

### **Anal Cancer**

### PATHOPHYSIOLOGY

### **CLASSIFICATION BY HISTOLOGY (WHO)**

- ANAL CANAL
  - SQUAMOUS CELL CARCINOMA (75%) large cell keratinizing (distal to the dentate line) or non keratinizing (above the dentate line).
  - ADENOCARCINOMA (20%) rectal type, of anal glands, within anorectal fistula
  - SMALL CELL CARCINOMA
  - UNDIFFERENTIATED
- ANAL MARGIN (PERIANAL SKIN)
  - SQUAMOUS CELL CARCINOMA
  - GIANT CONDYLOMA
  - BASAL CELL CARCINOMA
  - others Bowen's disease, Paget disease

### **RISK FACTORS**

- PERSONAL sexual activity (HPV, number of sexual partners, receptive anal intercourse, history of STD, genital warts)
- ENVIRONMENTAL smoking
- DISEASES HIV and other causes of chronic immu nosuppression (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 anor ectal condyloma (50%), while tumor of perianal skin can be associated with pruritus ani

**METASTATIC** RUQ pain, dyspnea

**CONSTITUTIONAL** weight loss, anorexia, fatigue

### STAGING

### TNM STAGING

### T stage

- **T1** < 2 cm
- **T2** >2 cm but ≤5 cm
- T3 >5 cm
- T4=invades adjacent organ(s) (involvement of sphincter muscle(s) alone is not classified as T4)

### N stage

- N1=perirectal LN
- N2=unilateral internal iliac LN and/or inguinal LN
- N3=perirectal and inguinal LN and/or bilateral internal iliac and/or inguinal lymph nodes

### STAGING (CONT'D)

### M stage

• M1=distant metastasis

### STAGE GROUPINGS

Stage	TNM @=any	5 year survival
1	T1N0M0 (10%)	85%
II	T2 T3N0M0 (55%)	75%
III	T1 3N1M0 (27%)	54%
IVA IVB	T4N@M0 T@N@M1 (6%)	17%

### INVESTIGATIONS

### BASIC

 LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, INR, PTT, albumin

### INVESTIGATIONS (CONT'D)

- IMAGING CXR, CT chest, CT, or MRI abd/pelvis  $\pm$  PET/CT
- BIOPSY mass biopsy

### MANAGEMENT

### SOUAMOUS CELL CANCER OF THE ANAL CANAL

chemoradiation (5 fluorouracil mitomycin). If evi dence of progression or persisting disease at 12 weeks after treatment, consider salvage abdomino perineal resection. For metastatic disease, consider palliative chemotherapy (5 fluorouracil cisplatin), regional therapy for isolated hepatic metastases

PRIMARY ADENOCARCINOMA OF THE ANAL CANAL managed like rectal cancer

**CANCER OF THE PERIANAL SKIN** treated like skin counterpart

### **Cancer of the Exocrine Pancreas**

### PATHOPHYSIOLOGY

### CLASSIFICATION BY HISTOLOGY

- ADENOCARCINOMA (85 90%) male predominance, 60% arising from head of pancreas, metastasizes widely
- DUCTAL CARCINOMAS
- ADENOSQUAMOUS CARCINOMA rare variant of duc tal adenocarcinoma, history of prior chemotherapy or radiotherapy, relatively poor prognosis
- COLLOID CARCINOMA (1 2%) composed of pools of mucous that contains clusters of malignant duct cells
- ACINAR CELL CARCINOMA (1%) lipase release, equal distribution throughout pancreas
- MUCINOUS CYSTIC NEOPLASMS (1%) cystic, significant malignant potential, strong female predominance, 70 90% in pancreatic body/tail
- SEROUS CYSTOADENOMAS cystic, benign
- SEROUS CYSTADENOCARCINOMA cystic, malignant behavior
- SOLID AND PSEUDOPAPILLARY CYSTIC TUMORS young female (childbearing) predominance, local 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

### PATHOPHYSIOLOGY (CONT'D)

### 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 syndrome, depression

### STAGING

### TNM STAGING

### T stage

- T1 <2 cm, limited to pancreas
- T2 >2 cm, limited to pancreas
- T3=extends beyond pancreas, but not involving celiac axis or superior mesenteric artery
- **T4**=invades celiac axis or superior mesenteric artery

Hepatocellular Carcinoma 205

### 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 Stage	GROUPINGS TNM @=any	Freq.	Median survival (months)
IA IB IIA	T1N0M0 T2N0M0 T3N0M0	10%	17
IIB III	T1 3N1M0 }	20 30%	8 9
IV	T@N@M1	50 60%	4 6

### INVESTIGATIONS

### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, 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 pro cedure plus either adjuvant chemotherapy (gemci tabine or 5 fluorouracil) or adjuvant chemoradiation (5 fluorouracil) ± gemcitabine in selected patients

**NON RESECTABLE** (locally advanced and metastatic disease)

- PALLIATIVE CHEMOTHERAPY gemcitabine  $\pm$  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 gang lion ablation
- PALLIATIVE RADIATION controversial with no clear benefit
- PALLIATIVE PROCEDURES if biliary obstruction, con sider ERCP stent placement or percutaneous trans hepatic cholangiography with drainage

### TREATMENT ISSUES

### RESECTABLE DISEASE CRITERIA<sup>a</sup>

- 1. No liver, peritoneal, or other metastases
- No involvement of celiac axis, superior mesenteric artery, and hepatic artery
- No encasement of portal vein and superior mesen teric vein (adherence of the tumor to a segment of these veins may allow resection with venous reconstruction)

<sup>a</sup>If in doubt, patients should be evaluated by a hepa tobiliary surgeon

### **Related Topics**

Cachexia (p. 397)

Cancer Pain (p. 391)

Jaundice (p. 138)

### **Hepatocellular Carcinoma**

# DIFFERENTIAL DIAGNOSIS OF FOCAL LIVER LESION (BY ULTRASOUND)

### SOLID LESION

- HYPOECHOIC malignant (hepatocellular carci noma, metastasis), benign (focal nodular hyperplasia, hepatic adenoma, hamartoma)
- HYPERECHOIC hemangioma, calcification, focal fat

### CYSTIC LESION

- SIMPLE benian
- **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 sati ety, obstructive jaundice, intra abdominal bleeding due to tumor rupture, decompensation of liver

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### CLINICAL FEATURES (CONT'D)

disease (ascites, encephalopathy, jaundice, and var iceal bleeding)

METASTATIC bone pain, dyspnea

**CONSTITUTIONAL** weight loss, fever due to cen tral tumor necrosis

**PARANEOPLASTIC SYNDROME** hypoglycemia, erythrocytosis, hypercalcemia, water diarrhea, cuta neous features

# STAGING FOR HEPATOCELLULAR CARCINOMA OR INTRAHEPATIC BILE DUCT CANCER

### TNM STAGING

### T stage

- T1=solitary tumor without vascular invasion
- T2=solitary tumor with vascular invasion or mul tiple tumors <5 cm</li>
- **T3**=multiple 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

Stage	TNM @=any	5 year survival
1	T1N0M0	55%
II	T2N0M0	37%
IIIA	T3N0M0	
IIIB	T4N0M0	16%
IIIC	T@N1M0	
IV	T@N@M1	<5%

### INVESTIGATIONS

### **BASIC**

- LABS CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, INR, PTT, albumin, AFP
- IMAGING CXR, CT abd (biphasic or triphasic), U/S abd, MRI abd, liver/spleen scan (if suspect FNH)
   SPECIAL
- BIOPSY liver biopsy if AASLD clinical criteria (atypical vascular pattern on imaging + AFP >100 U/L) not met or if biopsy would have an impact on management options

### DIAGNOSTIC ISSUES

**CT SCAN** characteristic features for hemangioma, FNH (central scar)

**LIVER SPLEEN SCAN** useful for distinguishing focal nodular hyperplasia and hepatoma

### DIAGNOSTIC ISSUES (CONT'D)

**GALLIUM SCAN** useful for identifying hepatoma and abscesses (increased blood flow)

**APPROACH TO HEPATOMA** start with U/S abd, followed by CT/nuclear scans to rule out other causes

- LOW CLINICAL SUSPICION consider percutaneous biopsy
- HIGH CLINICAL SUSPICION (known cirrhosis) patient should be referred to hepatobiliary surgeon for resection. Biopsy is not required

### MANAGEMENT

**EARLY STAGE** (1 lesion or 3 lesions <3 cm, Child Pugh A B, and ECOG 0) if only 1 lesion <2 cm or CIS, bilirubin not significantly elevated and no portal hypertension, proceed to resection. For unresectable disease up to 3 lesions <3 cm, consider liver trans plant 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. Chemoemboliza tion 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 com pensated cirrhosis, single lobe involvement, no vas cular invasion, NO, MO

CRITERIA FOR PERCUTANEOUS ETHANOL ABLA TION 1 lesion <5 cm or 3 lesions <3 cm, accessible, no ascites, not coagulopathic, non resectable or refuses surgery, awaiting transplantation. Radiofre quency 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

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### SPECIFIC ENTITIES (CONT'D)

**HEPATIC ADENOMA** mainly in young woman on oral contraceptive pills. May cause abdominal pain. Potential for malignant transformation. Treat initially by withdrawal of oral contraceptives and follow lesions by ultrasound. If fail to regress, consider resection

### **Related Topics**

Hepatitis B (p. 130) Hepatitis C (p. 131) Hepatic Failure (p. 128)

Chronic Liver Disease (p. 132)

### **Renal Cancer**

NEJM 2005 335:12 Cancer 2006 107:10

### DIFFERENTIAL DIAGNOSIS OF SOLID RENAL MASS

### **RENAL MALIGNANCIES**

**ANGIOMYOLIPOMA** distinctive fat density on CT. Association with tuberous sclerosis

**ONCOCYTOMA** a homogeneous, well circum scribed 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 cor tical 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 juxtaglomeru lar 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, heredi tary type 2 papillary renal cell carcinoma, Birt Hogg Dube syndrome, autosomal dominant poly cystic kidney disease

### CLINICAL FEATURES

**LOCOREGIONAL** classic triad of flank pain, hema turia, 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, fatique

**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=ex tends 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
Juge	Trum @-uny	surviva
1	T1N0M0	96%
II	T2N0M0	82%
Ш	T1 3N1M0, T3N0M0	64%
IV	T4N@M0 T@N2M0 T@N@M1	23%

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### INVESTIGATIONS

### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, INR, PTT, urinalysis (hematuria, proteinuria)
- URINE CYTOLOGY
- IMAGING CXR, US abd, CT abd/pelvis (most useful),
   IVP, bone scan (if suspicious), CT head (if suspicious)
- NEPHRECTOMY for solitary renal mass, needle biopsy is generally not done because of its low specificity and potential for seeding, while nephrectomy is both diagnostic and therapeutic

### DIAGNOSTIC AND PROGNOSTIC ISSUES

**DIAGNOSTIC NEPHRECTOMY CRITERIA** diameter >3 cm, enhancement with contrast, poorly defined margins, or areas of necrosis all suggest malignancies and resection is strongly recommended. Biopsy prior to surgery is usually not required

ADVERSE PROGNOSTIC FACTORS >10 cm, stage III IV, Fuhrman's grade 3 4 (based on nuclear size and shape, and nucleolar appearance, a score of 1 4 is given) MSK PROGNOSTIC SCORE FOR METASTATIC RENAL CELL CARCINOMA Karnofsky performance status <80%, LDH >1.5× upper normal limit, calcium >2.5 mmol/L [>10 mg/dL], hemoglobin lower normal limit, absence of nephrectomy

Factors	Risk	Freq.	1 year	3 year
	group		survival	survival
0	Good	25%	71%	31%
1 2	Inter.	53%	42%	7%
3 5	Poor	22%	12%	0%
			ICO	1000 17.9

### MANAGEMENT

**STAGE I, II** radical nephrectomy  $\pm$  regional node dissection

**STAGE III** radical nephrectomy  $\pm$  regional node dissection  $\pm$  renal vein or vena cava evacuation

### MANAGEMENT (CONT'D)

### STAGE IV

- PALLIATIVE RESECTION nephrectomy (particularly if primary is symptomatic), systemic therapy intended, limited metastatic disease, good 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 can cer syndrome due to mutation of the VHL gene. Disease spectrum includes renal cell carcinomas (clear cell type, 40%) and cysts, pancreatic carci nomas and cysts, pheochromocytomas, heman gioblastomas of the cerebellum and spinal cord. and retinal hemangiomas. HIF1 $\alpha$  is hydroxylated in normoxic conditions, which is then ubiquiti nated by VHL protein complex and destroyed. Accumulation of HIF1α happens with hypoxic conditions or mutated VHL protein, which then heterodimerizes with HIF1B and activates tran scription of various genes such as VEGF. Devel opment of targeted therapy for renal cell carci noma was facilitated by our understanding of the VHL HIF1α VEGF pathway

### **Bladder Cancer**

### PATHOPHYSIOLOGY

### **CLASSIFICATION BY HISTOLOGY**

- TRANSITIONAL CELL (90%)
- squamous (8%)
- ADENOCARCINOMA (2%)
- RHABDOMYOSARCOMA
- LYMPHOMA
- CARCINOID

### NATURAL HISTORY OF SUPERFICIAL TUMORS

low grade superficial tumors have high recurrence rate (80%) and low risk of becoming invasive (10%). High grade superficial tumors are frequently

### PATHOPHYSIOLOGY (CONT'D)

associated with carcinoma in situ, which is usually multifocal and has a high chance of becoming inva sive (80% within 10 years)

### RISK FACTORS

- PERSONAL age
- ENVIRONMENTAL smoking (4×), occupation (dye, rubber, textiles, leather, and petroleum industries with exposure to aniline, arylamines such as ben zidine and 2 naphthylamine and amides), drugs (cyclophosphamide), pelvic radiation
- FAMILY HISTORY affected relatives

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### PATHOPHYSIOLOGY (CONT'D)

 DISEASES (usually squamous cell carcinoma) schistosomiasis, chronic bladder infection, Balkan endemic nephropathy

### **CLINICAL FEATURES**

**LOCOREGIONAL** painless intermittent hematuria (80%), bladder irritability (25%, hesitancy, urgency, frequency, and dysuria), abdominal mass, suprapubic or flank pain, lymphedema

METASTATIC dyspnea, bone pain, jaundice
CONSTITUTIONAL weight loss, anorexia, fatigue
PARANEOPLASTIC hypercalcemia, systemic fibri
nolysis, 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

Stage	TNM @=any	5 year survival
0a	TaN0M0 \	>90%
0is	TisN0M0∫	/90/0
1	T1N0M0	85%
II	T2a bN0M0	60%
Ш	T3a bN0M0, T4aN0M0	35%
IV	T4bN0M0, T@N1 3M0	15%
	T@N@M1	

### INVESTIGATIONS

### BASIC

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

### PROGNOSTIC ISSUES

### RISK FACTORS FOR RECURRENCE OF SUPER FICIAL 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 OA, OIS, I transurethral resection (TUR)
 ± fulguration ± intravesicular therapy (BCG×6
 [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  $\pm$  pel vic lymph node dissection or curative radia tion, (neo)adjuvant chemotherapy (gemcita bine cisplatin [GC], methotrexate vinblastine doxorubicin cisplatin [MVAC], cisplatin metho trexate vinblastine [CMV])
- STAGE IV palliative chemotherapy (GC, MVAC, CMV)

210 Prostate Cancer

### **Prostate Cancer**

### PATHOPHYSIOLOGY

### **CLASSIFICATION BY HISTOLOGY**

- ADENOCARCINOMA (>95%)
- PROSTATE INTRAEPITHELIAL NEOPLASM (PIN)
- TRANSITIONAL CELL CARCINOMA
- SMALL CELL CARCINOMA
- SOUAMOUS 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  $5\times$ )
- ENVIRONMENTAL total and saturated fat intake

### CLINICAL FEATURES

muscular syndromes

**LOCOREGIONAL** mostly asymptomatic with diag nosis 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. Hypercal cemia and fractures are not very common as the meta static lesions tend to be osteoblastic instead of lytic CONSTITUTIONAL weight loss, anorexia, fatigue PARANEOPLASTIC systemic fibrinolysis, neuro

# 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=inciden tal finding by TURP in >5% of tissue, T1c=inci dental finding by needle biopsy due to ↑ PSA)
- T2=confined within prostate (T2a=invades less than or equal to half of one lobe, T2b=invades more than half of one lobe, T2c=invades both lobes)

### STAGING (CONT'D)

- T3=extends through the prostate capsule (T3a=extracapsular extension, T3b=invades seminal vesicle(s))
- T4=fixed or invades bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

**N stage** (obturator, hypogastric → iliac)

N1=regional LN

**M stage** (bone, liver. Biologically heterogeneous with variable course)

• M1=distant metastasis

### GRADE

- G1=Gleason score 2 4 and well differentiated
- G2=5 6 and moderately differentiated
- G3 4=7 10 and poorly/undifferentiated

### **STAGE GROUPINGS**

Stage	TNM	5 year survival
1	T1aN0M0+G1	>95%
II	T1aN0M0+G2 4	70%
	T1b cN0M0, T2N0M0	
Ш	T3N0M0	60%
IV	T4N0M0, T@N1M0, T@N@M1	30%

### INVESTIGATIONS

### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, INR, PTT, albumin, PSA, testosterone
- IMAGING CXR, CT or MRI abd/pelvis (if high risk disease), bone scan (if high risk disease), trans rectal 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 pro tease that liquidifies semen physiologically. Ele vated in prostate cancer, prostatitis, BPH, endo scopy, prostate surgery, prostate biopsy (remains elevated for 6 8 weeks), and with increasing age

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### 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 antic 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

### DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

warrant a biopsy. So far, PSA screening has not been proven to reduce mortality from prostate cancer

 BIOCHEMICAL RELAPSE for patients with previous prostatectomy, PSA relapse is indicated by any detectable value, particularly if >1 ng/mL. For patients with previous external beam radiation or brachytherapy, PSA relapse is indicated by PSA >2 ng/mL from nadir

**ADVERSE PROGNOSTIC FACTORS** pre treatment PSA, Gleason score, stage

RISK CATEGORIES FOR LOCALIZED DISEASE								
Risk category	PSA (ng/mL)	Gleason score	Stage					
Low (highly curable)	≤10	2 6	≤T2b					
Intermediate (curable) <sup>a</sup>	10 20	7	T2c					
High (rarely curable)	>20	8 10	≥T3					
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<sup>a</sup>lf only one of PSA or Gleason score meets criteria, considered low intermediate risk. If both PSA or Gleason score meet criteria, considered high intermediate risk

### MANAGEMENT

### LOCALIZED DISEASE (T1 3N0M0)

- LOW RISK consider active surveillance if significant comorbidities or <10 year life expectancy. Patients on active surveillance should have PSA testing every 6 months and prostate biopsy yearly, and consider treatment with disease progression (i.e. meet intermediate risk criteria, decrease in PSA doubling time <3 years, DRE changes, or prostate biopsy demonstrating Gleason score ≥7, >2 scores positive, >50% involvement in core sample). Curative options include brachytherapy and radical prostatectomy, which are preferred over external beam radiation
- INTERMEDIATE RISK consider brachytherapy or radical prostatectomy for low intermediate risk group. LHRH agonist ×6 months combined with external beam radiation (starting at 3 months) for high intermediate risk group
- HIGH RISK usually LHRH agonist ×1 year combined with external beam radiation (starting at 6 8 months)
- RELAPSE may consider salvage (i.e. external beam radiation for patients with radical prostatectomy or brachytherapy) for young and fit patients. Other wise, treat as advanced disease

**ADVANCED DISEASE** (T4, N1 3, M1) **life long cas tration** (surgical or medical with LHRH agonists

### MANAGEMENT (CONT'D)

[leuprolide 22.5 mg IM g3month, goserelin 10.8 mg SC q3month] plus flutamide for first few weeks to con trol 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 treat ment when patient become symptomatic, and thus not recommended. With disease progression, con sider 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, con sider anti androgen withdrawal. With further pro gression to castration resistant (formerly hormone refractory) prostate cancer, consider palliative che motherapy (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, keto conazole 400 mg PO TID, aminoglutethimide, predni sone 5 mg PO BID, and finasteride ( $\alpha$ 5 reductase inhibitor). Abiraterone is being investigated as a promising agent. Palliative radiation, bisphosphonates (zoledronic acid), and strontium infusion can be use ful for bone metastasis

TREATMENT ISSUES						
COMPARISON OF TREATMENTS FOR LOCALIZED DISEASE <sup>a</sup>						
	Impotence	Ur	inary incontinence	Ur	inary irritation	GI irritation
Prostatectomy <sup>b</sup>	50 90%	10	20%	15	60%	2 17%
Brachytherapy	50%	1	2%	12	30%	10%
External RT <sup>c</sup>	50%	1	2%	2	30%	30%
<sup>a</sup> side effects at 5 years are listed						
b symptoms tend to decrease over time						
c symptoms tend to						

### TREATMENT ISSUES (CONT'D)

### RADICAL PROSTATECTOMY

- BENEFITS 5 year disease free survival 85%
- INDICATIONS preferred for patients with low risk disease, life expectancy >20 years, or significant urinary symptoms
- **CONTRAINDICATIONS** age >70, high risk disease
- ADVERSE EFFECTS urinary (frequency, urgency, nocturia, dysuria, incontinence), impotence

### **BRACHYTHERAPY** implant of radioactive seeds

- **BENEFITS** 5 year disease free survival 96%
- INDICATIONS eligibility criteria include PSA ≤15 ng/mL, Gleason score ≤7, stage ≤T2c, pros tate volume <60 mL, and life expectancy >5 years
- CONTRAINDICATIONS significant urinary symptoms (as prostate swells significantly shortly after procedure), prior TURP
- ADVERSE EFFECTS urinary (frequency, urgency, nocturia, dysuria, incontinence), GI (diarrhea, tenesmus), and impotence; 3% require indwelling urinary catheter for >3 weeks and <1% chance of severe GI symptoms requiring colostomy. The symptoms typically peak at 6 weeks and generally resolve over time; 50% of patients return to base line symptoms at 3 months and 95% by 1 year</li>

### **EXTERNAL BEAM RADIATION**

• BENEFITS 5 year disease free survival 80%

### TREATMENT ISSUES (CONT'D)

- INDICATIONS preferred for patients with high risk disease or older
- CONTRAINDICATIONS pelvic kidney, inflammatory bowel disease, connective tissue disease (SLE, scleroderma), or prior radiation to same region
- ADVERSE EFFECTS urinary (frequency urgency, nocturia, dysuria, incontinence), GI (diarrhea, rectal bleeding), and impotence. Urethral stricture (1%), bowel obstruction (0.1%). Also risk of late onset second malignancy

### LHRH AGONISTS

- INDICATIONS high intermediate or high risk loca lized disease, salvage setting, or advanced disease setting. Requires the use of an antiandrogen (fluta mide) 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 andro gen independence 1.5 year. Median time from andro gen independence to death 1.5 year

EGCCCG Guidelines Ann Onc 2004 15

### **Testicular Cancer**

### PATHOPHYSIOLOGY

### CLASSIFICATION BY HISTOLOGY

- TESTICULAR INTRAEPITHELIAL NEOPLASIA (TIN) 70% chance of progression to testicular cancer in 7 years
- GERM CELL TUMOR (95%) can differentiate into any immature or mature tissue type, usually mixed
  - SEMINOMA (40%) neoplastic counterpart of spermatocyte. Age thirties to forties, pure, αFP nega4tive and sometimes slightly βhCG posi tive. Few metastasize. Very radiosensitive and very chemosensitive
  - NON-SEMINOMA (60%) age twenties to thirties, pure or mixed, more metastasize. Chemosensi tive. Include the following subtypes

### PATHOPHYSIOLOGY (CONT'D)

- EMBRYONAL CELL CARCINOMA neoplastic counterpart of inner cell mass of embryo.
   May be βhCG+, αFP+
- YOLK SAC TUMOR neoplastic counterpart of yolk sac. Usually αFP+
- CHORIOCARCINOMA neoplastic counterpart of chorionic villus. Usually βhCG+
- IMMATURE TERATOMA neoplastic counterpart of fetal tissue. Marker negative
- MATURE TERATOMA neoplastic counterpart of mature adult tissue. Marker negative. Com pletely resistant to chemotherapy. May trans form into malignant mesodermal, endoder mal. or ectodermal elements

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### PATHOPHYSIOLOGY (CONT'D)

- SEX CORD STROMAL TUMORS
  - SERTOLI CELL TUMOR
  - LEYDIG CELL TUMOR
  - GRANULOSA CELL TUMOR
  - MIXED CELL TYPE (SERTOLI-LEYDIG CELL)
- MIXED GERM CELL AND STROMAL TUMORS
  - GONADOBLASTOMA
- LYMPHOMA
- RHABDOMYOSARCOMA
- CARCINOID

**ISOCHROMOSOME 12P** characteristic of germ cell tumors. Poorly differentiated neoplasms of unknown primary with this cytogenetic feature are highly sen sitive to cisplatin based chemotherapy

### **RISK FACTORS**

- FAMILY HISTORY affected relatives
- DISEASES prior testicular cancer, cryptorchidism (10 40×), testicular feminization syndromes, Kli nefelter syndrome

### CLINICAL FEATURES

**LOCOREGIONAL** testicular mass  $\pm$  pain, acute epi didymitis (25% of embryonal cell tumor and mixed teratoma), back pain (10%), gynecomastia ( $\beta$ hCG), infertility (3%)

**METASTATIC** dyspnea, cough, headaches, stroke **CONSTITUTIONAL** weight loss, anorexia, fatigue

### STAGING

### TNM STAGING

### T stage

 T1=limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade into tunica albuginea but not tunica vaginalis

### STAGING (CONT'D)

- T2=limited to testis and epididymis with vascu lar/lymphatic invasion or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
- T3=invades the spermatic cord  $\pm$  vascular/lym phatic invasion
- T4=invades the scrotum  $\pm$  vascular/lymphatic invasion

### $\mathbf{N}$ stage (pelvic $\rightarrow$ paraaortic LN)

- N1=1 5 LN, all È2 cm
- N2=1 or more LN 2 5 cm or >5 LN E5 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

	$\alpha$ FP (ng/mL)	βhCG (IU/L)	LDH
S1	<1000	< 5000	<1.5×
S2	1000 10,000	5000 50,000	1.5 10×
S3	>10,000	>50,000	>10×

### STAGE GROUPINGS

STAGE GK	STAGE GROUPINGS						
Stage	TNM @=any						
IA	T1N0M0S0						
IB	T2 4N0M0S0						
IS	T@N0M0S1 3						
IIA	T@N1M0S0 1						
IIB	T@N2M0S0 1						
IIC	T@N3M0S0 1						
IIIA	T@N@M1aS0 1						
IIIB	T@N@M0 1aS2						
IIIC	T@N@M0 1aS3, T@N@M1bS@						

### Risk group

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
Any location, any marker, and any non pulmonary metastases
Not applicable

### INVESTIGATIONS

### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, INR, PTT, albumin, lipase, αFP, βhCG, LDH, TSH, T3, T4, total testosterone, LH, FSH
- IMAGING testicular U/S, CXR, CT abd/pelvis, CT head (if advanced disease with intermediate or poor prognosis), bone scan (if suspect metastasis)
- RADICAL INGUINAL ORCHIECTOMY

### **SPECIAL**

• SEMEN ANALYSIS if fertility a consideration

### DIAGNOSTIC AND PROGNOSTIC ISSUES

**DIFFERENTIAL DIAGNOSIS OF TESTICULAR MASS** epididymitis, hydroceles, varicoceles, sper matoceles, 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, chorio carcinoma. Half life 24 h
- αFP elevated in yolk sac tumor. Half life 2 3 days

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DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)							
Tumor	αFP						
Non seminoma	↑ in up to 85%	↑ in up to 80%					
Seminoma	↑ in 15 25%	Normal					

**PROGNOSTIC FACTORS** vascular invasion is most important indicator for relapse in non seminoma

### MANAGEMENT

NOTE: all cases should be discussed with an interdis ciplinary team experienced in the management of testicular cancer

### **EARLY SEMINOMA**

- STAGE I orchiectomy + one of adjuvant radia tion (paraaortic/paracaval LN, 3 4% relapse) or adjuvant carboplatin (1 2 cycles, 3 4% relapse) or surveillance (15 20% relapse (higher risk of recurrence if >4 cm or rete testis involvement)
- STAGE IIA orchiectomy + radiation (paraaortic/ ipsilateral iliac LN, 6 year RFS 95%)
- STAGE IIB orchiectomy + one of radiation (para aortic/ipsilateral iliac LN, 6 year RFS 89%) or che motherapy (if radiation not given, BEP×3 or EP×4, where B=bleomycin, E=etoposide, P=cisplatin)

### **EARLY NON SEMINOMA**

- STAGE I WITH NO VASCULAR INVASION (14 22% relapse) orchiectomy + one of surveillance (14 22% relapse) or chemotherapy (if surveil lance not chosen, BEP×2) or nerve sparing retro peritoneal [NSRP] LN dissection (if both surveil lance and chemotherapy not chosen). Surveillance is recommended
- STAGE I WITH VASCULAR INVASION (48% relapse) orchiectomy + one of chemotherapy (BEP×2, 3% relapse) or surveillance (if chemotherapy not given, 48% relapse) or NSRP LN dissection (if both surveillance and chemotherapy not chosen, 10% relapse). Surveillance is recommended
- STAGE IIA, MARKER NEGATIVE orchiectomy + one of
- NSRP LN dissection → if pathologic stage IIA or IIB, BEP×2; if stage I, surveillance only, or surveil lance (follow up every 6 weeks) → if regression, follow up only; if no change, NSRP LN dissection or close follow up; if progressive disease, BEP×3 or NSRP LN dissection
- STAGE IIA, MARKER POSITIVE orchiectomy + BEP×3 + resection if residual tumor
- STAGE IIB orchiectomy + BEP×3 + resection if residual tumor

# ADVANCED SEMINOMA AND NON SEMINOMA (IIC. IIIA C)

- GOOD RISK orchiectomy + chemotherapy (BEP×3 or EP×4)
- INTERMEDIATE/POOR RISK orchiectomy + che motherapy (BEP×4)

### MANAGEMENT (CONT'D)

- normalized (proceed to resection → if necrosis (40%), differentiated teratoma (40%) or <10% viable tumors, follow up only; if >10% viable tumors, consolidative chemotherapy with VIP×2; if incomplete resection of viable tumor, treat as marker increased), marker elevated but plateau (follow up 4 12 weeks → treat as marker normalized or marker increased depending on trend), marker increased after short inter val (salvage chemotherapy with PEI×4, VIP×4, VeIP×4, TIP×4)
- NOTE B=bleomycin, E/V=etoposide (VP16), P=cisplatin, I=ifosfamide, Ve=vinblastine, T=taxol RELAPSED SEMINOMA if systemic relapse, consider BEP ×4. If locoregional relapse, consider BEP or radiotherapy. Salvage chemotherapy regimens after first line chemotherapy include PEI×4, VIP×4, or VeIP×4 or TIP×4

**RELAPSED NON SEMINOMA** salvage chemother apy regimens after first line chemotherapy include  $PEI \times 4$ ,  $VIP \times 4$ , or  $VeIP \times 4$  or  $TIP \times 4$ . For late relapses, patients with negative tumor markers should have immediate radical surgery. If unresectable disease, consider salvage chemotherapy and then resection if possible. If unresectable disease and localized, con sider radiotherapy

### TREATMENT ISSUES

**GROWING TERATOMA SYNDROME** defined as enlargement of a residual mass post chemotherapy, despite complete normalization of tumor marker sug gesting 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 adeno carcinoma or rhabdomyosarcoma

**RADICAL ORCHIECTOMY** should always be done prior to any further treatment, except for life threa tening 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 replace ment should be given if bilateral orchiectomy. Patients planning to father children should have hormone and semen analysis for 1 to 3 year post treatment

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### **Brain Tumors**

See BRAIN TUMORS (p. 297)

### **Ovarian Cancer**

### PATHOPHYSIOLOGY

### HISTOLOGIC TYPE

- EPITHELIAL (90%)
  - SEROUS CYSTADENOCARCINOMA (75 80%)
  - MUCINOUS CYSTADENOCARCINOMA (10%)
  - ENDOMETRIOID CARCINOMA (10%)
  - CLEAR CELL (<5%)</li>
  - UNDIFFERENTIATED (<1%)</li>
  - Brenner's tumor (<1%)</li>
  - MIXED EPITHELIAL TUMOR
  - MALIGNANT MIXED MULLERIAN TUMORS (carcinosarcomas)
  - UNCLASSIFIED
- GERM CELL TUMORS
  - DYSGERMINOMA (ovarian counterpart of semi noma 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 bloat ing/distension, renal failure, urinary frequency
- METASTATIC cough
- CONSTITUTIONAL weight loss, weight gain (if ascites and edema), anorexia, fatigue
- PARANEOPLASTIC neurologic (peripheral neuropa thy, 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 sur face, ruptured capsule, positive pelvic washings

**STAGE III** (65%) peritoneal implants outside the pelvis with extensions to small bowel, omen tum, 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, ret roperitoneal/inguinal lymph nodes

**STAGE IV** (5%) distant metastasis; 10% 5 year survival

• **IV**=liver parenchyma, peripheral superficial lymph nodes, cytology positive pleural effusion

### **OVERALL SURVIVAL BY STAGE**

Stage	FIGO stage	stage Freq 5 year s					
1	IA C	35%	80 90%				
II	IIA C	5%	60 70%				
III	IIIA C	40%	30 50%				
IV	IV	10%	20%				

### INVESTIGATIONS

### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, Ca, albumin, CA125, βhCG, αFP
  - IMAGING CXR, U/S abd, CT abd/pelvis
  - BIOPSY laparoscopy, staging laparotomy

### DIAGNOSTIC AND PROGNOSTIC ISSUES

**DISTINGUISHING FEATURES BETWEEN OVARIAN CANCER AND BENIGN CYSTS** any of the following features should prompt consideration of ovarian can cer and biopsy: any postmenopausal women, >8 cm in premenopausal women, solid, or cystic but still present after 2 months of oral contraceptive pills, presence of ascites

**ADVERSE PROGNOSTIC FACTORS** advanced stage, high grade, residual disease after debulking (38 vs. 60 months), poor performance status

### **Related Topics**

BRCA Mutations (p. 225) Cancer Screening (p. 222) Tumor Markers (p. 220)

### MANAGEMENT

### **EPITHELIAL OVARIAN TUMORS**

- STAGE IA B, GRADE 1 total abdominal hysterect omy/bilateral salpingo oophorectomy (TAH/BSO).
   If premenopausal, consider unilateral oophorect omy 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

### MANAGEMENT (CONT'D)

(if greater than 6 months since last line of plati num based therapy; regimens include carbopla tin paclitaxel, carboplatin liposomal doxorubicin, and carboplatin gemcitabine) or single agent therapy using carboplatin, paclitaxel, cisplatin, topotecan, etoposide, gemcitabine, vinorelbine, fiosfamide, or liposomal doxorubicin. In plati num resistant disease, single agent therapy is recommended. Platinum resistance is commonly defined as clinical evidence of disease progression <6 months from last platinum therapy

**GERM CELL TUMORS** surgery is mainstay. May consider unilateral salphingo oophorectomy to pre serve fertility in young women. For advanced disease consider BEP (bleomycin etoposide cisplatin) che motherapy after surgery. The treatment paradigm is based entirely on germ cell tumors of the testicle (p. 212)

**SEX CORD STROMAL TUMORS** surgery is main stay. Excellent prognosis

### TREATMENT ISSUES

**OVARIAN CANCER SURGERY** for both staging and cytoreduction. Key features include (1) obtain ing free fluid or lavage for cytology, (2) systematic exploration of all intra abdominal organs, surfaces and retroperitoneum for pelvic and paraaortic lymph nodes, (3) biopsy of any suspicious areas or random biopsies from peritoneum of the cul de sac, paracolic gutters, bladder, intestinal mesentery and lymph nodes, (4) biopsy of diaphragm, (5) resection of omentum, and (6) total abdominal hysterectomy and bilateral salpingo oophorectomy. For patients who had a good response to neoadjuvant che motherapy (no prior maximal surgical effort), surgi cal resection to remove residual macroscopic dis ease is generally recommended

### **Endometrial Cancer**

### PATHOPHYSIOLOGY

### HISTOLOGIC TYPE OF UTERINE CANCER

- ENDOMETRIAL CARCINOMAS (97%)
  - ADENOCARCINOMA (>95%)
  - CLEAR CELL CARCINOMA associated with more aggressive disease and worse prognosis, but more responsive to chemotherapy
  - PAPILLARY SEROUS CARCINOMA associated with more aggressive disease and worse prognosis

### PATHOPHYSIOLOGY (CONT'D)

- SMALL CELL CARCINOMA
- MALIGNANT MIXED MULLERIAN TUMORS
- UTERINE SARCOMA (3%)

### RISK FACTORS

 PERSONAL age, excess estrogen (early menarche, late menopause, nulliparity, obesity with conver sion of androstenedione to estrone by aromatase in adipose tissue) Endometrial Cancer 217

### PATHOPHYSIOLOGY (CONT'D)

- FAMILY HISTORY HNPCC
- DISEASES ovarian granulosa cell and theca cell tumors (produce estrogen), polycystic ovary dis ease (chronic anovulation), diabetes (2×), tamox ifen (3 7×), unopposed estrogen administration (i.e. without progesterone, 6×)

### CLINICAL FEATURES

### SYMPTOMS

- LOCOREGIONAL abnormal vaginal bleed (97%, par ticularly in postmenopausal women), pelvic pain, pelvic mass, constipation, bowel obstruction, abdominal pain, abdominal bloating/distension, renal failure, urinary frequency
- **METASTATIC** dyspnea, cough, abdominal pain, sei zures, bony pain
- CONSTITUTIONAL weight loss, anorexia, fatigue

### PROGNOSTIC ISSUES

ADVERSE PROGNOSTIC FACTORS advanced stage, high grade, papillary serous carcinoma, small cell carcinoma, vascular invasion, ER negative, PR negative, DNA ploidy

### STAGING

### **REVISED FIGO STAGING 2009**

STAGE I confined to the corpus uteri

- IA=no or less than half myometrial invasion
- **IB**=invasion equal to or more than half of the myometrium

STAGE II involves cervical stroma

• II=invades cervical stroma, but does not extend beyond the uterus

**STAGE III** local and regional spread of the tumor

- IIIA=invades the serosa of the corpus uteri and/ or adnexae
- IIIB=vaginal and/or parametrial involvement
- IIIC=metastases to pelvic and/or para aortic LN
  - IIIC1=pelvic nodes
  - IIIC2=para aortic lymph nodes with or with out positive pelvic lymph

**STAGE IV** extends outside the true pelvis

- IVA=invasion of bladder and/or bowel mucosa
- IVB=distant metastases, including intra abdom inal metastases and/or inguinal LN

### GRADE

- **G1**=well differentiated (≤5% of solid growth pattern)
- G2=moderately differentiated (6 50%)
- **G3**=undifferentiated (>50%)

### STAGING (CONT'D)

### OVERALI SURVIVAL BY STAGE

OVERALL SORVIVAL DI SIAGL							
Surgical stage	Freq	5 year survival					
IA B	75%	80 90%					
II	11%	70%					
IIIA C	11%	50%					
IVΔ R	3%	20 30%					

### INVESTIGATIONS

### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, CA 125
- IMAGING CXR
- BIOPSY endometrial curettage with endocervi cal sampling, dilation and curettage, colono scopy (if symptomatic or relevant family history suggestive of HNPCC)

### **SPECIAL**

 ADDITIONAL IMAGING transvaginal U/S (not rou tinely required), CT abd/pelvis (not routinely required), MR pelvis with gadolinium (most sen sitive but not routinely required)

### MANAGEMENT

**STAGE I TAH/BSO**  $\pm$  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 **adju vant 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 ± lymphadenect omy), followed by **adjuvant chemotherapy** (gener ally a platinum taxane combination with or without doxorubicin)

### STAGE IV OR LOCALLY RECURRENT DISEASE

- **EXENTERATION** potentially curable if isolated cen tral recurrence
- PELVIC RADIATION if central local recurrence and not previously irradiated
- HORMONAL AGENTS for grade 1 2 disease, con sider 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 ther apy include well differentiated tumors (G1 2), ER/PR+ tumors, and long progression free survival before recurrence

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### MANAGEMENT (CONT'D)

 CHEMOTHERAPY regimens include carboplatin pa clitaxel, 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 LYM PHADENECTOMY this is an area of controversy. Two large trials have demonstrated no therapeutic benefit to lymphadenectomy. This has not been uni 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 junc tion. Slow progression from CIN to carcinoma over 15 years
- ADENOCARCINOMA (20%)
- SARCOMA

**HPV AND CERVICAL CANCER** types 16, 18, 45, 31, 33, 52, 58, 35 are associated with cervical cancer, and type 18 is particularly strongly associated with poorly differentiated carcinoma with nodal metastases. Viral proteins implicated in carcinogenesis include E6 and E7. Types 6 and 11 are usually associated with con dyloma acuminate

**RISK FACTORS** early age at first intercourse, early first pregnancy, multiple sexual partners, male part ners with multiple sexual partners, venereal diseases (especially HPV related), HIV, smoking

### CLINICAL FEATURES

### **SYMPTOMS**

- LOCOREGIONAL may be asymptomatic, abnormal vaginal bleeding, postcoital spotting, vaginal dis charge (may be malodorous), pelvic pain
- METASTATIC cough, jaundice, bony pain
- constitutional weight loss, anorexia, fatigue

### **Related Topic**

Cancer Screening (p. 222)

### TNM STAGING

### **TNM STAGING**

### T stage

- T1a=microscopic only (T1a1=stromal invasion ≤3 mm and ≤7 mm in lateral spread, T1a2=stromal invasion 3 5 mm and ≤7 mm in lateral spread)

### TNM STAGING (CONT'D)

- T2=beyond cervix but not pelvic wall (T2a=proximal 2/3 of vagina, T2b=with parame trial 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	JKUUPINGS		
Stage	TNM @=any		5 year survival
IA1	T1a1N0M0		050/
IA2	T1a2N0M0		95%
IB1	T1b1N0M0		
IB2	T1b2N0M0	•	80%
IIA	T2aN0M0		<b>60</b> 0/
IIB	T2bN0M0	-	60%
IIIA	T3aN0M0		200/
IIIB	T3bN@M0, T1a1 3aN1M0	-	30%
IVA	T4N@M0		
IVB	T@N@M1	-	5%

### INVESTIGATIONS

### BASIC

- BLOOD TESTS CBCD, lytes, urea, Cr, AST, ALT, ALP, bili
- IMAGING CXR, CT abd/pelvis
- SPECIAL pap smear → if lesion suspected, col poscopy, cone biopsy, loop electrosurgical excision, endocervical curettage

### MANAGEMENT

**STAGE IA1 simple hysterectomy**, excisional con ization. If lymphovascular invasion, treat as IA2 disease

Cancer of Unknown Origin 219

### MANAGEMENT (CONT'D)

**STAGE IA2, IB1 radical hysterectomy**, bilateral pelvic and paraaortic lymphadenectomy

STAGE IB2, IIA chemoradiation with cisplatin  $\pm$  5 FU. Alternatively, radical hysterectomy, bilateral pelvic and paraaortic lymphadenectomy, followed by adjuvant radiation or chemoradiation with cispla tin  $\pm$  5 FU

STAGE IIB, III, IVA (locally advanced) chemoradia tion with cisplatin  $\pm$  5 FU  $\pm$  additional brachytherapy STAGE IVB palliative chemotherapy (cisplatin topotecan, cisplatin paclitaxel, cisplatin, carboplatin, bleomycin, mitomycin C), palliative radiation

### MANAGEMENT (CONT'D)

**RECURRENCE** for locally recurrent disease, pelvic **exenteration** (32 62% 5 year survival). For recur rence in the pelvis following radical surgery, **chemor adiation** with cisplatin or 5 FU  $\pm$  mitomycin C (40 50% cure). If distant recurrence, treat with **pal liative chemotherapy** 

**HPV VACCINATION** may offer primary prevention although clinical data lacking at this time. Current vaccines are created against common serologic types only, including HPV 6, 11, 16, and 18

### **Cancer of Unknown Origin**

### PATHOPHYSIOLOGY

### CLASSIFICATION BY HISTOLOGY

- ADENOCARCINOMA well to moderately differentiated (60%)
- ADENOCARCINOMA/CARCINOMA poorly differen tiated (30%)
- SQUAMOUS CELL CARCINOMA (5%)
- UNDIFFERENTIATED NEOPLASMS (5%)

NATURAL HISTORY early, unpredictable, and aggressive metastasis. Primary too small to cause symptoms

### **Related Topic**

Tumor Markers (p. 220)

### **IMMUNOHISTOCHEMICAL MARKERS**

- CARCINOMA cytokeratin negative, common leuko cyte antigen, S100, vimentin negative. Breast can cer may be ER/PR positive
- LYMPHOMA common leukocyte antigen

### PATHOPHYSIOLOGY (CONT'D)

- SARCOMA vimentin positive (mesenchymal), des min positive (rhabdomyosarcoma), factor VII anti gen (angiosarcoma)
- MELANOMA S100, HMB 45, MART, vimentin, NSE positive
- NEUROENDOCRINE TUMORS neuron specific eno lase, synaptophysin, chromogranin

### INVESTIGATIONS

### **BASIC**

- LABS CBCD, lytes, urea, Cr, glucose, AST, ALT, ALP, bilirubin, LDH, INR, PTT, β hCG, AFP, PSA, Ca 125, CEA, CA 19 9
- IMAGING CT chest/abd/pelvis
- **SPECIAL** tissue biopsy

### MANAGEMENT

**TREAT UNDERLYING CAUSE** see table below for tailored treatment of cancer of unknown primary based on most likely tumor type

**SUPPORTIVE** symptom control, consider palliative care consult

Presentation Poorly differentiated midline disease in young men	<b>Likely primary</b> Germ cell tumor (testicular, retroperitoneal)	<b>Key history and physical</b> Gynecomastia suggests seminoma. Perform testicular examination	Investigations β-hCG, AFP. Look for isochromosome 12 which suggests tumor responsive to platinum-based therapy	Empiric treatment(s) Treat as germ cell tumor (BEP). Potentially curable
Squamous cell carcinoma with cervical lymphadenopathy	Head and neck cancer (hypopharynx, oropharynx, nasopharynx), skin, esophagus, lung	Smoker, alcohol use		Neck dissection and radiation. Potentially curable
Axillary lymphadenopathy in women	Breast cancer	Breast exam	Mammogram, U/S breast, MRI breast	Mastectomy with axillary dissection or whole breast irradiation, adjuvant chemotherapy. If lytic metastasis in postmenopausal women, consider hormonal treatment

**Tumor Markers** 

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

### **Tumor Markers**

### PATHOPHYSIOLOGY

**DEFINITION** substances that can be measured quan titatively 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, diagno sis, prognosis, monitor response to treatment, moni tor recurrence (after adjuvant therapy)

### PROSTATE SPECIFIC ANTIGEN (PSA)

**NORMAL RANGE** <4 ng/mL (age dependent range: 40 49 years old <2.5 ng/mL, 50 59 years old <3.5 ng/mL, 60 69 years old <4.5 ng/mL, 70 79 years old <6.5 ng/mL)

**ELEVATED** prostate cancer, BPH, prostatitis, peri

### 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</li>
- DIAGNOSIS, PROGNOSIS, RESPONSE, FOLLOW-UP FOR RELAPSE extremely useful. See PROSTATE CAN CER for more details (p. 210)

### CARCINOEMBRYONIC ANTIGEN (CEA)

**NORMAL RANGE** <4  $\mu$ g/L (<5  $\mu$ g/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  $\mu$ g/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 per formed every 3 months for at least 3 years if the

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### CARCINOEMBRYONIC ANTIGEN (CEA) (CONT'D)

patient is a potential candidate for surgery or chemotherapy for metastatic disease (even if pre viously CEA negative)

 METASTATIC SETTING CEA is the marker of choice for monitoring the response of metastatic disease to systemic therapy

### CA 19 9

NORMAL RANGE <37 kU/L

**ELEVATED** pancreatic cancer (sens 70 90%, spc 80 90%), cholangiocarcinoma, colorectal cancer (sens 20 40%), gastric cancer (sens 20 40%), ovarian cancer, pancreatitis, liver failure

### UTILITY IN PANCREATIC CANCER

- DIAGNOSIS level >120 kU/L is suggestive of malignancy. Level >1000 kU/L predicts metastatic disease (PPV of 97%)
- **RESECTABLE DISEASE** elevated CA19 9 postopera tively may predict for recurrent disease
- LOCALLY ADVANCED OR METASTATIC DISEASE eleva tions in serial CA 19 9 suggest progressive disease but confirmation with other studies needed

### CA 15 3

NORMAL RANGE <28 kU/L

**ELEVATED** breast cancer (sens for stage I 5 30%, stage II 15 50%, stage III 60 70%, stage IV 65 90%), ovarian cancer (46%), lung cancer (26%), liver cancer (30%)

### **UTILITY IN BREAST CANCER**

- **DIAGNOSIS** may be used sometimes to determine the presence of metastatic disease. 86 kU/L + his tory of breast cancer strongly suggests metastasis
- METASTATIC SETTING may be used to suggest treatment failure, particularly if disease is not read ily measurable

### CA 125

NORMAL RANGE <35 kU/L

### CA 125 (CONT'D)

**ELEVATED** epithelial ovarian cancer (sens 50% in stage I, 85% in all), breast cancer, colorectal cancer, pancreatic cancer, lung cancer, endometrial cancer, benign ovarian tumors (sens 26%), ascites, peritonitis, pelvic inflammatory disease, cirrhosis, menstruation, endometriosis, salpingitis, fibroids, right sided heart failure, first trimester pregnancy

### **UTILITY IN EPITHELIAL OVARIAN CANCER**

- SCREENING may have a role in early detection of ovarian cancer in women with hereditary ovarian cancer syndrome in combination with transvaginal ultrasound
- **DIAGNOSIS** in postmenopausal women with asymptomatic palpable pelvic masses, CA 125 >65 kU/L has PPV of 90% for ovarian cancer
- PROGNOSIS rate of decrease in CA 125 after cytor eductive surgery and during cytotoxic chemother apy has prognostic value
- RESPONSE useful for following disease response during cytotoxic chemotherapy
- ADJUVANT SETTING every 3 months for 2 years. However, limited treatment for relapsed disease limits clinical value of detection

### TUMOR MARKERS IN EVERYDAY PRACTICE

Tumor type Tumor marker
Prostate PSA
Colorectal (GI) CEA, CA 19 9
Pancreas CA 19 9, CEA
Liver #FP

Ovary CA 125, CA 15 3, CEA, CA 125, CA 27.29
Ovary CA 125, CA 15 3, CA 19 9, CEA
Lung CEA, CA 19 9, CA 125, LDH

Germ cell tumor αFP, βhCG, LDH

GTN βhCG

Carcinoid tumor Chromogranin, 5 HIAA

Non Hodgkin's LDH Hodgkin's ALP

Myeloma M protein, β2 microglobulin

UTILITY OF SPE	CIFIC TUMOR I	MARKERS				
Tumor marker	Tumor type	Screen	Diagnosis	Prognosis	Response	Follow up (recurrence)
PSA	Prostate	√?	$\sqrt{}$	$\sqrt{}$	$\sqrt{}$	$\sqrt{}$
CEA	Colorectal	×	×	$\checkmark$	$\checkmark$	$\sqrt{}$
CA 19 9	Pancreas	×	×?	×	√?	$\sqrt{?}$
CA 15 3	Breast	×	×	×	M	X
CA 125	Ovary	$\times$ ?	x?	$\checkmark$	$\checkmark$	$\sqrt{?}$
αFP	Germ cell	×	$\checkmark$		$\checkmark$	
	Liver	$\times$ ?	$\checkmark$		$\checkmark$	X
βhCG	Germ cell	×	$\checkmark$		$\checkmark$	$\sqrt{}$
	GTN	×				
LDH	Germ cell	×	$\checkmark$	$\checkmark$	$\checkmark$	$\checkmark$
	Lymphoma	×	×	$\checkmark$	$\checkmark$	X
$\sqrt{=}$ useful, ?=cor	ntroversial, x=no	ot useful, I	M=metastatic	setting only		

222 Cancer Screening

### **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 adminis ter, minimal discomfort), cost effective, high spe cificity (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 sig nificant 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, dyspla sia, 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 com paring the experience of screened and symptom detected cases at subsequent screening examinations

### **SCREENING FOR SPECIFIC CANCERS**

- BREAST self breast examination, clinical breast examination, mammography
- CERVICAL Pap smear, HPV DNA

### PRINCIPLES OF SCREENING (CONT'D)

- LUNG CXR, sputum cytology, CT chest. No role for routine screening at this time
- colorectal <u>fecal occult blood (FOB) sigmoido</u> <u>scopy,</u> double contrast barium enema, <u>colono</u> <u>scopy,</u> 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 coun seling 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 DRF

### 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. Poten tial 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 demon strated 50% reduction in mortality. Potential survival benefit. Negative test (i.e. no adenomatous polyps) in 50 80% of cases (2 12% negative even with advanced polyp)  $\rightarrow$  repeat in 10 years; positive (i.e.  $\geq$ 1 polyp) in 20 50%  $\rightarrow$  repeat colonoscopy depending on findings

**DOUBLE CONTRAST BARIUM ENEMA** insufficient evidence to support benefit

**CT COLONOGRAPHY** for polyps >10 mm, sens 85 93%, and spc 97%; for polyps 6 9 mm, sens 70 86%, and spc 86 93%. After detection of polyp,

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### 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 sigmoido
  scopy 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 recom
  mend 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, numer
   ous polyps, advanced adenoma, large sessile ade
   noma → repeat colonoscopy based on clinical
   judgment
- **POSITIVE FAMILY HISTORY** one first degree relative with cancer or adenomatous polyp at age <60 or two or more first degree relatives with cancer or adenomatous polyp at any age → colonoscopy every 5 years beginning at 40 or 10 years earlier than youngest index case (whichever first)
- HNPCC, FAP, OR ATTENUATED ADENOMATOUS POLYPO-SIS COLI (AAPC) genetic counseling and special screening. For HNPCC, colonoscopy every 1 2 years starting at 20 25 or 10 years earlier than youngest index case in family (whichever first); for FAP, colonoscopy annually beginning at 10 12 years of age. For AAPC, colonoscopy annually beginning at 16 18 years of age
- IBD (ulcerative colitis or Crohn's disease) staging colonoscopy 8 10 years after diagnosis; screening interval should decrease with increasing duration of disease (variable). Annual colonoscopy for any patient with PSC

### BREAST CANCER SCREENING

**BREAST SELF EXAMINATION** (BSE) no survival benefit demonstrated on its own

**CLINICAL BREAST EXAMINATION** (CSE) usually combined with mammography in studies

**MAMMOGRAPHY** sensitivity 16 40%. Meta analy sis 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 mammo graphy 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 unde termined significance (ASC US); atypical squamous cells cannot exclude HSIL (ASC H)
- LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION (LSIL) encompassing human papillomavirus, mild dysplasia, cervical intraepithelial neoplasia (CIN) 1

### CERVICAL CANCER SCREENING (CONT'D)

- HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (HSIL) encompassing moderate and severe dys plasia, carcinoma in situ, CIN2 and CIN3
- SQUAMOUS CELL CARCINOMA
- GLANDULAR CELL atypical glandular cells (AGC), aty pical 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

### CERVICAL CANCER SCREENING (CONT'D)

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

### HALLMARKS OF HEREDITARY CANCER (CONT'D)

≥2 FIRST OR SECOND DEGREE RELATIVES (same side of family)

RATIONAL CLINICAL E	EXAMINATION SERIES	: DOES THIS PATIENT	HAVE A FAMILY	HISTORY OF CANCER?
	Sens	Spc	LR+	LR
Accuracy of self repo	rted family history o	of cancer in a first de	gree relative by h	nealthy individuals
Colon cancer	53 86%	92 99%	23	0.25
Breast cancer	82%	91%	8.9	0.20
Endometrial ca	33%	98%	14	0.68
Ovarian cancer	50%	99%	34	0.51
Prostate cancer	70%	94%	12.3	0.32
Accuracy of self repo	rted family history o	of cancer in a first de	gree relative by o	ancer patients
Colon cancer	57 90%	96 99%	23	0.29
Breast cancer	85 98%	96 99%	41	0.07
Endometrial ca	29 56%	97 98%	20	0.55
Ovarian cancer	67 83%	96 99%	44	0.21
Prostate cancer	69 79%	93 99%	24	0.21
HEREDITARY NON PO	DI YPOSIS COLON CAL	NCFR (HNPCC) GENET	IC TESTING CRITI	FRIA (FOR PREMENO

# HEREDITARY NON POLYPOSIS COLON CANCER (HNPCC) GENETIC TESTING CRITERIA (FOR PREMENC PAUSAL WOMEN $\leq$ 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 SYNDROME	S	
	BRCA1	BRCA2
Genetics	Autosomal dominant with variable penetrance, 17q21	Autosomal dominant with variable penetrance, 13q13
Pathophysiology	Tumor suppressor, granin protein family with zinc finger motif, packaging and export of peptide hormones	Tumor suppressor
Cancer types	Breast (19% by age 40, 50% by age 50, 85% by age 70), ovarian (14 45% lifetime risk), prostate (8 16%), colon (6%)	Breast (50 85%), ovarian (<20%), male breast (6%), prostate (8 16%)
Clinical features	Young age of breast cancer, bilateral breast cancer, ER (70%), lobular	Young age of breast cancer, bilateral breast cancer, male breast cancer, lobular
Genetic testing	2 common mutations	1 common mutation
Surveillance	Breast starting at young age, clinical breast exam, man Ovarian screening decision individualized	mmogram, and MRI q6months
Prophylaxis	Prophylactic mastectomy breast cancer risk reduction	on of 90%
	<b>Prophylactic oophorectomy</b> when childbearing is co 75% and ovarian cancer risk reduction of 95%	implete. Breast cancer risk reduction of
	<b>Hormonal</b> tamoxifen or raloxifene are not routinely re families, where the majority of cancers are ER negative	

### LI FRAUMENI SYNDROME

**GENETICS** autosomal dominant

**PATHOPHYSIOLOGY** tumor suppressor, p53 mutation

**CANCER TYPES** soft tissue sarcoma, osteosarcoma, leukemia, breast, melanoma, colon, pancreas, adrenal cortex, brain

### VON HIPPEL LINDAU SYNDROME

PATHOPHYSIOLOGY VHL mutation

**CANCER TYPES** hemangioblastomas of the brain, spinal cord, retina, renal cysts, and clear cell renal cell carcinoma (40%), pheochromocytomas, endolympha tic 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,

# HEREDITARY NON POLYPOSIS COLORECTAL CANCER (HNPCC, LYNCH SYNDROME) (CONT'D)

pancreatic, kidney, ureter, brain (Turcot's syndrome), skin (sebaceous adenomas  $\pm$  keratoacanthomas in the Muir Torre variant syndrome)

**FEATURES** for colon cancer, predominant involve ment of right colon, poorly differentiated, increased frequency of mucinous and signet cell tumors, lym phocytic infiltration, MSI high (90%), and better prog nosis. Clinical diagnosis can be made by the Amster dam criteria  $\star 321 \star$ :  $\geq 3$  relatives with colorectal cancer (two of whom must be first degree relatives),  $\geq 2$  generations involved, and  $\geq 1$  family member diagnosed before age 50. FAP should be excluded

**SURVEILLANCE** for individuals who have a mis match 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 diag nosis of these cancers in the family. Median age of diagnosis is 48. Annual urinalysis and cytologic exam ination beginning at age 25 35. Annual skin surveil lance. Periodic upper endoscopy should be considered PROPHYLAXIS total or subtotal colectomy with ileorectal anastomosis for HNPCC patients with color ectal cancer or advanced adenoma (and post surgical rectal surveillance). Discussion of prophylactic hyster ectomy and salpingo oopherectomy at around age 35 or at the end of childbearing

226 Antineoplastic Agents

### FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

GENETICS autosomal dominant, 5q21 q22

**PATHOPHYSIOLOGY** adenomatosis polyposis coli (APC) gene, a tumor suppressor gene that normally prevents accumulation of  $\beta$  catenin by facilitating its phosphorylation and resultant degradation. One third of patients have no family history (new germline APC mutations or due to MYH gene mutations)

**CANCER TYPES** colorectal (risk approaches 100% by age 45), duodenal ampullary, gastric, follicular or papillary thyroid, hepatoblastoma, medulloblastoma (Turcot's syndrome)

**FEATURES** colon polyps (more than 100), duodenal adenomatous polyps, extraintestinal manifestations

# FAMILIAL ADENOMATOUS POLYPOSIS (FAP) (CONT'D)

(Gardner's syndrome) such as desmoid tumors, sebaceous or epidermoid cysts, lipomas, osteomas, supernumerary teeth, gastric polyps and juvenile nasopharyngeal angiofibromas

**SURVEILLANCE** (all at risk family member) sigmoi doscopy or colonoscopy annually starting age 10 12. Upper endoscopy. Annual thyroid palpation

**PROPHYLAXIS** total proctocolectomy at time of diagnosis in patients with multiple large (>1 cm) adenomas or adenomas with villous histology and/ or high grade dysplasia

Chemotherapeutic	Activity <sup>a</sup>	Myelo.	Emetogenic	Alopecia	Other major toxicities b	Dose
agents .		supp.	risk	mopeen	outer major toxicities	modification
Alkylating agents						
Cyclophosphamide (Cytoxan, IV/PO)	BR, GYN, NHL, BMT	+++	++(+)	+++	Hemorrhagic cystitis, muco, sterility	Renal, hepati
fosfamide (IV)	T, SA, NHL	+++	++	+++	Hemorrhagic cystitis, neuro	Renal
Melphalan (PO)	MM, BMT	++	+	+	Mucositis, sterility	Renal
Thlorambucil (PO)	NHL, CLL	++		+	Mucositis, sterility	
Bulsulfan (PO)	BMT	+++	+	++	Pulmonary	Renal
Carmustine (BCNU, IV)	CNS, NHL	+++	+++	+	Pulmonary, renal, muco, diarrhea, LFT	Renal
omustine (CCNU, PO)	CNS, NHL	+++	++	++	Pulmonary, renal, muco, diarrhea, LFT	Renal
Dacarbazine (DTIC, IV)	NHL, melanoma, SA	++	+++	+	Flu like symptoms, LFT, photo	Renal, hepati
Femozolomide (PO)	CNS, melanoma	++	++	+	Photosensitivity	Renal, hepati
Streptozocin (IV)	Carcinoid, islet cell	+	+++	+	Renal, diarrhea, LFT, hypoglycemia	Renal
Antimetabolites						
Methotrexate (IV/PO)	ALL, chorio, leptomeningeal	++	+	+	Muco, diarrhea, LFT, renal, pulm, neuro	Renal, hepati
Pemetrexed (IV)	LU, mesothelioma, BR	++	+	+	Mucositis, diarrhea, hand foot	Renal
Raltitrexed (IV)	GI, BR	++	+	+	Mucositis, diarrhea, LFT, fatigue	Renal
5 Fluorouracil (IV)	GI, BR	+	+	++	Muco, diarrhea, hand foot, cerebellar	Hepatic
Capecitabine (xeloda, PO)	GI, BR	++	+	+	Muco, diarrhea, LFT, hand foot, neuro	Renal
Cytosine arabinoside (Ara C, IV)	ALL, NHL, leptomeningeal	+++	+(+)	++	Mucositis, diarrhea, cerebellar	Renal, hepati neuro
Gemcitabine (IV)	GI, LU, BR, NPC, bladder	++	+	++	Diarrhea, LFT, flu like, rash	Renal, hepati
Hydroxyurea (PO, IV)	AML, CML	++	+	+	Mucositis, rash	Renal
Thioguanine (6 TG, IV)	AML	++	+	+	Mucositis, diarrhea, LFT	Hepatic
6 Mercaptopurine (6 MG, IV)	ALL	++	+	+	Mucositis, diarrhea, LFT	Renal, hepati
-ludarabine (IV, PO)	NHL, CLL	++	+	+	Neuro, AIHA, LFT	Renal
2 Chlorodeoxyadenosine	NHL, hairy cell	++	+	+	Constipation, fever	
(cladribine, IV)	leukemia					
Topoisomerase inhibitors						
Doxorubicin (hydroxydaunomycin, IV)	BR, SA	+++	++	+++	Cardiac	Hepatic
Doxorubicin (liposomal, IV)	KS, OV	++	+	+++	Cardiac, infusion, skin	Hepatic
Daunorubicin (IV)	AML, neuroblastoma	+++	++	+++	Cardiac	Hepatic
Idarubicin (PO)	AML	+++	++	+++	Cardiac (less)	Hepatic, rena
Epirubicin (IV)	BR	+++	++	+++	Cardiac	Hepatic
Mitoxantrone (IV)	AML, BR, prostate	++	+	+	Cardiac, LFT	Hepatic
Etoposide (IV/PO)	LU, T, NHL	++	+	+++	Neuro, LFT	Hepatic, rena
Fopotecan (IV)	OV, LU	+++	+	+++	Diarrhea, constipation, fever	Renal
rinotecan (IV)	GI, LU, GYN	++	+	+++	Diarrhea, constipation, fever	Hepatic
Platinating agents					,	
Cisplatin (IV)	Bladder, LU, T, OV	++	+++	+	Renal, neuro, ototoxicity	Renal, neuro
Carboplatin (IV)	Bladder, LU, T, OV	++	++	+	Renal, neuro, ototoxicity (less)	Renal
Oxaliplatin (IV)	GI	+	++	+	Neuro, diarrhea	Neuro, renal
Antimicrotubular agents						,
/incristine (oncovin, IV)	NHL		+	++	Neuro, constipation	Hepatic, neu
Vinblastine (IV)	T, NHL	++	+	++	Cramps, neuro, constipation	Hepatic, neu
/inorelbine (navelbine, IV)	LU, BR	++	+	+++	Neuro, constipation, diarrhea	Hepatic Hepatic
Oocetaxel (taxotere, IV)	BR, LU, prostate, OV	++	+	+++	Infusion, neuro, nails, myalgia, arthralgia, <b>edema</b>	Hepatic
Paclitaxel (taxol, IV)	BR, LU, prostate, OV	++	+	+++	Neuro, nails, myalgia, arthralgia	Hepatic, neu

Antineoplastic	Agents (Co	nt'd)				
Chemotherapeutic agents Others	Activity <sup>a</sup>	Myelo. supp.	Emetogenic risk	Alopecia	Other major toxicities <sup>b</sup>	Dose modification <sup>c</sup>
Bleomycin (IV)	Testicular	+	+	++	Pulmonary, hemorrhagic cystitis	Renal
Mitomycin C (IV)	GI, BR, GU	+++	+	+	Pulmonary, HUS, GU irritation	Renal

a BR breast, chorio choriocarcinoma, BMT bone marrow transplant, CML chronic myelogenous leukemia, CNS brain tumor, GI gastrointestinal, GIST gas trointestinal stromal tumor, GYN gynecological, KS Kaposi sarcoma, LU lung, OV ovarian, MM multiple myeloma, NHL non Hodgkin's lymphoma, NPC naso pharyngeal carcinoma, SA sarcoma, T testicular, TCL T cell lymphoma <sup>b</sup> LFT elevated liver enzymes/hepatic dysfunction, muco mucositis, photo photosensitivity

<sup>&</sup>lt;sup>c</sup> Dose modification may be required for **dose-limiting toxicities** (in **bold**) and also potentially renal and hepatic dysfunction

Hormonal and targeted agents	Activity	Cytopenia	Other major toxicities
Monoclonal antibodies			
Alemtuzumab (Campath) anti CD52 (SC/IV)	NHL, TCL	+++	Infusion rx'n, infections (e.g. CMV, HSV, TB, fungal), pancytopenia
Bevacizumab (Avastin) anti VEGF (IV)	GI		Infusion rx'n, HTN, bleed, thrombosis, GI perforations, proteinuria
Cetuximab (Erbitux) anti EGFR (IV)	GI, H&N		Infusion rx'n, rash, nail/hair changes, mucositis, diarrhea, hypomagnesemia
Gemtuzumab (Mylotarg) anti CD33 (IV)	AML	+++	Infusion rx'n, N&V, diarrhea, fever, LFT
Panitumumab (Vectibix) anti EGFR (IV)	GI		Rash, nail/hair changes, mucositis, diarrhea, hypomagnesemia
Rituximab (Rituxan) anti CD20 (IV)	NHL	+	Infusion rx'n, infections (e.g. JC virus, CMV, PJP), cardiac arrhythmia
Trastuzumab (Herceptin) anti Her2 (IV)	BR		Infusion rx'n, cardiomyopathy
Tyrosine kinase inhibitors			
Sunitinib (Sutent) VEGFR inhibitor (PO)	Renal, GIST	+	Fatigue, diarrhea, acral erythema, nail/hair changes, HTN, bleed, hypothyroidism, hypophosphatemia
Sorafenib (Nexavar) VEGFR inhibitor (PO)	Renal, liver	+	Fatigue, diarrhea, acral erythema, nail/hair changes, HTN, bleed, hypothyroidism, hypophosphatemia
Imatinib (Gleevec) bcr/abl, c kit inhibitor (PO)	CML, GIST	+	Periorbital edema, nausea, diarrhea, muscle cramps, bowel perforation, fatigue
Erlotinib (Tarceva) EGFR inhibitor (PO)	Lung		Rash, nail/hair changes, mucositis, diarrhea, interstitial lung dx
Gefitinib (Iressa) EGFR inhibitor (PO)	Lung		Rash, nail/hair changes, mucositis, diarrhea, interstitial lung dx
LHRH agonists	-		
Goserelin (Zoladex) (IM)	Prostate, BR		Hot flashes, mood changes, sexual dysfunction, diarrhea, anemia,
Leuprolide (Lupron) (IM)	Prostate, BR		loss of muscle mass, osteoporosis
Selective estrogen receptor modulators			
Tamoxifen (Nolvadex)	BR		Hot flashes, $mood\ \Delta$ , vaginal dryness/discharge, thromboembolism, hypercalcemia, endometrial cancer
Aromatase inhibitors			
Anastrozole (Arimidex) non steroidal (PO)	BR		Hot flashes, mood $\Delta$ , arthralgia, vaginal dryness and discharge,
Letrozole (Femara) non steroidal (PO)	BR		osteoporosis for all aromatase inhibitors
Exemestane (Aromasin) steroidal (PO)	BR		
Other hormonal agents			
Bicalutamide (Casodex) anti androgen (PO)	Prostate		Hot flashes, mood changes, sexual dysfunction, diarrhea, anemia,
Flutamide (Eulexin) antiandrogen (PO)	Prostate		loss of muscle mass, osteoporosis
Finasteride (Proscar) α5 reductase inhibitor	Prostate		Postural hypotension, sexual dysfunction, dizziness
Megestrol (Megace) progestin (PO)	BR, endometrial		Vaginal bleed and irregularities, nausea, weight gai
Fulvestrant (Faslodex) ER blocker (PO)	BR		Hot flashes, nausea, diarrhea, back pain, pharyngitis
Others			
Thalidomide (Thalomid) anti angiogenic (PO)	Myeloma	++	Sedation, fatigue, constipation, rash, peripheral neuropathy, thromboembolism
Bortezomib (Velcade) proteasome inhibitor (IV)	Myeloma, NHL	++	GI symptoms, fatigue, cytopenia, peripheral neuropathy
Interferon immune modulatory (IV)	Melanoma, renal	++	Fatigue, fever, myalgia, LFT, mood changes
Temsirolimus (Torisel) mTOR inhibitor (IV)	Renal	+	Rash, mucositis, fatigue, hyperglycemia, hypophosphatemia, hypertriglyceridemia

228 Oncologic Emergencies

### **Oncologic Emergencies**

### INFUSION REACTIONS

**TREAT UNDERLYING CAUSE** stop infusion **ABC O**<sub>2</sub> to keep sat >94%, *salbutamol* 2 puffs INH q1h PRN, *ipratropium* 2 puffs INH q6h PRN. *Diphen hydramine* 50 mg IV ×1 dose, *hydrocortisone* 100 mg IV ×1 dose. **If hypotensive**, give normal saline 500 1000 mL IV bolus and consider enigentine 0.1 0.25 mg slow IV push (1 mg in

epinephrine 0.1 0.25 mg slow IV push (1 mg in 10 mL of NS, give 1 2.5 mL). May restart chemother apy slowly for most drugs (infusion at 25% rate  $\times 5$  min, then 50% rate  $\times 5$  min, then 75% rate  $\times 5$  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, raniti dine 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 can cer, renal cell carcinoma, non Hodgkin's lymphoma, multiple myeloma, cancer of unknown primary, color ectal cancer, sarcoma

CLINICAL FEATURES back pain (particularly may worsen with recumbency), radicular pain (band like in abdomen, legs), weakness (hip flexion, arm exten sion), reflexes (hyperreflexic, Babinski upgoing), sen sory 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. Clin ical 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  $\times$ 1 dose, then 8 mg IV/PO BID. **Treat underlying cause urgently** (radiation  $\pm$  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 com pression of the SVC by contiguous pathologic pro cesses 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 collat eral drainage patterns, central venous pressures remain high, producing characteristic signs and symptoms of SVC syndrome

CAUSES neoplasm (NSCLC 50%, SCLC, lym phoma, 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 sus pected cancer, tissue diagnosis is required (supracla vicular lymph node, sputum cytology, mediastino scopy, thoracentesis, bronchoscopy)

**TREATMENTS** elevate patient's head. **Treat underlying cause** (radiation, chemotherapy for che mosensitive diseases). **Dexamethasone** 4 mg PO q6h (for lymphoma and thymoma). Consider **endovascu lar stenting** if urgent or refractory disease

NEJM 2007 356:18

### **Related Topics**

Febrile Neutropenia (p. 236) Spinal Cord Compression (p. 228)

### HYPERCALCEMIA

PATHOPHYSIOLOGY local osteolytic hypercalce mia 20% (cytokines), humoral hypercalcemia of malignancy 80% (PTHrP), 1,25(OH)<sub>2</sub>vitD secreting lymphomas, and ectopic hyperparathyroidism (PTH) are all known mechanisms. Median survival of 1 month post presentation with hypercalcemia

CLINICAL FEATURES bony pain, abdominal pain, constipation, polyuria, renal failure, renal stones,

DIAGNOSIS Ca, PO<sub>4</sub>, albumin, PTH, 1,25(OH)<sub>2</sub>vitD, bone scan

**SYMPTOM CONTROL** NS 200 500 mL/h IV  $\pm$  *fur* osemide 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), ster oids (prednisone 60 mg PO daily ×10 days, hydro cortisone 200 500 mg IV daily), plicamycin 25 µg/kg in 1 L NS over 4 6 h, *calcitonin* 200U SC/IM BID

### TREAT UNDERLYING CAUSE

See HYPERCALCEMIA for more details (p. 353)

NEJM 2005 352:4

### TUMOR LYSIS SYNDROME

PATHOPHYSIOLOGY treatment induced lysis of tumor cells, leading to release of cell contents →

### 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 prolif eration, high chemosensitivity (aggressive lympho mas, ALL, AML, solid tumors)

**DIAGNOSIS** a clinical diagnosis with a combination (but not necessary all) of the following criteria: high uric acid (>475  $\mu$ mol/L [>4 mg/dL] or 25% from baseline), high K (>6 mmol/L or 25% from baseline), high PO<sub>4</sub> (>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 prophy laxis with fluids (NS 150 250 mL/h), allopurinol 300 mg PO TID and consider rasburicase (promotes uric acid degradation). Monitor urine output, K, Ca, PO<sub>4</sub>, Cr, uric acid, and LDH q6h. Treatment of uric acid nephropathy with aggressive hydration, furo semide diuresis, rasburicase, and dialysis as a last resort

### **Febrile Neutropenia**

See FEBRILE NEUTROPENIA (p. 236)

### Chemotherapy-Induced Nausea and Vomiting

NEJM 2008 358:23 JCO 2006 24:18

### PATHOPHYSIOLOGY

REFLEX PATHWAY see p. 111

**RISK FACTORS** female, <50 years, previous treat ment related nausea and vomiting, concomitant radiation, and chemotherapy. Alcohol use predicts lower likelihood of chemotherapy induced nausea and vomiting (CINV)

### NCI CTC GRADING V4.0

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

### NCI CTC GRADING V4.0 (CONT'D) Nausea

Grade

3	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated
4	Not applicable
Grade	Vomiting
1	1 2 episodes (separated by 5 min) in 24 h
1 2	1 2 episodes (separated by 5 min) in 24 h 3 5 episodes in 24 h

intervention required

Life threatening consequences; urgent

230 Oral Mucositis

### **Related Topic**

Nausea and Vomiting (p. 111)

# EMETOGENIC LEVELS OF INTRAVENOUSLY ADMINISTERED ANTINEOPLASTIC AGENTS

**HIGH RISK** (>90%) carmustine, cisplatin, cyclopho sphamide ( $>1.5\,$  g/m $^2$ ), dacarbazine, mechloretha mine, streptozocin

**MODERATE RISK** (31 90%) carboplatin, cyclopho sphamide ( $\geq$ 1.5 g/m²), cytarabine (>1 g/m²), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin

**LOW RISK** (10 30%) bortezomib, cetuximab, cytar abine ( $\geq$ 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, vincris tine, vinorelbine

### MANAGEMENT

### PREVENTION IS KEY

ANTICIPATORY NAUSEA AND VOMITING (3 to 4h) 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) asso ciated 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 interven tions required. Avoid long term use of 5HT3/NK1 antagonists

### MANAGEMENT (CONT'D)

### 

High<sup>b</sup> / / / / /
Moderate / / / /
Low / /
Minimal /

<sup>a</sup>choices include *metoclopramide* 10 mg PO q4h PRN and *prochlorperazine* 10 mg PO q4h PRN <sup>b</sup>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 metoclo pramide 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 prochlorpera zine 10 mg PO q4h PRN

**LOW RISK CHEMOTHERAPY** dexamethasone 8 mg PO/IV day 1 PLUS metoclopramide 10 mg PO q4h PRN or prochlorperazine 10 mg PO q4h PRN

**LOW, RISK CHEMOTHERAPY** metoclopramide 10 mg PO q4h PRN or prochlorperazine 10 mg PO q4h PRN

**NOTE** for patients with significant nausea and vomiting despite proper oral antiemetic use, consider admission for intravenous hydration and medication administration

### **Oral Mucositis**

### PATHOPHYSIOLOGY

### **RISK FACTORS FOR ORAL MUCOSITIS**

- PERSONAL younger age, poor oral hygiene, smok ing, alcohol use
- CHEMOTHERAPY bleomycin, capecitabine, chlor ambucil, cytarabine, doxorubicin, etoposide, meth otrexate, vinblastine, 5 fluorouracil
- TARGETED AGENTS RAD001
- RADIATION head and neck region

**COMPLICATIONS OF ORAL MUCOSITIS** severe pain, bleeding, superinfections (bacteremia, febrile neutropenia)

### NCI CTC GRADING V4.0

# Grade Oral mucositis 1 Asymptomatic or mild symptoms; intervention not indicated 2 Moderate pain; not interfering with oral intake; modified diet indicated 3 Severe pain; interfering with oral intake 4 Life threatening consequences; urgent intervention indicated

### MANAGEMENT

**CRYOTHERAPY** sucking on ice chips during che motherapy 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 hydra tion and monitor nutritional intake. Assess patients for diarrhea as well. Providing optimal pain control is key

### MANAGEMENT (CONT'D)

- TOPICAL ANALGESIA
  - MAGIC/MIRACLE MOUTHWASH generally includes lidocaine for pain control. For a 100 mL solution, mix hydrocortisone 25 mg, glycerin 95% 2 mL, normal saline 52 mL, lidocaine 2% 25 mL, and nystatin 2083,300 IU or 20.833 mL. Use 10 mL squish and spit q4h q6h
  - MORPHINE SULFATE MOUTHWASH 2 mg/mL in 15 mL of water, swish and spit, q4h to q6h
  - LIDOCAINE VISCOUS 2% 10 mL, swish and spit, q4h PRN
- **SYSTEMIC OPIOIDS** morphine 5 mg IV q4h PRN or 10 mg PO q4h PRN, titrating up as needed
- INFECTIONS oral candidiasis (nystatin 500,000 IU swish and swallow QID, clotrimazole troches, or fluconazole), HSV infections (acyclovir or valacy clovir after cultures taken)

### **Chemotherapy-Induced Diarrhea**

JCO 2004 22:14

### PATHOPHYSIOLOGY

# RISK FACTORS FOR CHEMOTHERAPY INDUCED DIARRHEA

- chemotherapy 5 fluorouracil, capecitabine, irino tecan (active metabolite SN 30), cisplatin, docetaxel, paclitaxel, doxorubicin, cyclophosphamide, metho trexate, cytosine arabinoside, and topotecan
- TARGETED AGENTS imatinib, erlotinib, sunitinib, sorafenib

### MANAGEMENT

**DOSE ADJUSTMENTS** dose reduction or treatment termination may be considered in severe cases

**FIRST LINE** *loperamide* 4 mg PO, followed by 2 mg every 2 h (or 4 mg every 4 h) until 12 h has elapsed without any diarrhea

**SECOND LINE** octreotide 100 150  $\mu$ g SC as needed. Octreotide is a somatostatin analogue that decreases both intestinal transit time and fluid secretion into the small intestine

**NOTE** ensure adequate hydration and assess other related symptoms such as oral mucositis, nausea, and vomiting. Remember to stop all laxatives

### NCI CTC GRADING V4.0

# Grade Chemotherapy Induced Diarrhea 1 Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline 2 Increase of 4 6 stools per day over baseline; moderate increase in ostomy output compared to baseline 3 Increase of ≥7 stools per day over baseline; incontinence; hospitalization; severe increase in ostomy output compared to baseline; limiting self care ADL

Life threatening consequences; urgent intervention indicated

Notes Notes

# Notes

# INFECTIOUS DISEASES

Section Editor: Dr. Mark Joffe

# Fever of Unknown Origin

# Infect Dis Clin North Am 2007;21:4

#### DIFFERENTIAL DIAGNOSIS

This list is not exclusive, but highlights some important causes of FUO after the common causes of fever have been excluded:

INFECTIONS TB (pulmonary, extrapulmonary, miliary), abscess (liver, splenic, perinephric, psoas, diverticular, pelvis), osteomyelitis, endocarditis NEOPLASTIC hematologic (lymphoma, leuke mia, multiple myeloma, myelodysplastic syn drome), solid tumors (renal cell, hepatoma) COLLAGEN VASCULAR vasculitis (giant cell arteritis, Still's disease, polyarteritis nodosa, Takaya su's arteritis, Wegener's granulomatosis, mixed cryoglobulinemia), lupus, rheumatoid arthritis DRUGS antimicrobials (sulfonamides, penicil lins, nitrofurantoin, antimalarials), antihistamines, antiepileptics (barbiturate, phenytoin), NSAIDs/ ASA, antihypertensives (hydralazine, methyl dopa), antiarrhythmics (quinidine, procainamide), antithyroid, iodides, quinine, illicit (cocaine) UNCOMMON CAUSES OF FUO central fever. endocrine (hypothalamic dysfunction, pheochromocytoma, hyperthyroidism. adrenal insufficiency), infections (dental abscess, Q fever, leptospirosis, psittacosis, tularemia, melioidosis, syphilis, gonococcemia, chronic meningococcemia, Whipple's disease, versiniosis, brucellosis), heredi tary periodic fever syndromes (familial Mediter ranean fever, PFAPA syndrome [Periodic Fever with Aphthous Stomatitis and Adenitis], TNFR 1 asso

#### PATHOPHYSIOLOGY

#### DEFINITIONS

FEVER OF UNKNOWN ORIGIN (FUO)

hematoma, factitious fever

 CLASSIC DEFINITION (1961) ≥38.3°C [≥101°F], duration ≥3 weeks, diagnosis uncertain after 7 days of investigation in hospital

ciated periodic syndrome, hyper IgD syndrome, Muckle Wells syndrome, familial cold auto

inflammatory syndrome), alcoholic hepatitis,

#### PATHOPHYSIOLOGY (CONT'D)

- NEW DEFINITIONS
  - FUO ≥38.3°C [≥101°F], duration ≥3 weeks, diagnosis uncertain after 3 days in hospital or three outpatient visits
  - NOSOCOMIAL FUO hospitalized patients, ≥38.3°C [≥101°F], diagnosis uncertain after 3 days and infection not present or incubat ing on admission
  - IMMUNE-DEFICIENT (NEUTROPENIC) FUO >38.3°C [≥101°F], >3 days, neutrophil count ≤500/mm³. See p. 234 for details
  - HIV-RELATED FUO HIV patients, ≥38.3°C [≥101°F], duration ≥3 weeks for outpatients or ≥3 days for inpatients
- FEVER, NYD persistent fever that has not yet met the definition for FUO

### CLINICAL FEATURES

HISTORY pattern and duration of fever, associated symptoms (cough, dyspnea, hemoptysis, chest pain, diarrhea, abdominal pain, dysuria, urethral discharge, hematuria, neck stiffness, headache), rash (palpable purpura, exanthem), exposure (food, water, plants, animals, insects, infected human secretions), weight loss, night sweats, travel history, sexual history, risk factors, immunizations, past medical history (rheumatologic disorders, malignancy, alcohol), medications

PHYSICAL vitals (tachycardia, tachypnea, hypoten sion, fever, hypoxemia), oral ulcers, lymphadenopa thy, nuchal rigidity, respiratory and cardiac examination (murmurs), temporal artery, abdominal examination (hepatosplenomegaly), prostate examination, skin lesions (morphology, distribution), tick bite marks, joint examination

#### INVESTIGATIONS

#### BASIC

 LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, LDH, CK, serum protein electrophoresis, urinalysis, ESR, CRP, ANA, ENA, RF, C3, C4, ANCA, cryoqlobulin 234 Fever and Rash

#### INVESTIGATIONS (CONT'D)

- MICROBIOLOGY blood C&S (including Mycobac teria), 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 strat egy is a careful history and physical examination with frequent reassessment

**PROGNOSIS** up to 30 50% will not have a diag nosis 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 sever ity of patient's disease (see EMPIRIC ANTIBIOTICS p. 257). In general, therapeutic trials of antimicrobials or steroids are discouraged

TREAT UNDERLYING CAUSE

### **Fever and Rash**

#### **DIFFERENTIAL DIAGNOSIS**

#### INFECTIONS

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

#### RHEUMATOLOGIC

- SEROPOSITIVE lupus, dermatomyositis
- SERONEGATIVE inflammatory bowel disease, reactive arthritis
- VASCULITIS Wegener's, polyarteritis nodosa
- BEHCET'S DISEASE

**MALIGNANCY** lymphoma, leukemia, metastatic, paraneoplastic

**MEDICATIONS** penicillins, cephalosporins, sulfas, barbiturates, phenytoin, procainamide, quinidine

**OTHERS** sarcoidosis, erythema nodosum; Sweet's syndrome (acute febrile neutrophilic dermatosis)

#### **CLINICAL FEATURES**

#### **SETTINGS**

- AGE viral exanthems, scarlet fever, and acute rheumatic fever are more likely in children. Mono nucleosis 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 capsula tum (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, immunizations, past medical history (rheumatologic disorders, malignancy), medications

Fever and Rash 235

#### CLINICAL FEATURES (CONT'D)

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

# 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 rickett sii 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 ehrli chiosis) transmitted by lone star tick. Peaks in May to July. Infects lymphocytes, monocytes, and neu trophils 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 Ixodes 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

#### SPECIFIC ENTITIES (CONT'D)

#### 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 atrophi cans (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?

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

APPROACH "no single component of the history or physical examination emerges as one that makes the diagnosis of erythema migrans highly likely. These signs and symptoms have not been 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 ×1 dose within 72 h of the tick bite
- TREATMENTS stage 1 (doxycycline 100 mg PO BID × 10 21 days, or cefuroxime 500 mg PO BID × 10 21 days). Lyme carditis (ceftriaxone 2 g IV × 14 21 days if third degree AV block; otherwise, same as stage I with oral antibiotics). Neurologic Lyme (ceftriaxone 2 g IV × 14 21 days). Lyme arthritis (doxycycline 100 mg BID × 28 days, amoxicillin)
- JARISCH—HERXHEIMER REACTION up to 15% of patients may experience transient worsening of symptoms during first 24 h of treatment. This results from the host immune response to antigen release from dying organisms (typically Lyme and

#### SPECIFIC ENTITIES (CONT'D)

syphilis) causing fever, chills, myalgias, and exacer bation 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 England, southern New York, Wisconsin, and Minnesota
- DIAGNOSIS blood smear, PCR, serology
- TREATMENTS atovaquone plus azithromycin

#### **Related Topic**

Exanthematous Lesions (p. 364)

### **Fever and Joint Pain**

See JOINT PAIN AND FEVER (p. 276)

#### **Sepsis**

See SEPSIS (p. 97)

### **Febrile Neutropenia**

### IDSA Guidelines 2002

### DIFFERENTIAL DIAGNOSIS

#### **BACTERIAL**

- GRAM POSITIVE S. aureus, coagulase negative staphylococci, Streptococcus pneumoniae, corynebacterium
- GRAM NEGATIVE Enterobacter, Escherichia. coli, K. pneumoniae, Pseudomonas, C. difficile, anaerobes
- TB

VIRAL HSV, VZV, CMV, EBV, HHV6, enterovirus, RSV FUNGAL Candida, Aspergillus, Cryptococcus, Fusarium

**REACTIVATION OF LATENT INFECTION** Histo plasma, Coccidioides, Toxoplasma, Tuberculosis

#### PATHOPHYSIOLOGY

**DEFINITION** single temp >38.3°C [101°F] or >38°C [100.4°F] for >1 h, ANC <0.5×10 $^9$ /L or <1.0×10 $^9$ /L + expected nadir <0.5×10 $^9$ /L

# PATHOPHYSIOLOGY (CONT'D)

**ABSOLUTE NEUTROPHIL COUNT (ANC)** neutro phils + bands

**PATHOGENESIS** chemotherapy induced injury to mucosal barriers, immune defects due to drugs or underlying disease and invasive devices. With the attenuated immune response, patients may be relatively asymptomatic until they decompensate due to overwhelming infection. Fever is sometimes the only warning sign and should always be taken seriously in patients at risk of developing neutropenia

#### **NEUTROPENIA ASSOCIATED FEBRILE EPISODES**

most commonly idiopathic; bacterial source identi fied 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 237

#### CLINICAL FEATURES

HISTORY patients usually asymptomatic other than fever. Determine severity and duration of fever, associated signs and symptoms (cough, dys pnea, 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, rheumatolo gic disorders), medications (chemotherapy, GCSF)

PHYSICAL vitals (tachycardia, tachypnea, hypoten

PHYSICAL Witals (tachycardia, tachypnea, nypoten sion, fever, hypoxemia), oral ulcers, lymphadenopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenome galy), skin lesions (morphology, distribution). Important sites to examine include venous access devices, sinuses, and perianal region for abscess. Digital rectal examina tion is not recommended as potential rectal tear

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, urinalysis
- MICROBIOLOGY blood C&S×2 (culture periph eral 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  $>0.1\times10^9$ /L, peak temperature  $<39^\circ$ C [102.2°F], no significant symptoms or signs, no significant comorbidities, nearly normal renal and hepatic function, neutropenia <7 days) *ciprofloxa cin* 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, mer openem 2 g IV q8h, ceftazidime 2 g IV q8h, cefepime 2 g IV q8h, piperacillin/tazobactam 4.5 g IV q8h, piperacillin 3 g IV q4h plus tobramycin 2 2.5 mg/kg IV q8h, clindamycin 600 mg IV q8h plus tobramycin 7 mg/kg IV q24h, or piperacillin/tazobactam 4.5 g IV q8h plus qentamicin 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 (fluco nazole 400 mg IV daily, itraconazole 200 mg IV daily, amphotericin B 0.5 1 mg/kg IV daily over 4 h, caspofun gin 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 antibio tics, 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 ≥0.5×10<sup>9</sup>/L for 2 consecutive days, afebrile for ≥48 h, cultures negative, and no obvious signs of infection, or if (2) ANC <0.5×10<sup>9</sup>/L by day 7, but afebrile for 5 7 days, patient initially at low risk, and no subsequent complications
  - CONTINUE ANTIBIOTICS if above criteria not met
- IF PERSISTENT FEVER ON DAY 3
  - STOP ANTIBIOTICS if ANC  $\geq$ 0.5 $\times$ 10 $^{9}$ /L for 4 5 consecutive days
  - CONTINUE ANTIBIOTICS if ANC <0.5×10<sup>9</sup>/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), med ical history (poor performance status, previous febrile neutropenia, extensive prior treatment, poor nutrition, open wounds, active infections), disease characteristics (bone marrow involve ment), and myelotoxicity of the chemotherapy regimen (chemoradiation)
  - CHEMOTHERAPY REGIMENS 20% or higher risk of febrile neutropenia or dose dense regimens
- SECONDARY PROPHYLAXIS GCSF is recommended for patients who experienced a neutropenic complication from a prior cycle of chemotherapy (in which

#### TREATMENT ISSUES (CONT'D)

primary prophylaxis was not received), in which a reduced dose may compromise disease free survi val overall survival, or treatment outcome

- TREATMENT OF PATIENTS WITH FEBRUE NEUTROPENIA GCSF should be given to those with high risk of developing complications, including expected pro longed (>10 days) and profound ( $<0.1\times10^9/L$ ) neutropenia, age >65 years, uncontrolled primary disease, pneumonia, hypotension and multi organ dysfunction (sepsis), invasive fungal infection, being hospitalized at the time of the development of fever
- SPECIAL SITUATIONS
  - STEM CELL TRANSPLANT to mobilize peripheral blood progenitor cell often in conjunction with chemotherapy. Also administered after autolo gous, 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 neutro penia by approximately 1 week
  - MDS may be used to increase the ANC in neutropenic patients. Intermittent administra tion of CSFs may be considered in a subset of

#### TREATMENT ISSUES (CONT'D)

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 extend ing 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, nutri tional support, broad spectrum antibiotics (includ ing metronidazole for C. difficile and amphotericin B/fluconazole for fever >72 h), GCSF. Surgical indi cations include peritonitis, perforation, persistent GI bleeding, or clinical deterioration

#### **Related Topics**

Chemotherapy (p. 226) Neutropenia (p. 148)

Sepsis (p. 97)

Stem Cell Transplant (p. 180)

# **Fever with Travel History**

NEJM 2002 347:7 http://www.cdc.gov

#### **DIFFERENTIAL DIAGNOSIS**

#### FEVER WITH CNS INVOLVEMENT

- BACTERIAL meningococcal, typhoid fever, rick ettsial, leptospirosis
- MYCOBACTERIAL tuberculosis
- VIRAL Japanese encephalitis, West Nile encepha litis, tick borne encephalitis, poliomyelitis, rabies
- FUNGAL coccidioidomycosis
- PARASITIC malaria, angiostrongyliasis, trypan osomiasis

#### FEVER WITH RESPIRATORY INVOLVEMENT

- BACTERIAL S. pneumoniae, mycoplasma, Legio nella, Q fever, typhoid fever, scrub typhus
- MYCOBACTERIAL tuberculosis
- VIRAL influenza, parainfluenza, metapneumovirus, respiratory syncytial virus, adenovirus, dengue
- FUNGAL histoplasmosis, coccidioidomycosis

### DIFFERENTIAL DIAGNOSIS (CONT'D)

 PARASITIC malaria, Loeffler's syndrome (migra tion of larval helminths such as ascaris, strongy loides, and hookworm)

#### FEVER WITH RASH see FEVER AND RASH (p. 234) HEMORRHAGIC FEVER

- BACTERIAL rickettsial, meningococcemia, leptos pirosis
- 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 schistoso miasis, visceral larva migrans, lymphatic filariasis, acute trichinosis)

Fever with Travel History 239

#### DIFFERENTIAL DIAGNOSIS (CONT'D)

**FEVER WITH THROMBOCYTOPENIA** malaria, typhoid fever, dengue shock syndrome, ehrlichio sis, Rocky Mountain spotted fever

#### ACUTE TRAVELER'S DIARRHEA ± FEVER

- BACTERIAL Enterotoxigenic or enteroaggrega tive E. coli, Campylobacter jejuni, Salmonella, Shi qella, Vibrio, Aeromonas, Plesiomonas, C. difficile
- VIRAL Caliciviruses (Norwalk, Norwalk like), rotaviruses, enteroviruses
- PARASITIC Giardia lamblia, Cryptosporidium par vum, Entamoeba histolytica, Cyclospora cayeta nensis, Isospora belli, E. polecki, Balantidium coli, Trichinella spiralis

#### CHRONIC TRAVELER'S DIARRHEA ± FEVER

- BACTERIAL Enteroaggregative or enteropatho genic E. coli, C. jejuni, Shigella, Salmonella, Yersi nia enterocolitica, Aeromonas, Plesiomonas, C. difficile, Tropheryma whippelii
- MYCOBACTERIAL tuberculosis, M. avium complex
- FUNGAL Paracoccidioides brasiliensis, Histo plasma capsulatum
- PARASITIC G. lamblia, E. histolytica, C. parvum, C. cayetanensis, Trichuris trichiura, Strongyloides stercoralis, Schistosomiasis, Capillaria philippi nensis, Fasciolopsis buski, Metagonimus yokoga wai, Echinostoma
- NON-INFECTIOUS small bowel overgrowth syn drome, disaccharidase deficiency, tropical sprue, irritable bowel syndrome, inflammatory bowel disease, cancer, laxative use, endocrino pathy, dysmotility, idiopathic

www.phac aspc.gc.ca/publicat/ ccdr rmtc/06vol32/acs 01/index eng.php

#### CLINICAL FEATURES

**HISTORY** pattern and duration of fever, asso ciated symptoms (cough, dyspnea, chest pain, diar rhea, 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, immuni zation status, antimalarial chemoprophylaxis (medications, degree of adherence), past medical history (rheumatologic disorders, malignancy), medications

PHYSICAL vitals (tachycardia, tachypnea, hypo tension, fever, hypoxemia), oral ulcers, lymphade nopathy, nuchal rigidity, respiratory and cardiac examination (murmurs), abdominal examination (hepatosplenomegaly), skin lesions (morphology, distribution), tick bite marks, joint examination

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, urinalysis
- MICROBIOLOGY blood C&S, sputum Gram stain/ AFB/C&S, urine C&S, stool C&S, O&P, C. diff toxin A/B, malaria thick and thin smear (repeat ×1 within 12 24 h if initially negative result), serol ogies (HIV, dengue, rickettsiae, schistosomiasis, strongyloidiasis, leptospira, HAV, HBV, HCV, Hepatitis E)
- IMAGING CXR, U/S abd guided by symptoms SPECIAL
- LUMBAR PUNCTURE

#### PRE TRAVEL CONSIDERATIONS

**VACCINATIONS** standard regardless of travel (influ enza, pneumococcal if age >65, hepatitis B, MMR, DPT), developing countries (hepatitis A), specific coun tries (meningococcal, Japanese encephalitis, yellow fever), high risk activity (rabies), outbreaks (cholera)

MALARIA PROPHYLAXIS see below

**DIARRHEA PROPHYLAXIS** ciprofloxacin and imo dium if diarrhea develops

#### SPECIFIC ENTITIES

**PRIORITY** focus on those illnesses that are poten tially 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 circula tion → 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 schisto somiasis 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 (sei zures, focal deficit, transverse myelitis) involvement

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#### SPECIFIC ENTITIES (CONT'D)

- DIAGNOSIS serology, schistosome eggs in feces or urine, biopsy of rectum or bladder
- TREATMENTS praziquantel 20 mg/kg PO q8h ×2 doses (3 doses for S. japonicum and mekongi); adjunctive corticosteroids for Katyama fever

**MALARIA** the most important cause of fever in returning travelers. *P. falciparum* can be rapidly fatal and must be ruled out in all febrile travelers returning from malaria endemic regions. It has the shortest incubation period and >90% of affected travelers will become ill within 30 days of return

- PATHOPHYSIOLOGY anopheline mosquito transmits sporozoites → travel to liver and invade hepatocytes  $\rightarrow$  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 schi zonts (asexual form) over 48 (P. vivax, P. ovale, *P. falciparum*) or 72 (*P. malariae*) hours  $\rightarrow$  mero zoites released from erythrocytes (fever, anemia, lactic acidosis, cytokine release) and infect new red cells -- few merozoites differentiate into male or female gametocytes (sexual forms) can circulate in blood until ingested by mosquito. P. vivax and P. ovale may stay dormant in the liver as hypno zoites and may cause late relapse by reactivating after many months. In contrast, P. falciparum and P. malariae have no liver stage and do not cause relapse. P. falciparum specifically can induce obstruction of microvascular blood flow, and may lead to organ dysfunction (e.g. cerebral malaria, renal failure, ARDS, hypoglycemia, anemia, DIC, and gastroenteritis)
- CLINICAL FEATURES P. falciparum is acquired mostly from sub Saharan Africa, while P. vivax is mostly from Asia or Latin America. Symptoms include spiking fevers, chills, headache, back pain, cough, GI problems. Splenomegaly and thrombocytopenia without leukocytosis may be present. Cerebral malaria (P. falciparum) presents as altered level of consciousness or seizures and is universally fatal if untreated
- DIAGNOSIS thick and thin smear (need to repeat over 48 h to rule out malaria)
- PROPHYLAXIS the relative risk of contracting malaria varies by geographic region: Caribbean 4, North Africa 7, South America 8, Southeast Asia 12, Central America 38, South Asia 54, Oceania 77, and sub Saharan Africa 208. Travelers should be advised to wear long sleeves/pants between dusk and dawn, use mosquito repellents containing 30 50% DEET, and consider permethrin treated mosquito nets. Chloroquine may be used for travel to destina tions with chloroquine sensitive P. falciparum (e.g.

#### SPECIFIC ENTITIES (CONT'D)

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 doxycy cline 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, Cambo dia, China, Laos, and Vietnam). Atavaquone proguanil associated with fewest side effects. Meflo quine has ease of weekly dosing. Doxycycline is the cheapest, but requires prolonged course and causes sun sensitization. CDC 2010 risk assessment and prophylaxis recommendations are available online at

http://wwwnc.cdc.gov/travel/yellowbook/2010/ chapter 2/malaria risk information and prophylaxis.aspx

 TREATMENTS artesunate has emerged as the treatment of choice for complicated malaria.
 Other options include quinine doxycycline, atova quone proguanil, and mefloquine. Chloroquine primaquine for non falciparum

> NEJM 2008 359:6 www.phac aspc.gc.ca/publicat/ccdr rmtc/ 09vol35/35s1/index eng.php

# RICKETTSIAL INFECTIONS (OUTSIDE OF NORTH AMERICA)

- PATHOPHYSIOLOGY African tick typhus (Rickettsia africae), Mediterranean tick typhus (R. conorii), and scrub typhus (Orientia tsutsugamushi) are all transmitted by ticks
- CLINICAL FEATURES tick bite  $\pm$  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, zoono sis more common in tropical areas
- CLINICAL FEATURES history of exposure to fresh water. Fever, headache, myalgia, rash, conjunctival suffusion. May be associated with aseptic menin gitis, uveitis, elevated transaminases, jaundice, proteinuria, and microscopic hematuria; fulminant syndrome with jaundice, renal failure, and hemor rhage (Weil's Disease)
- DIAGNOSIS serology; culture of blood, urine, and CSF
- TREATMENTS doxycycline or amoxicillin for mild disease; penicillin/ampicillin or ceftriaxone/cefo taxime IV for severe disease

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#### SPECIFIC ENTITIES (CONT'D)

#### TYPHOID FEVER

- PATHOPHYSIOLOGY acquired after exposure to food or water contaminated by Salmonella typhi
- CLINICAL FEATURES mainly in developing coun tries. Fever, chills, headache, myalgia, abdominal pain and constipation (uncommonly diarrhea), relative bradycardia, splenomegaly, and rose spots (faint salmon colored macules on the abdo men and trunk). Septic symptoms from intestinal perforation may occur in second week
- DIAGNOSIS blood, stool, urine, or bone marrow (highest sensitivity) culture; CBC may show leukopenia
- TREATMENTS fluoroquinolones, ceftriaxone, azithro mycin

BRUCELLOSIS (undulant fever, Mediterranean fever)

- PATHOPHYSIOLOGY Gram negative facultative intra cellular coccobacilli
- CLINICAL FEATURES transmitted by drinking or eat ing infected animal products (milk), inhalation, or direct animal contact through skin wounds. Other than fever, may involve any organ system, particu larly joints (sacroiliitis), GU (epididymo orchitis), CNS (meningitis), eyes (uveitis), cardiac (endocar ditis), pulmonary (pneumonitis, pleural effusion, empyema), and can cause abscesses (hepatic, sple nic, thyroid, epidural). May develop into chronic hepatosplenic disease

#### SPECIFIC ENTITIES (CONT'D)

- DIAGNOSIS blood cultures, serology
- TREATMENTS doxycycline plus streptomycin or rifampin

#### **DENGUE FEVER** (break bone fever)

- PATHOPHYSIOLOGY flavivirus transmitted by mos quito → flu like illness 4 7 days later → may develop lymphadenopathy, maculopapular/pete chial rash → dengue shock syndrome and dengue hemorrhagic fever if previously exposed to other serotypes
- CLINICAL FEATURES acquired mostly from tropical and subtropical areas. Fever, headache, retro orbi tal pain, severe myalgia/arthralgia. Leukopenia and thrombocytopenia
- DIAGNOSIS serology
- TREATMENTS supportive

#### CHIKUNGUNYA FEVER

- PATHOPHYSIOLOGY mosquito borne viral infection acquired in Africa and Asia. Large outbreaks ongoing in Indian Ocean islands and India
- CLINICAL FEATURES fever (usually within 2 4 days of exposure) with severe joint pains involving small joints of hands, wrists, and ankles; may be prolonged. Leukopenia, thrombocytopenia, and elevated transaminases may be seen
- **DIAGNOSIS** serology (acute and convalescent)
- TREATMENTS symptomatic with NSAIDs

NEJM 2007 356:8

### Pneumonia

See PNEUMONIA (p. 6)

# **Endocarditis**

See ENDOCARDITIS (p. 52)

### Meningitis

NEJM 2006 354:1

# DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS

#### **★DIMS**★

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

#### INFECTIOUS

 MENINGITIS bacterial (S. pneumoniae, N. meningi tidis, H. influenzae, L. monocytogenes, Klebsiella, E. coli, Serratia, Pseudomonas), viral (enterovirus, VZV, influenza, mumps, HIV), TB, fungal (Cryptococcus)

# DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS (CONT'D)

- ENCEPHALITIS HSV, West Nile, St. Louis, Equine, La Crosse
- ABSCESS bacterial

**METABOLIC** thyroid storm

#### STRUCTURAL

- HEMORRHAGE subarachnoid, epidural, subdural, intracerebral
- CEREBRAL INFARCT

# DIFFERENTIAL DIAGNOSIS FOR FEVER AND NEUROLOGICAL SYMPTOMS (CONT'D)

- TUMOR
- PITUITARY APOPLEXY
- VASCULAR TTP/HUS, lupus, vasculitis, granulo matous 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. pneu moniae, 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. epider midis, aerobic Gram negative bacilli\*

### PATHOPHYSIOLOGY (CONT'D)

- CSF SHUNT S. aureus, S. epidermidis, aerobic Gram negative bacilli\*, diphtheroids
- BASILAR SKULL FRACTURE S. pneumoniae, H. influ enzae, group A Streptococci
- \*aerobic Gram negative bacilli include Klebsiella, E. coli, Serratia, and Pseudomonas

RISK FACTORS FOR S. PNEUMONIAE pneumonia, oti tis 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 hemiation, stroke, vasculitis, acute cerebral hemorrhage, and aneurysm formation of cerebral ves sels, with symptoms such as seizures, hearing loss, and neuropsychological impairment. Systemic complications include septic shock, pneumonia, and ARDS

#### CLINICAL FEATURES

#### RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS ADULT PATIENT HAVE ACUTE MENINGITIS? Sens History Headache 50% Nausea and vomiting 30% 28% Neck pain **Physical** Fever 85% Neck stiffness 70% Altered mental status 67% 23% Focal neurological findings 22% Kernig sign (patient lying supine with hip flexed >90°. Extension of knee from 9% 100% this position elicits resistance or pain in lower back or posterior thigh) Brudzinski sign (passive neck flexion in supine patient results in flexion of knees Jolt accentuation of headache (patient turns head horizontally at a frequency of 97% 60% 2 3 rotations per second. Worsening headache represents positive sign)

**APPROACH** "absence of all 3 signs of the classic triad of fever, neck stiffness, and altered mental status virtually eliminates a diagnosis of meningitis. Fever is most sensitive of triad, stiff neck and altered mental status second and helpful to exclude meningitis in low risk patients. Kernig and Brudzinski signs appear to have low sensitivity and high specificity. Jolt accentuation of headache may be a useful adjunctive maneuver for patients with fever and headache. In patients at sufficient risk of meningitis, a positive test result may aid in the decision to proceed to lumbar puncture, whereas a negative test result essentially excludes meningitis"

JAMA 1999 282:2

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, Cr/urea, INR, PTT, AST, ALT, ALP, bilirubin, fibrinogen, urinalysis
- MICROBIOLOGY blood C&S, sputum Gram stain/ AFB/C&S, urine C&S

### INVESTIGATIONS (CONT'D)

- IMAGING CXR, head CT (see below)
- LUMBAR PUNCTURE (1) cell count and differential; (2) Gram stain, C&S and AFB; (3) cell count and differential; (4) protein, glucose, lactate; (5) PCR for HSV, VZV, enteroviruses; (6) cytology

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### DIAGNOSTIC AND PROGNOSTIC ISSUES

**LUMBAR PUNCTURE** suspect bacterial infection if high neutrophils, low glucose, high protein, with cul ture. Suspect viral infection if high lymphocytes, *normal* glucose, and normal/high protein (**NEJM 2006 355:e12**)

- OPENING PRESSURE normal is 60 250 mmH<sub>2</sub>O.
   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)</li>
- XANTHOCHROMIA lysed RBC. Present in >90% of patients within 12 h of subarachnoid hemorrhage onset
- GRAM STAIN sensitivity is 60 80% in untreated bacterial meningitis and 40 60% in partially trea ted 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 bac terial meningitis, mildly lower in fungal and TB infections, and usually normal in viral infections

#### RATIONAL CLINICAL EXAMINATION SERIES: HOW DO I PERFORM A LUMBAR PUNCTURE AND ANALYZE THE RESULTS TO DIAGNOSE BACTERIAL MENINGITIS?

**TECHNIQUE** "use of an **atraumatic needle** compared with a standard needle and use of a **26 gauge** standard needle compared with a 22 gauge standard needle have been shown to be associated with reduced risk of headache after lumbar puncture. **Reinsertion of the stylet** before needle removal should occur (ARR 11%). **Patients do not require bed rest** after the procedure"

	LR+
CSF analysis	
CSF blood glucose ratio ≤0.4	18
CSF glucose >2.2 mmol/L [>40 mg/dL]	23
CSF WBC $\geq$ 500/ $\mu$ L	15
CSF lactate $\geq$ 3.5 mmol/L [ $\geq$ 32 mg/dL]	21
JAMA 2006	296:16

#### DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

CT HEAD indicated before lumbar puncture only if age >60, immunocompromised, history of CNS dis ease, seizures within 1 week, focal neurological abnormalities, papilloedema, obtunded or uncon scious, 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. pneu moniae* meningitis and 3 13% for *N. meningitidis* meningitis. Factors conferring poor prognosis include systemic compromise, ↓ level of consciousness, and *S. pneumoniae* 

NEJM 2004 351:18

#### MANAGEMENT

**ACUTE** ABC, O<sub>2</sub>, 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). Cefotaxime 2 g IV q6h or ceftriaxone 2 g IV q12h. Add vancomycin 500 750 mg IV q6h if concerned about penicillin resistant Pneumococci. Add ampicillin 2 g IV q4h if age >50 for Listeria coverage. If neurosurgery/trauma, CSF shunt, or basilar skull fracture, give ceftazidime 2 g IV q8h plus vancomycin. If HSV encephalitis, give acyclovir 10 mg/kg IV q8h

**SPECIFIC ANTIBIOTICS** *S. pneumoniae* (penicillin G or ampicillin if MIC <0.1 μg/mL, ceftriaxone or cefo taxime  $\pm$  vancomycin  $\times$ 10 14 days if MIC >1.0 μg/mL), *N. meningitidis* (ceftriaxone, penicillin G or ampi cillin  $\times$ 7 days), *L. monocytogenes* (ampicillin or peni cillin G, plus gentamicin  $\times$ 14 21 days), *H. influenzae* (ampicillin, ceftriaxone, or cefotaxime  $\times$ 7 days), **Enterobacteriaceae** (ceftriaxone or cefotaxime  $\times$ 7 days)

#### SPECIFIC ENTITIES

**CHRONIC MENINGITIS** (>4 weeks symptoms and persistent CSF abnormalities) consider TB, fungal infections, neurosarcoidosis, lymphoma, and lepto meningeal carcinomatosis

**RECURRENT MENINGITIS** congenital predisposi tion (myelomeningocele, dermal sinus), acquired (trauma, tumor, shunt), immunologic defects (com plement defects, antibody defects, splenectomy)

#### **HSV ENCEPHALITIS**

- PATHOPHYSIOLOGY usually infects the temporal lobe → subacute illness with fever, focal neurolo gic abnormalities, aphasia, mental status changes, and seizures. May have long term sequelae
- DIAGNOSIS lumbar puncture (mild lymphocytic pleocytosis <500 cells/μL, erythrocytes, xanthochro mia, ↑ protein, normal glucose, PCR for HSV1 and HSV2), MRI (hyperintense lesion in the inferior med ial temporal lobe, often extending into the insula)
- TREATMENTS acyclovir 30 mg/kg/day ×14 days

#### SPECIFIC ENTITIES (CONT'D)

#### **WEST NILE VIRUS ENCEPHALITIS**

- PATHOPHYSIOLOGY flavivirus West Nile virus trans mitted by mosquitoes between late spring and early autumn
- CLINICAL FEATURES wide spectrum from asympto matic to severe neurologic disorder. Fever, erythe matous rash, meningitis, encephalitis, and flaccid paralysis. Risk of progression to severe neurologi cal 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

#### SPECIFIC ENTITIES (CONT'D)

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)

# Urinary Tract Infections and Sexually Transmitted Infections

Urol Clin N Am 2008;35:1; Can J Infect Dis Med Microbiol 2005;16:6; www.phac-aspc.gc.ca/std-mts/sti-its/guide-lignesdir-eng.php

#### DIFFERENTIAL DIAGNOSIS OF DYSURIA

#### \*SUV\*

SEXUALLY TRANSMITTED DISEASES Chlamy dia 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, Tricho monas, bacterial vaginosis

### PATHOPHYSIOLOGY OF URINARY TRACT INFECTIONS

COMPLICATED UTI presence of functional or ana tomic 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, incon tinence, diabetes, cystoceles, previous GU surgery

**PATHOPHYSIOLOGY OF CATHETER ASSOCIATED BACTERIURIA** bacteria establish biofilm in or on catheter and enter bladder intra or extraluminally. Common organisms include *E. coli* and enterococci. Responsible for 80% of urosepsis. Risk factors include duration of catheterization, errors in catheter care, diabetes mellitus, and female sex

# CLINICAL FEATURES OF URINARY TRACT INFECTIONS

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

	LR+	LR
History		
Dysuria	1.5	0.5
Frequency	1.8	0.6
Hematuria	2.0	0.9
Fever	1.6	0.9
Flank pain	1.1	0.9
Lower abdominal pain	1.1	0.9
Vaginal discharge	0.3	3.1
Vaginal irritation	0.2	2.7
Back pain	1.6	0.8
Physical		
Vaginal discharge	0.7	1.1
CVA tenderness	1.7	0.9
Urine dipstick		

Leukocyte esterase or nitrite positive 4.2 'four symptoms (dysuria, APPROACH quency, 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 rela tively high, a urine culture should be considered to rule out infection"

JAMA 2002 287:20

# INVESTIGATIONS FOR URINARY TRACT INFECTIONS BASIC

- LABS CBCD, lytes, Cr/urea
- MICROBIOLOGY urinalysis (nitrite or leukocyte esterase sens 75%, spc 82%), urine C&S (pyuria sens 95%, spc 71%; bacteria sens 40 70%, spc 85 95%. Not necessary if symptomatic uncom plicated 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 symp toms, sensitivity increases and specificity only decreases slightly

**URINE CULTURE** not always needed if sympto matic and biochemical evidence (i.e. leukocyte ester ase) of uncomplicated UTI (see Clinical Features). However, antimicrobial resistance is increasing, so culture and sensitivity may become more important

#### MANAGEMENT OF URINARY TRACT INFECTIONS

**UNCOMPLICATED UTI IN WOMEN** trimethoprim sulfamethoxazole (DS 160/800 mg) 1 tab PO BID  $\times$ 3 days, ciprofloxacin 250 500 mg PO BID  $\times$ 3 days, levofloxacin 250 500 mg PO daily  $\times$ 3 days, nitrofur antoin macrocrystals 50 mg PO QID  $\times$ 5 7 days, nitro furantoin monohydrate macrocrystals 100 mg PO BID  $\times$ 5 7 days, amoxicillin clavulanate 500 mg PO BID  $\times$ 7 days, fosfomycin trometamol 3 g PO  $\times$ 1 dose

**COMPLICATED UTI** treatment duration 7 14 days **RECURRENT UTI** (consider below measures if >3 episode of UTI/year) **daily low dose prophylaxis** (trimethoprim sulfamethoxazole DS ½ tab PO qhs or 1 tab 3×/week ×6 months, nitrofurantoin 50 mg or macrocrystals 100 mg PO qhs ×6 months), **post coital prophylaxis** (trimethoprim sulfamethoxazole DS ½ 1 tab PO post coital, nitrofurantoin 50 mg PO macrocrystals 100 mg PO post coital), **patient initiated treatment** (start standard dose of antibio tics with onset of UTI symptoms)

acute uncomplicated pyelonephritis treat empircally with oral fluoroquinolones ×7 d (ciproflox acin 500 mg PO BID or levofloxacin 750 mg PO daily). If isolate susceptible, may treat with trimethoprim sulfamethoxazole, amoxicillin, or amoxicillin clavula nate ×14 d. Most otherwise healthy, non pregnant women with pyelonephritis can be treated on an outpatient basis. Otherwise, treat with IV antibiotics, at least initially (aminoglycoside ± ampicillin, third generation cephalosporin, or carbapenem)

# MANAGEMENT OF URINARY TRACT INFECTIONS (CONT'D)

**CATHETER ASSOCIATED BACTERIURIA** remove or replace catheter and initiate antibiotics for sym ptomatic infection; switch to intermittent catheterization

**PREGNANCY AND UTI** urinalysis for all pregnant women at 16 weeks. Treat all bacteriuria with amox icillin or nitrofurantoin ×3 7 days even if asympto matic as there is a 20 40% risk of pyelonephritis. Avoid fluoroguinolones

#### VAGINITIS

**CANDIDA** vulvovaginitis with cheesy vaginal dis charge, 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 vagi nal discharge, strawberry cervix. Diagnosis by micro scopy showing motile trichomonads, pH 5 6. Treat with oral *metronidazole* 2 g as a single dose

**BACTERIAL VAGINOSIS** gray, fishy smelling vagi nal 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 tra chomatis, and other non gonococcal (Ureaplasma urealyticum, Mycoplasma genitalium, Trichomonas vaqinalis, HSV)
- DIAGNOSIS Gram stain of discharge, urine for chla mydia/gonorrhea (nucleic acid amplification test, NAAT) or urethral/cervical swab for gonorrhea cul ture; 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 part ners 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

# SEXUALLY TRANSMITTED INFECTIONS (STIs) (CONT'D)

- SECONDARY SYPHILIS develops within 2 weeks to 6 months, with symptoms such as fever, maculopapular rash, mucocutaneous lesions, alopecia, lymphadenopathy, meningitis, uveitis, and cranial neuritis
- TERTIARY SYPHILIS develops after year(s) and may involve the heart (aortitis), eyes (iritis, Argyll Robertson pupil), bones/soft tissues (gummas), and neurologic system (general paresis, a rapidly progressive dementia with psychotic features and tabes dorsalis which

# SEXUALLY TRANSMITTED INFECTIONS (STIs) (CONT'D)

- affects posterior columns of the spinal cord and the dorsal roots, leading to pain episodes, decreased vibration and proprioception, absent reflexes, and bowel/bladder dysfunction)
- DIAGNOSIS first line diagnostic test of choice for a primary syphilitic chancre should be either DFA or PCR, if available. Otherwise, treponemal serologies are more sensitive and become positive earlier than non treponemal serologies and would be preferred if primary syphilis is a consideration

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

Abbreviations: DFA, direct fluorescent antibody; EIA, enzyme immunoassay; FTA ABS, fluorescent treponemal antibody absorption; MHA TP, microhemagglutination assay for antibody to TP; PCR, polymerase chain reaction; RPR, rapid plasma reagin test; TP, treponema pallidum; TPPA, TP particle agglutination assay; VDRL, Venereal Disease Research Laboratory; INNO LIA, line immunoassay

# SEXUALLY TRANSMITTED INFECTIONS (STIs) (CONT'D)

• TREATMENTS for primary, secondary and early latent (<1 year) syphilis, benzathine penicillin G 2.4 M units IM ×1 (preferred) or doxycycline 100 mg PO BID ×2 weeks. For late latent (>1 year) syphilis, gummatous and cardiovascular syphilis, benzathine penicillin G 2.4 M units IM q7days ×3 weeks. For neurosyphilis or syphilitic eye disease, give benzathine penicillin G 3 4 M units q4h IV ×10 14 days. Follow up is essential. Treatment failure is defined as persistent symptoms or failure of serologic test to decline by 4 fold within 6 months

#### JAMA 2003 290:11

#### PELVIC INFLAMMATORY DISEASE

 PATHOPHYSIOLOGY includes endometritis, tubo o varian abscess, salpingitis, and pelvic peritonitis. Most commonly due to N. gonorrhoeae, C. tracho matis, M. hominis, U. urealyticum; may involve

# SEXUALLY TRANSMITTED INFECTIONS (STIs) (CONT'D)

endogenous (gut) organisms including anaerobes. Complications include infertility, ectopic preg nancy, and chronic pelvic pain

- CLINICAL FEATURES lower abdominal pain, abnor mal vaginal bleeding/discharge, and dyspareunia may be mild and non specific. Findings include lower abdominal tenderness, adnexal tenderness, and cervical motion tenderness
- DIAGNOSIS high index of clinical suspicion. Cervi cal swab and urine NAAT for Chlamydia and gonor rhea. Ultrasound. Pregnancy test
- TREATMENTS outpatients (ceftriaxone 250 mg IM ×1 and doxycycline 100 mg PO BID ×14 days, or levofloxacin 500 mg PO daily ×14 days); add metronidazole 500 mg PO BID ×14 days if there are risk factors for anaerobic pathogens. Inpatients (doxycycline 100 mg PO q12h and cefoxitin 2 g IV q6h ×14 days, or clindamycin 900 mg IV q8h and gentamicin 1.5 mg/kq IV q8h ×14 days)

Soft Tissue Infections 247

### Soft Tissue Infections

NEJM 2004 350:9; NEJM 2007 357:4; CID 2005 41:10

#### **DIFFERENTIAL DIAGNOSIS**

DISCRETE, LOCALIZED CUTANEOUS INFECTIONS superficial (impetigo, folliculitis, furuncu losis), deep (carbuncles, subcutaneous abscesses)

SPREADING, DIFFUSE CUTANEOUS INFECTIONS (involves deeper dermis and subcutaneous tis sues) erysipelas, cellulitis

**DEEP SOFT TISSUE INFECTIONS** necrotizing fasciitis (polymicrobial, *S. pyogenes*), gas gangrene (*C. perfringens*)

#### PATHOPHYSIOLOGY

#### **RISK FACTORS FOR CELLULITIS**

- COMPROMISED SKIN trauma, IDU, psoriasis, eczema, fungal disease (especially tinea pedis)
- COMPROMISED SENSORY/PROPRIOCEPTIVE NERVES diabetic neuropathy
- COMPROMISED BLOOD/LYMPHATIC VESSELS diabetes, malignancy, lymphatic or venous insufficiency, venectomy, radiation, prior cellulitis

**CELLULITIS** acute spreading infection involving the dermis and subcutaneous tissue, mostly caused by Staphylococci and group A *Streptococcus*. It usually presents as a swollen, erythematous plaque with ill defined border

**ERYSIPELAS** superficial cellulitis involving the upper dermis and lymphatics, mostly caused by group A *Streptococcus*. It usually presents as a raised, erythematous plaque with well demar cated border. It occurs more commonly in infants and elderly

RISK FACTORS FOR SKIN AND SOFT TISSUE INFEC TIONS 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 tococci (β, C, G, and F)
- SURGICAL WOUND S. aureus, S. pyogenes
- HUMAN BITE oral anaerobes, Eikenella corrodens
- ANIMAL BITE Pasteurella multocida, Capnocyto phaga canimorsus
- TICK BITE Borrelia burgdorferi, Tularemia
- FRESHWATER Aeromonas hydrophila
- SEAWATER Vibrio vulnificus
- FISH EXPOSURE Erysipelothrix rhusiopathiae, Strep tococcus iniae
- HOT TUB Pseudomonas aeruginosa folliculitis

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, lactate (if suspicion of necrotizing fasciitis)
- MICROBIOLOGY swab of portal of entry or any open wound for Gram stain and C&S, blood C&S

#### MANAGEMENT

TREAT UNDERLYING CAUSE incision and drain nage of abscesses. Elevation of affected area if possible, compression and skin hydration. Antibiotics for mild cellulitis (cephalexin 500 mg PO QID, diclox acillin 500 mg PO QID, or clindamycin 150 300 mg PO QID ×5 14 days); for systemic toxicity or severe cellulitis (cefazolin 1 2 g IV q8h, ceftriaxone 1 g IV q24h, nafcillin 1 2 g IV q4 6 h  $\times$ 7 14 days). For MRSA associated skin infections, consider vancomycin 1 2 g IV g12h, clindamycin 600 mg IV TID or 300 mg PO QID, daptomycin 4 6 mg/kg IV daily, tigecycline 100 mg loading dose, then 50 mg IV g12h, doxycycline 100 mg PO BID, linezolid 600 mg PO/IV g12h or quinupristin dalfopristin 7.5 mg/kg IV q8 12h. For mild erysipelas, consider penicillin 500 mg PO QID or amoxicillin 500 mg PO TID. For severe erysipelas with fevers and chills, consider ceftriaxone 1 g IV q24h or cefazolin 1 2 g IV g8h  $\times$ 5 14 days

#### SPECIFIC ENTITIES

#### NECROTIZING FASCIITIS

- TYPES type 1 (polymicrobial infections including Enterococci, E. coli, non group A Streptococcus, Klebsiella, anaerobes. Mixed infections occurring postoperatively or in those with diabetes or per ipheral 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, lacera tion, 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, obe sity), compromised skin (burns, trauma, postopera tive infection), compromised blood vessels (per ipheral vascular disease, diabetes)

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#### SPECIFIC ENTITIES (CONT'D)

- CLINICAL FEATURES typically happens over body areas with limited fibrous tissue (trunk, extremi ties). Pain disproportionate to physical findings. Gangrenous skin changes, bullae, tense edema, and crepitus may be seen as late signs
- DIAGNOSIS high index of suspicion (pain >>physical findings). Plain X ray to check for gas with type 1 necrotizing fasciitis. CT or MRI maybe useful. Early deep incisional biopsy is gold standard

#### SPECIFIC ENTITIES (CONT'D)

TREATMENTS urgent surgical debridement of all necrotic tissue. Consider IVIG if significant hypo tension in Group A Streptococcus necrotizing fas ciitis. 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). Strepto coccus (penicillin G 4 MU IV q4h plus clindamycin 600 900 mg IV q8h)

### Osteomyelitis

#### **DIFFERENTIAL DIAGNOSIS**

**HEMATOGENOUS** (monomicrobial) *S. aureus*, coagulase negative staphylococci, Gram negative bacilli (*P. aeruginosa, Serratia, E. coli*), TB, fungi

**CONTIGUOUS SPREAD FROM SOFT TISSUE OR JOINTS** (polymicrobial) *S. aureus*, coagulase negative Staphylococci, *S. pyogenes, Enterococcus*,

Gram negative bacilli, anaerobes

CONTIGUOUS SPREAD WITH GENERALIZED

VASCULAR INSUFFICIENCY (polymicrobial) S.
aureus, Streptococcus, Enterococcus, Proteus mir
abilis, 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 ulcar
- 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  $\sim$ 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)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT WITH DIABETES HAVE OSTEOMYELITIS OF THE LOWER EXTREMITY? Wagner grading scale

- 0 no open lesions; may have evidence of healed lesions or deformities
- 1 superficial ulcer
- **2** deeper ulcer to tendon, bone, or joint capsule
- **3** deeper tissues involved, with abscess, osteomyelitis, or tendinitis
- 4 localized gangrene of toe or forefoot
- 5 gangrene of foot (partial or total)

gangrene or root (partial c		
	LR+	LR
Clinical gestalt		
Clinical judgment	9.2	0.70
Wagner grade >2	5.5	0.54
Physical		
Bone exposure	9.2	0.70
Positive probe to bone finding	6.4	0.39
Ulcer area >2 cm <sup>2</sup>	7.2	0.48
Ulcer inflammation	1.5	0.84
Laboratory		
ESR ≥ 70 mm/h	11	0.34
Swab culture	1	1
Abnormal plain radiograph	2.3	0.63
Abnormal MRI	3.8	0.14
	2	

APPROACH "an ulcer area >2 cm², a positive probe to bone test result, an ESR ≥70 mm/h, and an abnormal plain radiograph are helpful in diag nosing the presence of lower extremity osteomye litis in patients with diabetes. A negative MRI result makes the diagnosis much less likely when all of these findings are absent. No single historical fea ture or physical examination reliably excludes osteomyelitis. The diagnostic utility of a combina tion of findings is unknown. The gold standard for diagnosis is bone biopsy"

JAMA 2008 299:7

Osteomyelitis 249

#### CLINICAL FEATURES (CONT'D)

#### SYMPTOMS

- ACUTE OSTEOMYELITIS (<2 weeks) typically asso ciated with bone pain, tenderness, warmth, swel ling, febrile, and chills. Hip, vertebrae, and pelvis tend to manifest few signs and symptoms
- SUBACUTE OSTEOMYELITIS (weeks to few months) longer duration of above symptoms, but less severe. Over time, draining sinus tracts, deformity, instability, and vascular/neurologic changes may develop
- CHRONIC OSTEOMYELITIS (>few months) similar to subacute osteomyelitis

#### INVESTIGATIONS

#### **BASIC**

- LABS CBCD, ESR (monitor disease progress if elevated), urinalysis
- MICROBIOLOGY blood C&S, urine C&S
- IMAGING plain films (specific but insensitive), three phase bone scan (sensitive), CT, MRI (most sensitive and specific, particularly spine and diabetic foot), indium labeled WBC scan (specific), U/S, bone marrow scan, dual tracer scan

#### SPECIAL

- ULCER PROBING
- BONE BIOPSY C&S, AFB, TB culture, fungal culture, histology; generally required for vertebral osteomyelitis (CT guided biopsy can provide microbiological diagnosis to guide therapy)
- ANKLE BRACHIAL INDEX ischemic ulcers suspected

#### DIAGNOSTIC ISSUES

**PLAIN FILMS** soft tissue swelling and gas, cortical destruction, periosteal new bone formation, foreign bodies, deformities, fractures, and soft tissue gas. Usually the first imaging to investigate for osteomye litis. However, may not detect changes until after 2 3 weeks of infection. May help make diagnosis of osteo myelitis but never excludes it (sens 61%, spc 72%, PPV 80% for diabetic foot osteomyelitis)

**BONE SCAN** more sensitive but less specific than plain films (sens 70 100%, spc 36% for diabetic foot osteomyelitis). Useful for ruling out osteomyelitis, but cannot make the diagnosis

**INDIUM LABELED LEUKOCYTE SCAN** better sen sitivity and specificity (but still poor) than bone scans in diabetic foot. Since WBC accumulates in the mar row, the scan is less sensitive in areas with red mar row (vertebrae, pelvis). Excellent for fracture non union osteomyelitis (sens 91%, spc 97%)

**MRI** provides great anatomic details, more sensi tive and specific than bone scan. Imaging of choice for specific body sites (vertebrae, diabetic foot) (sens 72%)

#### DIAGNOSTIC ISSUES (CONT'D)

**ULTRASOUND** fluid collection adjacent to the bone without intervening soft tissue, elevation of the periosteum by >2 mm, and thickening of the periosteum. Sensitivity and specificity uncertain

**BONE BIOPSY** gold standard for osteomyelitis and generally required in vertebral osteomyelitis. Positive blood cultures and corresponding radiologic findings may support diagnosis and sometimes replace bone biopsy. Consider holding off antibiotic therapy if not life threatening infection to facilitate identification of organisms. Organisms from skin swabs have little correlation with the actual organisms growing inside the bone, except for *S. aureus* 

#### **Related Topic**

Diabetes Mellitus (p. 337)

#### MANAGEMENT

**HEMATOGENOUS** for vertebral osteomyelitis, need blood and bone cultures, then start empiric antibiotics with *cloxacillin* 2 g IV q4 6 h or *cefazolin* 2 g IV q8h. Consider *vancomycin* 15 mg/kg IV q12h if high local MRSA rates. Once organism identified, treat with specific antibiotic (total 6 12 weeks of antibiotics guided by susceptibility from time of biopsy or definitive surgery, with at least 2 weeks of IV therapy). If failed therapy, consider bone/soft tis sue debridement and another 4 6 weeks of antibio tics after definitive surgery

CONTIGUOUS SPREAD WITHOUT VASCULAR INSUFFICIENCY after orthopedic surgery and specimen collection, start vancomycin 15 mg/kg IV q12h ± ceftazidime 2 g IV q8h. For sternal osteomyelitis, give vancomycin 15 mg/kg IV q12h, then switch to specific antibiotics (total 6 weeks of antibiotics from time of definitive surgery, usually intravenous for the duration)

#### CONTIGUOUS SPREAD WITH VASCULAR INSUFFI

**CIENCY** 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 complica tion of spine and disc surgery. Risk factors include extraspinal infection site, urinary tract instrumenta tion, 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 gen erally required for confirmation and microbiologi cal 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 pros thesis may be possible with early onset infection

#### SPECIFIC ENTITIES (CONT'D)

(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 antibio tic therapy is also provided for 6 weeks following the initial surgery

NEJM 2009 361:8

### **Septic Arthritis**

See SEPTIC ARTHRITIS (p. 273)

# **Tuberculosis: Pulmonary**

NEJM 1999 340:5; NEJM 2001 345:3; NEJM 2004 350:20

#### PATHOPHYSIOLOGY

**ORGANISMS** genus *Mycobacterium* consists of >50 species. TB is caused by *M. tuberculosis* complex including *M. tuberculosis*, *M. bovis*, and others. The cell envelope contains mycolic acid  $\rightarrow$  resists destain ing by acid alcohol, thus termed acid fast bacilli

**TRANSMISSION** TB transmission is almost exclusively airborne through inhalation of minute droplet nuclei. Therefore, lungs are the primary focus. How ever, any organs can become infected during the bacteremia that follows initial lung infection

**LATENT TB INFECTION (LTBI)** follows initial infection; asymptomatic; detected by tuberculin skin test. Risk of active infection generally is 5% in the first 2 years with 5% risk of reactivation thereafter

FACTORS THAT INCREASE THE RISK OF INFEC TION 1/3 of the world's population is infected with TB. Birth in endemic area (less commonly travel) is the major risk factor; other risk factors include aboriginal populations and racial/ethnic minorities, household/institutional contacts and crowding (healthcare workers, long term care, correctional facilities, substance abuse, and shelters)

FACTORS INCREASING THE RISK OF REACTIVA TION 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/immunosup pression, silicosis, chronic steroid use, TNF  $\alpha$ 

#### PATHOPHYSIOLOGY (CONT'D)

inhibitors, alcohol abuse, malnutrition, liver or kidney disease, poorly controlled diabetes, smoking, gas trectomy, jejunoileal bypass

#### CLINICAL FEATURES

#### PRIMARY TB

- symptoms fever, night sweats, pleuritic chest pain, chronic cough, anorexia, weight loss, fatigue, erythema nodosum
- SIGNS often none. Primary TB usually involves the mediastinal lymph nodes; hilar lymphadenopathy in the presence of *RML collapse* is the most com mon radiologic finding (2/3) with pleural effusion in 1/3. Lung infiltrates may be seen and involve lower lungs or middle lung fields most commonly with possible cavitation in areas of consolidation

#### **REACTIVATION TB** (active pulmonary)

- SYMPTOMS cough, yellow green sputum (increases over time), hemoptysis (25%), chest pain/dyspnea (33%), fever/night sweats (50%), fatigue (50 66%), weight loss
- **signs** reactivation TB usually involves the apical posterior segments of upper lobes (80 90%), cavi tation (19 40%), hilar lymphadenopathy (more likely than cavitation in AIDS patients)
- ELDERLY WITH REACTIVATION TB presents with fever, night sweats, or hemoptysis less often. Lesions less often cavitary and less often TST positive

Tuberculosis: Pulmonary 251

#### CLINICAL FEATURES (CONT'D)

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

#### **Related Topic**

Tuberculosis in Pregnancy (p. 412)

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, 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 Quanti FERON 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 con sidered 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 (ende mic, 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 cul ture), induced sputum if necessary, bronchoscopic lavage if cannot obtain sputum. Three consecutive

#### DIAGNOSTIC ISSUES (CONT'D)

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 use ful in non endemic countries to rule out other com mon mycobacteria. High specificity but variable sen sitivity (if AFB positive, sens 94 96%, spc 99.7 100%. If AFB positive, sens 9 100%, spc 25 100%)

**INTERFERON GAMMA RELEASE ASSAYS** sensitiv ity >95%; not affected by prior BCG vaccination. Most useful for evaluation of latent TB in those with posi tive 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 suscept ibility results are available. This is followed by isonia zid and rifampin daily, twice weekly, or three times weekly for 16 more weeks. Alternatives include iso niazid, 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. How ever, 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 (\( \preceiv \) 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

#### TREATMENT ISSUES (CONT'D)

- injury, hyperuricemia due to  $\downarrow$  renal excretion, arthraligias
- ETHAMBUTOL mostly bacteriostatic. Main side effect is optic neuritis

#### DRUG MONITORING

- BASELINE platelet, Cr, AST, ALP, bilirubin, uric acid (pyrazinamide), visual acuity, and red green color discrimination (ethambutol)
- 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 subopti mal. Also beware of TB and HIV drug interactions (protease inhibitors and non nucleoside reverse tran scriptase 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. saprophyti cus, S. hominis, S. luqdunesis, S. schleiferi

#### PAIRS/CHAINS (catalase negative)

- α-hemolytic streptococci S. pneumoniae, viri dians 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 var iant Strep"), Leuconostoc, Lactococcus, Aerococcus
   ANAEROBIC Peptostreptococcus, Streptococcus,

Peptococcus, Anaerococcus

#### GRAM POSITIVE BACILLI

**ACID FAST** (mycobacterium) *M. tuberculosis, M. leprae, M. avium intracellulare* complex, or non tuber culous Mycobacteria (NTM, also known as mycobacteria other than TB (MOTT)). These organisms have Gram positive type cell walls, but do not stain Gram positive due to the waxy mycolic acids in the cell envelope

#### GRAM POSITIVE BACILLI (CONT'D)

#### SPORE FORMING

- AEROBIC Bacillus anthrax, Bacillus cereus
- ANAEROBIC Clostridium perfringens, C. difficile, C. botulinum

#### NON SPORE FORMING

- AEROBIC, FACULTATIVE, AEROTOLERANT Corynebac terium/diphtheroids, Lactobacillus, Listeria, Garden erella, Nocardia
- ANAEROBIC Actinomyces, Propionibacterium, Eubacterium

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

#### GRAM NEGATIVE COCCI

**NEISSERIA** *N. meningitidis* (diplococci), *N. gonor rhoeae* (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 FERMENT-ING Shigella, Salmonella, Hafnia, Morganella, Pro teus, Yersinia, Edwardsiella, Vibrio (oxidase posi tive), Aeromonas (oxidase positive), Pleisiomonas (oxidase positive)
- NON-GLUCOSE AND NON-LACTOSE FERMENTING
  - OXIDASE POSITIVE Pseudomonas, Ralstonia, Bur kholderia, Roseomonas, Sphingomonas
  - OXIDASE NEGATIVE Stenotrophomonas, Acineto bacter, Chryseomonas

**ANAEROBIC** Bacteroides fragilis, Fusobacterium, Prevotella, Porphyromonas

OTHERS Eikenella\*, Pasteurella (cats), Capnocyto phaga (dogs), Kingella\*, Actinobacillus\*, Cardiobacter ium\*, 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** cellu litis, erysipelas, necrotizing fasciitis, pharyngitis, bacteremia, Streptococcal toxic shock syndrome, scarlet fever, acute rheumatic fever (post strepto coccal glomerulonephritis)

**STREPTOCOCCUS PNEUMONIAE** may develop resistance to penicillin by altered penicillin binding protein

# ANTIBIOTIC SUSCEPTIBILITY AND RESISTANCE (CONT'D)

**S. AUREUS** (MSSA) may develop resistance to peni cillin by  $\beta$  lactamase

**PSEUDOMONAS** various intrinsic mechanisms con ferring 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 penicil lin, but also penicillinase resistant penicillins (methicil lin, nafcillin, oxacillin). In general, hospital MRSA strains have broader resistance (e.g. clindamycin, trimetho prim 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

 $\begin{array}{lll} \textbf{\beta LACTAMASE RESISTANT} & \textbf{BACTERIA} & \textbf{constitu} \\ \textbf{tive} (\textit{E. coli*}, \textit{Klebsiella*}, \textit{Haemophilus}, \textit{Neisseria}, \textit{bacter} \\ \textit{oides}), & \textbf{inducible} & (\textit{S. aureus}, \textit{Serratia}^{\dagger*}, \textit{Providencia}^{\dagger}, \\ \textit{Pseudomonas}, & \textbf{Indole positive} & \textit{Proteus}^{\dagger*}, \textit{Citrobacter}^{\dagger*}, \\ \textit{Enterobacter}^{\dagger*}, & \textit{Morganella}^{\dagger*}) \end{array}$ 

†**★SPICE M**★ organisms with inducible, chromoso mally mediated cephalosporinases (AmpC type  $\beta$  lac tamases) resistant to penicillins, first and second generation cephalosporins, cephamycins, and  $\beta$  lactamase inhibitors

\*these organisms may have extended spectrum  $\beta$  lactamase (ESBL) resistant to all  $\beta$  lactams except carbapenems

Antibiotics						
Antibiotics Penicilins	Mechanism	Gram positive	Gram negative	Anaerobes Others	Others	Renal adjustments
Penicillin G 2–4 M units IV q4–6h Penicillin V 250–500 mg PO TID/QID Cloxacillin/nafcillin/oxacillin 1–2 g IV q4–6h	Bactericidal, cell wall synthesis inhibition and Iysis	++ Strep ++ Strep ++5. aureus	Meningococcus	<b>+ +</b>	Syphilis	Yes (dose + interval) Yes (dose + interval) No
Amino-Penidilins Ampilin 1-2 g V q-6 h Amoxidilin 1-2 g V q-6 h Amoxidilin 250-1000 mg PO TID Amox/davulanate 875/125 mg PO BID	Bactericidal, cell wall synthesis inhibition and lysis	+++Strep/Entero +++Strep/Entero +++Strep/Entero	+/-H. flu, +/-E. coli +/-H. flu, +/-E. coli ++H. flu, E. coli	‡ ‡	Listeria	Yes (interval) Yes (interval) Yes (interval)
Anti-pseudomonal Penicillins Piperacillin 3-4 g W q4-6h Pip/tazo 3375 g q6h-4.5 g W q8h Tracrillin 3-4 g IV q4-6h Tracrillin/clavulanate 3.1 g IV q4-6h	Bactericidal, cell wall synthesis inhibition and lysis	++ ++ ++ ++ ++	++Pseudo ++Pseudo/H. flu ++Pseudo ++Pseudo	‡ <del>‡</del> ‡ ‡		Yes (dose + interval) Yes (dose + interval) Yes (dose + interval) Yes (dose + interval)
Monobactam and Carbapenems Aztreonam 1–2 g IV q6–8h Imipenem 500 mg IV q6h Meropenem 1 g IV q8h Ertapenem 1 g IV q24h Doripenem 500 mg IV q8h	Bactericidal, cell wall synthesis inhibition and lysis	‡ ‡ ‡ ‡	+++ Pseudo ++Pseudo ++(no Pseudo) +++	<b>####</b>		Yes (dose) Yes (dose + interval) Yes (dose + interval) Yes (dose) Yes (dose)
<b>First-Generation Cephalosporins</b> Cefazolin 1–2 g IV q8h Cephalexin 250–1000 mg PO QID	Bactericidal, cell wall synthesis inhibition and lysis	‡‡	+ +			Yes (interval) Yes (interval)
Second-Generation Cephalosporins Cefuroxime 750–1500 mg IV q8h Cefuroxime 125–500 mg PO BID Cefprozil 250–2500 mg PO q12h Cefaclor 250–500 mg PO BID	Bactericidal, cell wall synthesis inhibition and lysis	::::	<b>:</b>			Yes (interval) Yes (interval) Yes (interval) Yes (interval)
Third/Fourth Generation Cephal. Cefovain 1-2 g IV qG-8h Cefovaine 1-2 g IV qG-8h Ceftriaxone 1-2 g IV q24h Ceftriaxone 1-2 g IV q24h Ceftriam 1-2 g IV q12h Cefspine 1-2 g IV q12h Cefspine 1-2 g IV q12h Cefspine 500 mg PO daily	Bactericidal, cell wall synthesis inhibition and lysis	+ + + + + + + + + + + + + + + + + + +	opnasd++++ ++++++++++++++++++++++++++++++++	‡		Yes (interval) No No Yes (interval) Yes (interval) Yes (interval) Yes (interval)
Aminoglycosides Gentamich 5-7 mg/kg IV q24h Tobramycin 5-7 mg/kg IV q24h Amikacin 75 mg/kg IV q24h Streptomycin 15 mg/kg IM or IV q24h	Bactericidal, binds to 30S and 50S ribosomes	Entero (syn) +/-Entero (syn) +/-Entero (syn) Entero (syn)	opnasd++ opnasd++ opnasd++		AFB, Plague	Yes (dose + interval) Yes (dose + interval) Yes (dose + interval) Yes (dose + interval)

Antibiotics (cont'd)						
Antibiotics	Mechanism	Gram positive	Gram negative	Anaerobes Others	Others	Renal adjustments
Ciprofloxacin 500 mg PO/400 mg IV BID	Bactericidal, inhibit DNA synthesis through inhibition of DNA owase and topoisomerase		+++Pseudo		AFB	Yes (interval)
Norfloxacin 400 mg PO BID Ofloxacin 200–400 mg PO BID			‡ ‡		AFB	Yes (dose ± interval) Yes (dose ± interval)
Levofloxacin 500–750 mg PO/IV daily		‡	‡ ‡		AFB	Yes (dose $\pm$ interval)
Moxifloxacin 400 mg PO/IV daily		++	± + +	‡	AFB	Yes (dose ± interval)
Gemifloxacin 320 mg PO daily		‡	++++		AFB	Yes (dose ± interval)
<b>Macrolides</b> Azithromycin 250 mg PO daily Clarithromycin 250-500 mg PO BID	Bacteriostatic, binds to 50S ribosomes	+ +	+H. flu/legion +H. flu/legion		++Mycoplasma No and <i>Ghlamydia</i> for Yes (dose)	No Yes (dose)
Erythromycin 250–500 mg PO q6–12h		+	+Legion		all lilaci Olides	No
<b>Tetracyclines</b> Doxycycline 100 mg PO/IV q12h Minocycline 50–100 mg PO daily–BID	Bacteriostatic, binds to 305 ribosomes	+	+ +		+Chlamydia +Chlamydia	8 S
Tetracycline 500 mg PO QID Tigecycline 100 mg IV, then 50 mg q12h		+++MRSA, VRE	+ ++Acinetobacter		+Chlamydia +Chlamydia	Avoid No
<b>Sulfa</b> Sulfamethoxazole/Trimethoprim 1–2 SS/DS tab PO BID (also available IV)	Bactericidal, blocks DNA synthesis	+	++Steno, +PJP			Yes (interval)
<b>Clindamydin</b> Clindamydin 150–450 mg PO QID or 300–600 mg IV q6–12h	Bacteriostatic, binds to tRNA complex	<b>+</b>		‡ ‡		<sub>N</sub>
Metronidazole Metronidazole 500 mg PO/IV q12h	Bactericidal, DNA breakage		H. pylori, G. vaginalis	+++C. diff	+++C. diff ++protozoa	No No
<b>Glycopeptides</b> Vancomycin 15 mg/kg IV q12h	Bactericidal, interferes with peptidoglycan and RNA synthesis	‡ ‡ +				
		S. epidermidis, MRSA, Entero		++C. diff		Yes (interval)
<b>Oxazolidinones</b> Linezolid 600 mg PO/IV q12h	Bactericidal (Strep) and bacteriostatic (Staph, entero), binds to 50S ribosomes	++MRSA, VRE		+	++AFB	O <sub>N</sub>
Streptogramins Quinupristin/dalfopristin 7.5 mg/kg IV q8h via central line	Inhibits late + early protein synthesis	++MRSA, VRE (not <i>E. faecalis</i> )		+		ON.
<b>Lipopeptides</b> Daptomycin 4–6 mg/kg q24h	Bactericidal, disrupts cell membrane	++MRSA, VRE		+		Yes (interval)

256 Antibiotics

#### GENTAMICIN AND TOBRAMYCIN DOSING

**TOXICITY** nephrotoxicity, ototoxicity, neuromuscu lar blockade (rare). Serum aminoglycoside levels cor relate with nephrotoxicity

#### LOADING DOSE (TRADITIONAL DOSING: Q8H)

dependent on indication. For mild infection, uncomplicated UTI, synergy with  $\beta$  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: O8H)

- 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 infu sion. 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 ser ious 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 sched uled dose. Should be <4.2  $\mu$ mol/L [<2  $\mu$ g/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 receiv ing concurrent ototoxins (e.g. furosemide) neonates, pediatric patients with significant renal dysfunction, duration of therapy >14 days

LOADING DOSE 5 7 mg/kg IV

MAINTENANCE DOSE (5 7 mg/kg IV q24 48h)

START monitor serum level 6 14h after first dose.
 Monitor renal function and ototoxicity q3d

# ONCE DAILY GENTAMICIN AND TOBRAMYCIN DOSING (CONT'D)

ADJUSTMENTS dosing interval (q24 48h) is based on 6 14 h serum level (Hartford nomogram, Antimicrob Agents Chemother 1995 39:3). Pharmacy consult to assist with dosing (Once daily dosing provides peak levels of 15 31 46 μmol/L [22 μg/mL] and trough levels <2.1 μmol/L [<1 μg/mL] to prevent toxicity. Peak and trough levels do not need to be monitored)</li>

**DOSING WEIGHT FOR AMINOGLYCOSIDES** for obese patient (i.e. actual body weight (BW) >125% of ideal body weight (IBW)), use adjusted body weight (ABW) for dose determination:

• ABW (kg)=IBW +0.4(BW IBW)

Note: 1 kg=2.2 lbs. See p. 406 for IBW calculation

#### Related Topic

Drug Eruptions (p. 372)

#### VANCOMYCIN TOXICITY AND DOSING

**TOXICITY** rash, infusion related red man syn drome, rarely nephrotoxicity (especially combined with aminoglycoside), and ototoxicity. However, serum vancomycin levels do not predict toxicity

**LOADING DOSE** 15 20 mg/kg (usually 1 1.5 g) IV **MAINTENANCE DOSE** 30 mg/kg (actual body weight) per day divided into 2 4 doses (maximum usually 1.5 g/dose)

- START monitoring after steady state, i.e. after third dose normally, or after second dose if dosing interval >48 hour. Monitor only if >14 days in patients with stable renal function and mild/mod erate 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 propor tional changes in both peak and trough serum drug concentrations. Prolongation of dosing inter val will also reduce both, particularly trough level

#### PENICILLIN ALLERGY

**HISTORY** characterize reaction (age when reaction occurred, timing of reaction after penicillin adminis tration, type of reaction, route of administration, rea son for penicillin, any other medications at the time, resolution), any similar antibiotics since

**CROSS REACTIVITY** incidence of cross reactivity to cephalosporins when patient has penicillin allergy by history is <2%. Carbapenems and first/second generation cephalosporins have higher cross reactivity in the penicillin allergic than third generation cephalosporins and aztreonam. It is often safe to use these medications, with the first dose monitored. If safety unclear, skin testing provides reassurance. For patients with a history of penicillin allergy, those with positive and negative skin test have 5.6% and 1.7% chance of developing cross reactivity with cephalosporin, respectively

NEJM 2006 354:6

# RATIONAL CLINICAL EXAMINATION SERIES: IS THIS PATIENT ALLERGIC TO PENICILLIN?

**HISTORY** history of penicillin allergy (LR+ 1.9, LR 0.5)

#### TYPES OF ALLERGIC REACTIONS

**★ACID★** Antibody mediated (IgE), Cytotoxic (antibody dependent), Immune complex mediated, Delayed hypersensitivity reaction

#### PENICILLIN ALLERGY (CONT'D)

- TYPE I immediate <1 h, IgE antibodies mediated, anaphylaxis, hypotension, laryngeal edema, wheezing, angioedema, urticaria
- TYPE II >72 h, IgG and complement mediated, increased clearance of RBC and platelets by lym phoreticular system
- TYPE III >72 h, IgG and IgM immune com plexes 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 patho physiology 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  $\pm$  vancomycin if community set ting, anti pseudomonal plus ciprofloxacin if hospi tal setting. For urinary source, ceftriaxone or

# SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

carbapenem or fluoroquinolone or aminoglycoside. For intra abdominal source, pipericillin tazobactam plus aminoglycoside. Duration of treatment is at least 10 14 days with rationalization of antibiotics when susceptibility results available. See p. 97 for details

**MENINGITIS** (*S. pneumoniae, N. meningitidis, Listeria,* HSV) ceftriaxone/cefotaxime  $\pm$  ampicillin  $\pm$  vanco mycin. Add acyclovir if CSF suggests viral picture. Duration of treatment is 7 21 days. See p. 241 for details

**COMMUNITY ACQUIRED PNEUMONIA** (*5. pneumo niae, Klebsiella, Mycoplasma*) macrolides  $\pm$  cefotax ime or respiratory fluoroquinolones. Duration of treatment is usually 7 days. See p. 6 for details

**ASPIRATION PNEUMONIA** (anaerobes, Staph, GNB) cefotaxime  $\pm$  clindamycin or metronidazole. Duration of treatment is usually at least 7 days. See p. 6 for details

# SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

# **ICU/VENTILATOR ASSOCIATED PNEUMONIA** (GNB, *Pseudomonas*) ciprofloxacin plus ceftazidime or pipericillin tazobactam or carbapenem. Duration of treatment is usually 8 days (p. 94)

**ENDOCARDITIS** (*S. aureus*, *S. viridans*, *Enterococcus*). Duration of treatment is highly variable. See AHA quidelines and p. 52 for details

- NATIVE VALVE DISEASE ampicillin + cloxacillin/naf cillin 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 treat ment is 3 days. See p. 122 for details

**ANTIBIOTIC ASSOCIATED DIARRHEA** (*C. difficile*) oral metronidazole. Duration of treatment is 10 days. See p. 123 for details

**PERITONITIS/INTRA ABDOMINAL SEPSIS** (coli forms, anaerobes) pipericillin tazobactam, imipe nem, or ampicillin plus ciprofloxacin plus metronida zole. Treat until WBC/peritonitis resolved

**FEVER IN SPLENECTOMIZED PATIENT** (*H. influenza, N. meningitidis, S. pneumoniae, Capnocytophaga cani morsus*) cefotaxime/ceftriaxone. Duration of treat ment is usually 10 14 days. See p. 148 for further information

**URINARY TRACT INFECTION** (*E. coli, Klebsiella, Enter ococcus, Proteus, S. saprophyticus*) nitrofurantoin, trimethoprim sulfamethoxazole, ciprofloxacin. Dura tion of treatment is 3 days if uncomplicated UTI, otherwise 14 21 days. See p. 244 for details

# SPECIFIC INFECTIONS AND EMPIRIC ANTIBIOTIC CHOICES (CONT'D)

**CELLULITIS** (*Staphylococcus*, *Streptococcus*) cefazo lin, cloxacillin, or cephalexin. Duration of treatment is usually 7 10 days. See p. 247 for details

**HUMAN BITE** (Gram positive, *Eikenella*, anaerobes) amoxicillin clavulanate, or clindamycin plus Ciprofloxacin

**DIABETIC FOOT** (polymicrobial) amoxicillin clavu lanate or ciprofloxacin plus clindamycin, or trimetho prim sulfamethoxazole plus metronidazole. Treat until resolution. May require IV antibiotics with *Pseu domonas* coverage (e.g. pipericillin tazobactam; car bapenem). Osteomyelitis likely if ulcer >2 cm² or probe touches bone. See p. 248 for details

**NECROTIZING FASCIITIS** surgical treatment is mandatory. For polymicrobial infection, cefotaxime plus clindamycin, pipericillin tazobactam, or ampicil lin/penicillin G plus ciprofloxacin/gentamicin plus metronidazole. For *Streptococcus*, penicillin G plus clindamycin. See p. 247 for details

**OSTEOMYELITIS** (Gram positive, Gram negative, anaerobes) for Gram positive coverage, clinda mycin, cefazolin, or vancomycin. For Gram negative coverage, cefotaxime or ciprofloxacin. For *Pseudomonas*, piperacillin or carbapenem or cefta zidime, plus ciprofloxacin or aminoglycoside. Duration of therapy usually at least 6 weeks. See p. 248 for details

**SEPTIC ARTHRITIS** vancomycin, cloxacillin, or cefa zolin for Gram positive coverage, ciprofloxacin or ceftriaxone for Gram negative coverage. Usual dura tion 4 weeks. See p. 273 for details

### **Hepatitis B**

See HEPATITIS B (p. 130)

### **Hepatitis C**

See HEPATITIS C (p. 131)

### **Herpes Simplex Virus Infection**

### **Human Immunodeficiency Virus**

NEJM 2005 353:16; MMWR 2009 58:RR-4; www.aidsinfo.nih.gov/Guidelines/

#### RISK FACTORS FOR HIV

SEXUAL CONTACT homosexual, heterosexual

PARENTERAL IDU, transfusion, or unsafe needle
use in developing world, health workers

MATERNAL FETAL in utero, delivery, breast

**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. Hema tologic (lymphopenia, thrombocytopenia) and liver enzyme abnormalities

**DIAGNOSIS** ELISA assay (sens  $\sim$ 100%, spc <100%)  $\rightarrow$  if positive, repeat ELISA  $\rightarrow$  if positive, Western blot  $\rightarrow$  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 ser ology, 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 abnor mal, consider HCV RNA testing. If HCV positive, assess genotype ± liver biopsy), Pap smear, anal screening for HPV in gay men (no consensus yet), Chlamydia and gonorrhea screen, RPR (syphilis), TB skin test, toxoplasma serology, CMV serology

#### NATURAL HISTORY OF HIV

**VIRAL LOAD** rate of progression (speed of train). Indicates activity of viral replication. Critical measure of effect of antiretroviral therapy, once started

**CD4 COUNT** progress and stage of disease (distance to crash). Indicates relative health of immune system and risk of opportunistic complication

**FOLLOW UP** viral load and CD4 count (usually 3 4 month intervals, or q2 8weeks if change of HAART) **AIDS** CD4 <200/mm<sup>3</sup> or any AIDS defining diseases

- BACTERIAL MAC, TB, recurrent Salmonella sepsis
- VIRAL CMV retinitis, chronic HSV, PML

#### NATURAL HISTORY OF HIV (CONT'D)

- FUNGAL esophageal candidiasis, extrapulmonary coccidioidomycosis, histoplasmosis or cryptococcosis
- PARASITIC Pneumocystis jiroveci pneumonia (PJP), toxoplasmosis, chronic Cryptosporidiosis or isosporiasis
- HIV HIV encephalopathy, wasting syndrome
- NEOPLASMS Kaposi's sarcoma, CNS lymphoma, non Hodgkin's lymphoma, cervical carcinoma

MAJOR CAUSES OF DEATH IN HIV PATIENTS ON HAART AIDS (30%), liver disease (14%), cardiovas cular disease (9%), non AIDS cancers (8%)

CD4 COUNT AN	D PATH	HOLOGIES	IN HIV PA	TIENTS
CD4 count	>500	200 500	100 200	<100
(/mm) <sup>3</sup>				
Kaposi sarcoma	+	+	+	+
Bacterial	+	+	+	+
TB	+	+	+	+
HSV	+	+	+	+
Candida		+	+	+
Coccidioides		+	+	+
Histoplasma		+	+	+
PJP			+	+
Cryptococcus				+
Toxoplasma				+
CMV				+
MAC				+
CNS lymphoma				+

#### CNS LESIONS IN HIV PATIENTS

#### DIFFERENTIAL DIAGNOSIS

- BRAIN ABSCESS toxoplasma (CD4 <100/mm³, usually multiple ring enhancing lesions), tubercu losis (any CD4), Cryptococcus (CD4 <100/mm³), Histoplasma (CD4 <500/mm³), aspergillosis</li>
- CNS LYMPHOMA (CD4 < 100/mm<sup>3</sup>)
- PROGRESSIVE MULT-IFOCAL LEUKOENCEPHALOPATHY (PML, CD4 <100/mm³) reactivation of JC virus, hypo dense white matter lesion

**DIAGNOSIS** CBCD, lytes, urea, Cr, blood C&S, tox oplasma lgG antibodies, EBV PCR, JC virus PCR, CT/MR head, PET scan (CNS lymphoma has higher activity than abscess), brain biopsy (if suspect CNS lymphoma). The combination of (1) multiple ring enhancing lesions, (2) positive antitoxoplasmosis antibodies, and (3) lack of toxoplasma prophylaxis in a HIV patient with CD4 count < 100/mm³ has 90% PPV for diagnosing toxoplasma

**TREATMENT OF TOXOPLASMOSIS** pyrimetha mine plus either sulfadiazine or clindamycin

#### CHRONIC MENINGITIS IN HIV PATIENTS

#### **DIFFERENTIAL DIAGNOSIS**

- cRYPTOCOCCUS (CD4 <100/mm<sup>3</sup>) ubiquitous fun qus. High opening pressure (>200 cmH<sub>2</sub>O)
- 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 CRYPTOCOCUS** 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)  $170 \times$  increased risk in HIV patients. May be extrapulmonary
- NON-TB MYCOBACTERIUM MAC (CD4 <100/mm³, pulmonary involvement alone is rare, usually disseminated)
- FUNGAL (CD4 <500/mm³) Histoplasma, Cocci dioides, Cryptococcus
- PNEUMOCYSTIS JIROVECII PNEUMONIA (PJP, CD4 <200/ mm<sup>3</sup>)

**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, broncho scopy (lavage, biopsy)

**TREATMENT OF PJP** trimethoprim sulfamethoxa zole 15 mg of TMP/kg PO/IV divided q8h daily ×21 days. If severe disease (PaO<sub>2</sub> <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/mm<sup>3</sup>) 50 70%
  - HSV (any CD4) 5 10%
  - CMV (CD4 < 100/mm<sup>3</sup>) 5 15%
- NON-INFECTIOUS GERD, pill esophagitis, neoplasms
- **IDIOPATHIC** (any CD4) 10 30%

**DIAGNOSIS** empiric therapy (fluconazole), endo scopy with cultures for fungus, virus, and biopsy

# HEPATITIS/CHOLANGITIS/PANCREATITIS IN HIV PATIENTS

#### DIFFERENTIAL DIAGNOSIS

- INFECTIONS
  - TB (any CD4)
  - MYCOBACTERIUM AVIUM COMPLEX (MAC, CD4 <100/mm<sup>3</sup>) *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, Campylobac ter, Yersinia, EHEC, EIEC, C. difficile
  - **TB** (any CD4)
  - MYCOBACTERIUM AVIUM COMPLEX (MAC, CD4 <100/mm³) *M. avium, M. intracellulare*
  - CMV (CD4 <100/mm³)</li>
     PARASITIC ★MAGIC★ Microsporidium, EntA
  - PARASITIC ★MAGIC★ Microsporidium, EntA moeba, 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/mm<sup>3</sup>)

### AIDS ASSOCIATED MALIGNANCIES

#### AIDS DEFINING MALIGNANCIES

- KAPOSI'S SARCOMA (any CD4) strongly asso ciated with HHV8. Lesions may involve skin, oral mucosa, lungs, and Gl tract. Treat with liposomal doxorubicin
- NON-HODGKIN'S LYMPHOMA (CD4 <100/mm<sup>3</sup>) diffuse large B cell lymphoma, primary effusion lymphoma (associated with HHV8 and EBV), and plasmablastic lymphomas. Treat with combination chemotherapy (CHOPR)
- PRIMARY CNS LYMPHOMA (CD4 < 100/mm³) strongly associated with EBV. Treat with radiation and/or high dose methotrexate or intrathecal chemotherapy
- CERVICAL CARCINOMA (any CD4) strongly asso ciated 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, color ectal 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

PIP 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/mm<sup>3</sup>. *Azithromycin* 1200 mg PO once weekly

**HISTOPLASMOSIS PROPHYLAXIS** for patients with CD4 <150/mm<sup>3</sup> and living in endemic area. *Itraconazole* 200 mg PO daily

**TB PROPHYLAXIS** for patients with positive tuber culin 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 ×9 months. *Rifampin* 600 mg PO daily ×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, hepa titis B vaccine (if non immune), hepatitis A vaccine (if non immune and especially if homosexual), influenza vaccine annually
- GENERALLY AVOID live vaccines (oral polio, vari cella, 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 TRAN SCRIPTASE INHIBITORS (NRTI) zidovudine (ZDV, AZT), stavudine (d4T), didanosine (ddl), lamivudine (3TC), abacavir (ABC), tenofovir (TDF), and emtricita bine (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), indi navir (IDV), nelfinavir (NFV), lopinavir ritonavir (LPV/ RTV), fosamprenavir (FPV), atazanavir (ATV), tiprana vir (TPV), and darunavir (DRV). Major side effects include hyperglycemia, fat redistribution syndrome, insulin resistance, and Gl intolerance

INTEGRASE INHIBITORS raltegravir
FUSION INHIBITOR (FI) enfuvirtide (T 20)
CCR5 ANTAGONIST maraviroc

### EXAMPLES OF PREFERRED HIGHLY ACTIVE ANTI RETROVIRAL THERAPY (HAART) REGIMENS

- NRTI (tenofovir plus emtricitabine) plus NNRTI (efavirenz)
- NRTI (tenofovir plus emtricitabine) plus PI (ataza navir/ritonavir or darunavir/ritonavir)
- NRTI (tenofovir plus emtricitabine) plus integrase inhibitor (raltegravir)

#### THERAPEUTIC DECISIONS IN HIV

**GOALS OF HIV THERAPY** durable suppression of HIV viral load to undetectable levels, reduction in HIV related morbidity, improvement in quality of life, prolongation of survival, restoration of immune function, and prevention of HIV transmission

APPROACH start treatment in all symptomatic patients and in asymptomatic patients if CD4 <350/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  $\downarrow$  by 2 logs after 8 weeks and  $\downarrow$  to <50 copies/mL after 6 months of therapy. Need to continue therapy or may develop viral load rebound/drug resistance. If failure, consider

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#### 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 dissemi nated MAC or worsening CXR and fever in patients with TB). In general, treat opportunistic infections for 2 weeks prior to initiating antiretroviral therapy

# VIRAL HEPATITIS IN HIV CO INFECTED PATIENTS HEPATITIS B

**TREATMENTS** supportive, continue antiretrovirals,

 PATHOPHYSIOLOGY HIV/HBV co infection rate is up to 20 30% in Asia/sub Saharan Africa where trans mission is mostly vertical or between young chil dren and 5 10% in the USA and Europe where transmission is mostly via IDU and sexual contact. Co infection is associated with increased risk of progression to end stage liver disease

# VIRAL HEPATITIS IN HIV CO INFECTED PATIENTS (CONT'D)

- DIAGNOSIS for patients with isolated HBcAb, 10 45% have occult HBV infection with detectable levels of HBV DNA
- PREVENTION hepatitis B vaccination of family and sexual partners
- TREATMENT long term combination therapy with a nucleoside analogue and nucleotide analogue (e.g. tenofovir plus either emtricitabine or lamivu dine) 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 hepa tocellular 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  $\alpha$  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

NEJM 2007 356:14

### Influenza NEJM 2008 359:24

### DIFFERENTIAL DIAGNOSIS

give corticosteroids

VIRAL influenza A, B, C, parainfluenza, RSV, metapneumovirus, adenovirus, rhinovirus
BACTERIAL PNEUMONIA Streptococcus pneumo niae, 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 antiqenic 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.

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#### PATHOPHYSIOLOGY (CONT'D)

Thus, antibodies against previous strains are ineffective. Can result in seasonal epidemics

**ANTIGENIC SHIFT** an abrupt and significant emer gence 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 sub type through a process called genetic reassortment (e.g. swine flu, avian flu). Rarely, avian strains of

#### PATHOPHYSIOLOGY (CONT'D)

influenza may directly infect humans. Antigenic shift generates new virus and triggers pandemics as the majority of the population have no immunity against this new virus

**PANDEMIC** (worldwide outbreak) based on the following criteria: (1) emergence of a new subtype of influenza A virus, (2) this virus is able to infect humans, (3) this virus can spread easily from person to person in a sustained manner

DISTINGUISHING FE	DISTINGUISHING FEATURES BETWEEN INFLUENZA A, B, AND C					
Influenza A Influenza B Influenza C						
Hosts	Humans, Birds, Mammals	Humans only	Humans, Swine			
Antigenic shift	Yes, creating new subtypes	No	No			
Antigenic drift	Yes, creating new strains	Yes	Yes			
Epidemics	Yes	Yes	No			
Pandemics	Yes	No	No			

#### CLINICAL FEATURES

**SYMPTOMS** acute onset of systemic symptoms, such as fever, headache, myalgia, arthralgia, fatigue, and respiratory symptoms such as cough, dyspnea, and sore throat

#### CLINICAL FEATURES (CONT'D)

**COMPLICATIONS** respiratory (bacterial pneumo nia), muscular (rhabdomyolysis, myositis), neurolo gic (encephalitis, aseptic meningitis, transverse mye litis, Guillain Barre syndrome)

RATIONAL CLINICAL EXAMINATIO	N SERIES: DOES T	HIS PATIENT HAV	/E INFLUENZA?	
	Sens	Spc	LR+	LR
All age groups				
Fever			1.8	0.4
Feverishness			1.0	0.7
Cough			1.1	0.42
Myalgia			0.93	1.2
Malaise	73%	26%	0.98	1.1
Headache			1.0	0.75
Sore throat			1.0	0.96
Sneezing			1.2	0.87
Nasal congestion			1.1	0.49
Chills	83%	25%	1.1	0.68
Vaccine history			0.63	1.1
Fever and cough	64%	67%	1.9	0.54
Fever, cough, and acute onset	63%	68%	2.0	0.54
Age ≥60				
Fever	34%	91%	3.8	0.72
Feverishness	47%	78%	2.1	0.68
Cough			2.0	0.57
Myalgia			2.4	0.68
Malaise	57%	78%	2.6	0.55
Headache			1.9	0.70
Sore throat			1.4	0.77
Sneezing	32%	33%	0.47	2.1
Nasal congestion	47%	50%	0.95	1.0

CLINICAL FEATURES (CONT'D)					
RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE INFLUENZA?					
	Sens	Spc	LR+	LR	
Chills	46%	82%	2.6	0.66	
Vaccine history			0.63	1.1	
Fever and cough	30%	94%	5.0	0.75	
Fever, cough, and acute onset	27%	95%	5.4	0.77	

**APPROACH** "clinical findings identify patients with influenza like illness but are not particularly useful for confirming or excluding the diagnosis of influenza. Clinicians should use timely epidemiologic data to ascertain if influenza is circulating in their communities, then either treat patients with influenza like illness empirically or obtain a rapid influenza test to assist with management decisions"

JAMA 2005 293:8

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, urinalysis
- MICROBIOLOGY nasopharyngeal swab for rapid assays (variable sensitivity/specificity), RT PCR (preferred), or DFA (Direct Fluorescent Antigen detection). Blood C&S, sputum Gram stain/AFB/ C&S, urine C&S
- IMAGING CXR

#### **SPECIAL**

- LUMBAR PUNCTURE if neurologic symptoms
- ABG

#### MANAGEMENT

**PREVENTION IS KEY** annual vaccination for the fol lowing 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  $\times$ 5 days, or zanamivir 10 mg inhaled BID  $\times$ 5 days) are active against influenza A and B. Antiviral treatment is most effective when started within 48 h of symptom onset. Treatment decreases

#### MANAGEMENT (CONT'D)

the duration of symptoms by 1 day, reduces viral shedding, and may reduce complications in those at risk. Inhaled zanamivir is relatively contraindicated in patients with asthma or chronic respiratory conditions. Household contacts of infected individuals should be vaccinated and may be given prophylaxis with oseltamivir 75 mg PO daily or zanamivir 10 mg inhaled daily  $\times$ 10 days. Resistance to oseltamivir is a problem in some strains of influenza A, and amanta dine or rimantidine may have a role. Treatment of pneumonia with antibiotics

#### TREATMENT ISSUES

**NEURAMINIDASE INHIBITORS** neuraminidase plays an important role for viral release from the host cell. Oral oseltamivir and inhaled zanamivir are active against both influenza A and influenza B

**ADAMANTANES** block replication of influenza A RNA through inhibition of M2 protein ion channels. Amantadine and rimantadine are inactive against influenza B and C and resistance is now widspread in influenza A

**VACCINE PRODUCTION** every February/March, the World Health Organization makes recommen dations 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 sea son. Vaccines are then produced based on this decision

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

# **Fungal Infections**

### GENERAL APPROACH

**CLASSIFICATION** fungal infections can be classified into three main categories: yeasts, molds ("fila mentous fungi"), and dimorphic fungi

- YEASTS grow as single cells (via budding) and include Candida, Malassezia, Rodotorula, Trichosporon
- MOLDS these filamentous fungi grow as hyphae (via sexual and asexual reproduction) and include Aspergillus, zygomycetes, Fusarium, and dematiac eous (pigmented) fungi. Ubiquitous in the envir onment (e.g. soil, decaying vegetation, water, air). Infection may cause blood vessel invasion, throm bosis, 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, Blasto myces, and Cryptococcus. At low temperatures, found as multicellular molds (which release spores that are inhaled). In warm temperatures (e.g. inside the body), inhaled spores germinate into yeasts, which are infectious to the patient, but no longer contagious (i.e. these patients do not require isolation)

#### CANDIDIASIS

**PATHOPHYSIOLOGY** Candida albicans ("Germ tube positive" with pseudohyphae) or non albicans species ("Germ tube negative," e.g. C. glabrata, C. tropicalis, C. parapsilosis, C. krusei), mostly in patients with hemato logical malignancy, neutropenia, on immunosuppres sants, 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,

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#### CANDIDIASIS (CONT'D)

prior to cystoscopy or invasive GU procedure, neo nates, severe illness, and possibly neutropenia (controversial). Fluconazole 200 mg PO/IV daily  $\times 2$  weeks

ACUTE DISSEMINATED CANDIDEMIA remove all intravascular devices. Fluconazole 800 mg then 400 mg PO/IV daily ×2 weeks (minimum), or one of the echinocandins, including caspofungin 70 mg then 50 mg IV daily, micafungin 100 mg IV daily, or anidulafungin 200 mg then 100 mg IV daily ×2 weeks (minimum) after last positive culture for C. albicans. Echinocandin and lipid formulation of amphotericin B are preferred for initial therapy in neutropenic patients. Almost all (>95%) C. albicans are sensitive to fluconazole. Some laboratories report C. albicans as "C. albi cans complex" because of structural resemblance between albicans and dubliniensis. This is of no clinical significance because albicans and dubli niensis have same susceptibility patterns. Sus ceptibility patterns for other non albicans infec significantly differ. mav echinocandin for non albicans

CID 2009 48:5

#### ASPERGILLOSIS

**MICROBIOLOGY** genus contains >185 species including *A. fumigatus* (80% of clinical infections), *A. flavus*, *A. niqer*, and *A. terreus* 

**PATHOPHYSIOLOGY** mostly in patients with neu tropenia, organ or stem cell transplants, advanced AIDS, or on corticosteroids. Invasive aspergillosis has mortality of >50%

**CLINICAL FEATURES** spectrum of pulmonary involvement includes colonization, pulmonary aspergilloma ("fungal ball"), allergic bronchopul monary aspergillosis (ABPA), chronic necrotizing aspergillus pneumonia (CNPA), and invasive asper gillosis. Second most common cause of fungal endo carditis (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, galacto mannan 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  $\times$ 24 h then 4 mg/kg IV q12h or 200 mg PO BID until resolved. Alternatives include *caspofungin* 70 mg then 50 mg IV

#### ASPERGILLOSIS (CONT'D)

q24h, lipid formulation *amphotericin B* 3 5 mg/kg IV daily, *micafungin* 100 150 mg IV daily, *posaconazole* 200 mg PO QID then 400 mg BID after clinical stabi lization. Some species, especially *A. terreus*, are resis tant to amphotericin. *Aspergillus* is the only filamen tous fungus that can be treated with echinocandins

CID 2008 46:3

#### ZYGOMYCETES (MUCORMYCOSIS)

**MICROBIOLOGY** large group of filamentous fungi including *Rhizopus, Absidia, Rhizomucor, Mucor,* and *Cunninghamella* 

**PATHOPHYSIOLOGY** mostly affecting immuno compromised 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 formula tions of amphotericin B and pozaconazole. Note that susceptibility testing of Zygomycetes is not always reliable, and that caspofungin and "azoles" (apart from pozaconazole) are not generally effective

#### HISTOPLASMOSIS

**PATHOPHYSIOLOGY** *H. capsulatum* endemic along St. Lawrence seaway and in Midwestern states located along the Ohio and Mississippi River valleys. Symptoms typically occur in patients who are immunocompromised or exposed to a large inoculum

CLINICAL FEATURES usually asymptomatic. Pul monary manifestations may mimic sarcoidosis and include pneumonia (localized or diffuse), granu loma/cavitary lung lesions, and hilar and mediast inal lymphadenopathy. Pericarditis, arthritis, arthritiga and erythema nodosum may also occur without pulmonary symptoms. Disseminated dis ease may present with hepatosplenomegaly, pan cytopenia, oropharyngeal ulcers, skin, and CNS involvement

**DIAGNOSIS** fungal culture of blood and tissue, urine antigen, *Histoplasma* serology, and histopathol ogy. *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  $\times$ 3 days, then 200 mg PO daily BID, lipid formulation of amphotericin B (preferred for ill patients)

CID 2007 45:7

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#### CRYPTOCOCCOSIS

**MICROBIOLOGY** formerly believed to be unicellu lar yeast, although now confirmed to be dimorphic. Unlike other dimorphic fungi (e.g. *Histoplasma, Blas tomyces, and Coccidioides*), *Cryptococcus* is ubiquitous and not geographically isolated. *Cryptococcus neofor mans* has two varieties: *C. neoformans* var. *neofor mans* and var. *aattii* 

#### **PATHOPHYSIOLOGY**

- C. NEOFORMANS almost invariably in immunocom promised patients including HIV with CD4 <100/ mm³, transplantation, hematologic malignancies, chronic kidney diseases, diabetes mellitus, cirrho sis, 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 immunocom petent hosts and paradoxically uncommon in immunosuppressed hosts. Symptomatic infection is usually pulmonary  $\pm$  focal parenchymal brain infection

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

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

CID 2010 50:3

#### COCCIDIOIDOMYCOSIS

**PATHOPHYSIOLOGY** endemic to lower deserts of southern Arizona, central California, southwestern New Mexico, and west Texas in USA. Also Mexico, Central and South America. Peak incidence from May July and October December. Affects mostly patients with immunosuppression

**CLINICAL FEATURES** an acute pulmonary infection that is often asymptomatic, but can cause a flu like illness or pneumonia. Pulmonary symptoms include chest pain, cough, fever, and hemoptysis if cavitary

#### COCCIDIOIDOMYCOSIS (CONT'D)

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

**DIAGNOSIS** fungal culture and serology. Note that *Cocciodioides* is a level 3 pathogen. Therefore, cul tures 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 pul monary infections. *Fluconazole* 400 mg PO daily, *itra conazole* 200 mg PO daily (duration dependent on site of infection and may last months to years). *Cocci dioides* meningitis should be treated with amphoter icin 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). Extrapul monary 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

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	Mechanism	Candida	Cryptococcus	Aspergillus	Other molds <sup>a</sup>	Dimorphic <sup>b</sup>	Zygomycota <sup>c</sup>	Renal adjustments
Azoles								,
Fluconazole <sup>d</sup> 100–400 mg PO/IV daily	Inhibits CP450 (convert lanosterol	++C. alb	+++			+		Yes (dose)
traconazole <sup>e</sup> 100–200 mg PO daily–BID	to ergosterol on cell membrane)	+++		++	++	++		No
Voriconazole <sup>f</sup> 4 mg/kg IV q12h or 200 mg PO BID		+++		+++	++Fusa/ Scedo	++		No but avoid I form
Posaconazole 200 mg PO QID		+++	+++	+++	+++Fusa	++	+++	No
Amphotericin B <sup>g</sup>								
Amphotericin B 0.3–1 mg/kg IV g24h	Binds to ergosterol on cell wall, causing cell	+++	+++	++	+	+++	+++	Yes (interval)
Liposomal AmphoB 3–5 mg/kg IV g24h	leakage	+++	+++	++	+	+++	+++	Yes (interval)
AmphoB colloidal dispersion		+++	+++	++	+	+++	+++	Yes (interval)
AmphoB lipid complex 5 mg/ kg IV q24h Echinocandin <sup>h</sup>		+++	+++	++	+	+++	+++	Yes (interval)
Caspofungin 70 mg then 50 mg IV q24h	Inhibits synthesis of β-1,3-d-glucan on cell wall	+++		+++	+Scedo	+/-		No
Micafungin 150 mg IV q24h		+++		+++				No
Anidulafungin 200 mg then 100 mg IV q24h		+++		+++				No
<b>5-Flucytosine</b> 5 Flucytosine	Inhibits synthesis of DNA (thymidylate synthetase)	+++	+++				++	Yes (dose)

<sup>a</sup> other than Aspergillus, Fusarium, Scedosporium, and Pseudallescheria boydii are all examples of molds

#### INDICATIONS FOR VORICONAZOLE

**INVASIVE ASPERGILLOSIS** first line treatment for invasive and CNS

**INVASIVE CANDIDIASIS** second or third line treat ment for patients who are refractory or intolerant of fluconazole (first line for some) or amphotericin B (first line for others)

#### INDICATIONS FOR VORICONAZOLE (CONT'D)

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

**FEBRILE NEUTROPENIA** empiric antifungal treat ment for patients intolerant of amphotericin B

<sup>&</sup>lt;sup>b</sup> dimorphic fungi include Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Paracoccidioides brasiliensis, and Sporothrix schenckii

c zygomycota fungi include Rhizopus, Mucor, and Absidia

d fluconazole is ineffective against some Candida, Molds, and Zygomycetes

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

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

<sup>&</sup>lt;sup>9</sup> amphotericin B is ineffective against molds (Fusarium, Scedosporium, Trichosporum, Aspergillus terreus), C. guilliermondii and C. lusitaniae

h caspofungin is ineffective against Zygomycetes, Cryptococcus, and Fusarium but probably has activity against other molds

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#### INDICATIONS FOR CASPOFUNGIN

**INVASIVE ASPERGILLOSIS** third line treatment for patients who are refractory or intolerant of voricona zole (first line) or amphotericin B (second line)

**INVASIVE CANDIDIASIS** second or third line treat ment 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 flucona zole can be used

**FEBRILE NEUTROPENIA** empiric antifungal treat ment 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

 $\begin{array}{ll} \textbf{INTOLERANCE} & \text{doubling from baseline and serum} \\ \text{Cr} \geq \! 450 \; \mu \text{mol/L} \; [\geq \! 5.1 \; \text{mg/dL}], \; \text{creatinine clearance} \\ \leq \! 40 \; \text{mL/min or concomitant administration of nephro} \\ \text{toxins, tripling of serum creatinine from baseline, documented allergy, or intolerable infusion reactions} \\ \end{array}$ 

### **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 urin

ary catheters. Infection rates are 1 5%, up to 100% for long term catheterization. Complications include cystitis, prostatitis, pyelonephritis, and urosepsis

**VENTILATOR ASSOCIATED PNEUMONIAS** sec ondary to endotracheal tube insertion (>48h, p. 94) **BACTEREMIA** secondary to central venous cathe ters. 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/stan dard/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 train ing 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 (hepa titis B vaccine at 0, 1, 6 months, influenza)

**RISK OF TRANSMISSION** depends on the mechan ism of exposure, source patient characteristics, pre and post exposure prophylaxis

- HBV 6 30% if source positive. Transmission via urine, feces, and saliva unlikely
- HCV 1.8% if source positive. Transmission via urine and feces unlikely
- HIV 0.3% if source positive. Transmission via urine, feces, and saliva unlikely

#### POST EXPOSURE PROCEDURE

- SOURCE PATIENT TESTING HBV, HCV, HIV
- EXPOSED PERSON BASELINE TESTING HBV, HCV, HIV (ELISA, Western), CBCD, lytes, urea, Cr, AST, ALT, ALP, bili
- HBV PROPHYLAXIS HB Ig (only if source patient is HBsAg positive or unknown and the exposed person is unvaccinated) and start vaccination for HBV
- HIV PROPHYLAXIS antiretroviral (if source patient HIV positive). Therapy may include zidovudine and lamivudine ± protease inhibitor such as lopinavir/

#### NEEDLE STICK INJURY (CONT'D)

ritonavir (if source patient had been treated and drug resistance possible). Treatment should be started within 4 h

 COUNSELING protective sexual intercourse, hold blood donation and breastfeeding, side effects of prophylactic medication(s), follow up in 2 weeks
 MMWR 2005 54:RR 9 NEEDLE STICK INJURY (CONT'D)

PROPHYLAXIS FOR OTHER INFECTIOUS AGENTS

diphtheria (penicillin or erythromycin), meningococcal (rifampin, ciprofloxacin, ceftriaxone), pertussis (tri methoprim sulfa, erythromycin), rabies (rabies immune globulin, vaccine), varicella zoster (varicella zoster immune globulin, vaccine), hepatitis A (immune globulin, vaccine)

Immuniza	ition for A	dults	Ann Intern A	Med 2009 150:1
Vaccine Viral vaccines	Туре	Schedule	Indications	Contraindications
Measles SC	Live	0, +1 months (if high risk)	All adults not previously immunized in childhood	Preg, immunocomp.
Mumps SC	Live	0, +1 months (if high risk)	All adults not previously immunized in childhood	Preg, immunocomp.
Rubella SC	Live	0, +1 moths (if high risk)	All adults not previously immunized in childhood	Preg, immunocomp.
Polio IM/SC	Inactivated	_	Not routinely recommended for adults	-
HBV IM	Recombinant	0, +1 months, +6 months	All adults not previously immunized in childhood, particularly high risk groups for parenteral or sexual exposure, chronic liver disease (e.g. chronic HCV/ HBV), chronic renal disease, healthcare workers, men who have sex with men, household and sexual contacts of those with chronic HBV, those with or evaluated for STDs	-
HAV IM	Inactivated	0, +6 months	Travelers (esp. developing world), chronic liver disease (e.g. chronic HCV/HBV), men who have sex with men, ?food handlers	-
Influenza IM	Inactivated	Annually (Oct)	Adults >50year, >6 month 50years with chronic disease, pregnancy, healthcare workers	
Varicella SC	Live	0, 1–2 months	All who have not had chicken pox by adulthood, especially healthcare workers	Preg, immunocomp.
Herpes zoster SC	Live	1 dose	Adults >60years. Note this vaccine has higher dose of attenuated virus than varicella vaccine	Preg, immunocomp, no history of Varicella
HPV IM	Recombinant	0, +1-2 months, +6 months	Females aged 9–26years (licensed also for males in some countries) Controversial as outcomes data pending	-
Bacterial vacci	200			
Pertussis	Cellular	1 dose	All adults <i>not</i> previously immunized in childhood; single dose of acellular Pertussis vaccine combined with Tetanus/diphtheria (Tdap) recommended for adults aged 19–64	-
Td (tetanus, diphtheria) IM	Toxoid, inactivated	0, +2 months, +6-12 months, q10year	All adults <i>not</i> previously immunized in childhood (see Tdap under Pertussis)	-
Pneumococcal IM/SC	Polysaccharide		Adults >65years, >6 months 50years with chronic disease, pregnancy, splenectomy, malignancy, smokers	-
Haemophilus type B	Conjugated	1 dose	Splenectomy	-
Meningococcal SC	Polysaccharide	1 dose	Splenectomy, college dormitory students, lab workers, travelers to endemic areas	-

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#### PRINCIPLES

#### **RISK FACTORS FOR SPECIFIC ORGANISMS**

- HBV household contacts/sexual partners of hepatitis patients, IDU, homosexual, multiple sex ual partners, tattoo, piercing, transfusions, health care workers (prior to vaccine era), residents/work ers of institutions for mentally ill or criminals, birth in endemic country
- HCV sexual partners (controversial), IDU, tattoo, piercing, transfusions, residents/workers of institu tions for mentally ill or criminals

#### PRINCIPLES (CONT'D)

• PNEUMOCOCCAL, MENINGOCOCCAL, HAEMOPHILUS INFLUENZAE splenectomy

#### CONTRAINDICATIONS

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

SIDE EFFECTS local erythema, fever

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### Notes

# **9** Rheumatology

Section Editor: Dr. Elaine Yacyshyn

### **Septic Arthritis**

#### DIFFERENTIAL DIAGNOSIS OF MONOARTHRITIS

#### **★ICU RN★**

#### INFECTIONS

- BACTERIAL Gonococci, Staphylococcus aureus, Streptococcus, Enterobacteriaceae, Borrelia burg dorferi, Syphilis, TB
- VIRAL HIV, HBV, Parvovirus, rubella, mumps, enterovirus, adenovirus
- FUNGAL Cryptococcus, Blastococcus
- OSTEOMYELITIS/OSTEONECROSIS EXTENDING TO JOINT

# CRYSTAL gout, pseudogout, hydroxyapatite, basic calcium phosphate UNCLASSIFIED

- TRAUMA
- OSTEOARTHRITIS
- HEMARTHROSIS coagulopathy, thrombocytope nia, pigmented villonodular synovitis, trauma
- NON-ARTHRITIS
  - BONE osteomyelitis, avascular necrosis, fracture
  - **SOFT TISSUE** tendonitis, ligament tear, bursi tis, myositis, meniscus tear

# RHEUMATOLOGIC (early stage, unusual presentation as monoarthritis)

- SEROPOSITIVE★PSSR★ Polymyositis, Palindro mic rheumatism, SLE, Scleroderma, Rheumatoid arthritis
- **SERONEGATIVE**★**PEAR**★ **P**Soriatic arthritis, **E**nteric arthritis, **A**nkylosing spondylitis, **R**eactive arthritis
- SARCOIDOSIS, POLYMYALGIA RHEUMATICA

**NEOPLASTIC** chondrosarcoma, osteoid osteoma, metastasis

#### PATHOPHYSIOLOGY

**RISK FACTORS** 50% of sexually active adults with septic arthritis are due to gonococcal infections, while most patients with risk factors for septic arthritis listed below are due to non gonococcal infections (*S. aureus*, Streptococci, Gram negative bacilli)

- COMORBIDITIES diabetes, chronic kidney disease, rheumatologic disease, cancer, advanced disability
- TREATMENT RELATED immunosuppressive therapy (glucocorticoids, cytotoxic agents), prosthetic joint

#### PATHOPHYSIOLOGY (CONT'D)

 SPECIFICS IDU (more axial joints with MRSA, Gram negative especially *Pseudomonas*), endocarditis (sterile fluid as autoimmune process)

**GONOCOCCAL ARTHRITIS** more common in women. Less destructive and has better outcome than non gonococcal arthritis. The synovial fluid Gram stain is only positive in <10%, and culture is often negative in gonococcal arthritis

**COMPLICATIONS** osteomyelitis (30%), permanent joint damage, sepsis

#### CLINICAL FEATURES

**HISTORY** arthritis (location, duration, pain, range of motion, function), adenopathy, fever, rash, oral ulcers, alopecia, Raynaud's, photosensitivity, sicca, trauma, recent infections, cervical/urethral discharge, sexual encounters, diarrhea, recent travel, past med ical history (pre existing joint disease, gout, rheuma toid arthritis, SLE, IBD, psoriasis, diabetes, IDU), med ications (anticoaqulants)

PHYSICAL vitals (fever), joint examination (ten derness, swelling, range of motion). Look for nail pitting, onycholysis, tophi, rheumatoid nodules, track marks, psoriasis, keratoconjunctivitis sicca, uveitis, conjunctivitis, episcleritis, murmurs, ure thral discharge, and penile ulcers. Examine all joints and pay particular attention to the affected one. Soft tissue injuries (bursitis, tendonitis, muscles) usually have decreased active range of motion but normal passive range of motion, while both active and passive range of motion would be affected in joint diseases. Pelvic examination to inspect the cervix

### RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS ADULT PATIENT HAVE SEPTIC ARTHRITIS?

	Sens	Spc	LR+	LR
History				
Age >80	19%	95%	3.5	0.86
Diabetes	12%	96%	2.7	0.93
Rheumatoid arthritis	68%	73%	2.5	0.45

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CLINICAL FEATURES (CONT'D)					
	Sens	Spc	LR+	LR	
Recent joint surgery	24%	96%	6.9	0.78	
Hip/knee prosthesis	35%	89%	3.1		
Skin infection	32%	88%	2.8	0.73	
HIV infection	79%	50%	1.7	0.47	
Joint pain	85%				
Joint edema	78%				
Fever	57%				
Sweats	27%				
Rigors	19%				
Physical					
Fever	46%	31%	0.67	1.7	
Investigations					
Elevated WBC	90%	36%	1.4	0.28	
Elevated ESR	95%	29%	1.3	0.17	
Elevated CRP	77%	53%	1.6	0.44	
Synovial fluid analysis					
WBC >100,000/mL	29%	99%	28	0.71	
WBC >50,000/mL	62%	92%	7.7	0.42	
WBC >25,000/mL	77%	73%	2.9	0.32	
PMN ≥90%	73%	79%	3.4	0.34	

**APPROACH** "when evaluating a patient with a painful, peripheral, swollen joint, the underlying pathology of a monoarthritis may be difficult to diagnose by clinical history and examination alone due to nonspecific symptoms and signs. Identifiable risk factors and arthrocentesis are most helpful in predicting septic arthritis. In particular, synovial WBC count and percentage of polymorphonuclear cells provide the best utility in identifying septic arthritis while waiting for Gram stain and culture test results. There is no evidence that a patient's symptoms or the physical examination are useful for predicting non gonococcal bacterial arthritis"

JAMA 2007 297:13

### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, uric acid, ANA, RF, ESR, CRP, INR, PTT
- IMAGING joint XR (chondrocalcinosis in pseu dogout (the presence of crystals does not rule out sepsis)
- ARTHROCENTESIS ★3C★ (Cell count with diff, Culture and Gram stain, Crystal)

#### **SPECIAL**

 INFECTIOUS WORKUP urethral/rectal swabs, blood C&S

#### DIAGNOSTIC ISSUES

**GOLDEN RULE** patients with monoarthritis have septic arthritis until proven otherwise. Joint infection

#### DIAGNOSTIC ISSUES (CONT'D)

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 arthri tis, a focus of infection may be found

#### 

JOINT ASPIRATIONS/INJECTIONS for diagnostic and sometimes therapeutic reasons. Absolute contra indication is infection overlying site of injection. Rela tive contraindications include *significant hemostasis* defects and bacteremia (NEJM 2006 354:e19)

- KNEE flex 10 15°, enter either medially or later ally immediately beneath the undersurface of the patella slightly above midway
- ANKLE foot perpendicular to leg, medial approach immediately medial to the extensor hallucis longus tendon. Lateral approach just distal to fibula
- WRISTS flex slightly. Medial approach at dorsal surface between the distal ulna and the carpal bones. Lateral approach at dorsum just distal to the end of the radius, between the extensor ten dons of the thumb
- ADVERSE EFFECTS OF ASPIRATIONS/INJECTIONS
   hypersensitivity to anesthetic, pain, infection, ten
   don 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 q IV q12h, plus ceftriaxone 2 q IV q24h or cefotaxime 2 g IV q8h. If at risk of sexually transmitted disease, nafcillin 2 g IV g4h for Gram positive organisms on Gram stain; otherwise, give ceftriaxone 2 g IV g24h or cefotaxime 2 g IV g8h if organisms not identifiable yet). Gonococcal (ceftriaxone 1 q IV q24h). Lyme arthritis (amoxicillin 500 mg PO QID, doxycycline 100 mg PO BID, ceftriax one 2 g IV daily, cefotaxime 3 g IV BID  $\times$ 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 275

**Gout** NEJM 2003 349:17

#### CAUSES

#### **DECREASED URATE EXCRETION (90%)**

- RENAL DISEASE
- DRUGS \*CAN'T LEAP \* Cyclosporine, Alcohol,
   Nicotinic Acid, Thiazides, Loop diuretics, Etham
   butol, ASA (low dose), Pyrazinamide

#### **INCREASED URATE PRODUCTION (10%)**

- **METABOLIC SYNDROME** obesity, hyperlipidemia, hypertension
- INCREASED METABOLISM alcohol, hemolytic ane mia, psoriasis, Lesch Nyhan syndrome
- NEOPLASTIC myeloproliferative disease, lym phoproliferative disease, chemotherapy

#### PATHOPHYSIOLOGY

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

**PRECIPITANTS** surgery, dehydration, fasting, binge eating, binge drinking, exercise, trauma

### **CLINICAL FEATURES**

#### SYMPTOMS

- ARTHRITIS mono/oligo and asymmetric, especially first MTP joint. Podagra, inflammation of the first MTP joint, is the presenting symptom in 75% of gout patients. However, the first MTP is also commonly affected in pseudogout, psoriatic arthritis, sarcoidosis, osteoarthritis, and trauma
- TOPHI yellowish white nodular urate crystals collection in subcutaneous tissues (particularly colder extremities such as ear, fingers, olecranon bursa, ulnar aspect of forearm), bone, tendons (Achilles), cartilage, and joints. Generally painless but may lead to erosions
- KIDNEYS urolithiasis (radiolucent), uric acid nephropathy (reversible acute renal failure sec ondary 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 ioint XR

#### INVESTIGATIONS (CONT'D)

• ARTHROCENTESIS ★3C★ (Cell count with diff, Culture and Gram stain, Crystal, for gout, sens 85%, spc 100%)

#### **SPECIAL**

TOPHI ASPIRATION

#### DIAGNOSTIC ISSUES

**SERUM URIC ACID LEVELS** may be falsely lowered in an acute attack

**JOINT X RAY** soft tissue swelling, normal joint space, erosions ('punched out" and sclerotic lesions with overhanging edge)

**JOINT FLUID** ALWAYS confirm diagnosis with a synovial fluid tap if possible. Microscopy shows pre dominantly 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  $\times$ 3 days, then 250 375 mg PO BID  $\times$ 4 7 days; *sulindac* 150 200 mg PO BID  $\times$ 7 10 days; *indomethacin* 25 50 mg PO TID  $\times$ 3 days, then 100 mg PO div BID QID  $\times$ 4 7 days; *celecoxib* 200 mg PO BID  $\times$ 1 day, then 100 mg PO BID  $\times$ 6 10 days). **Systemic corticosteroids** (avoid if joint sepsis not excluded; *prednisone* 30 60 mg PO daily  $\times$ 3 days, then  $\downarrow$  10 15 mg daily  $\times$ 3 days until discontinuation, *triamcinolone* 50 mg IM  $\times$ 1 dose). **Intra articular corticosteroids** (for mono and oli goarthritis only. *Methylprednisolone* 100 150 mg intra articularly once). **Colchicine** 0.6 mg PO daily BID during acute attack (avoid the approach of giving colchicine q1h until development of diarrhea)

LONG TERM MANAGEMENT purine restricted diet (↓ red meats, ↓ seafood, ↑ low fat dairy products, ↑ fruit and veges). *Allopurinol* 50 300 mg PO daily (first line, xanthine oxidase inhibitor, renal correction required, do not give in acute attack; however, continue allopurinol if already on it prior to acute attack). *Probenecid* 250 1000 mg PO BID (first line, ↓ renal urate reabsorption. Ensure normal renal 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 ( $\geq$ 3/year, tophaceous deposits,

#### TREATMENT ISSUES (CONT'D)

overproduction of uric acid, or continued cyclospor ine treatment)

**ALLOPURINOL TREATMENT** remember to start colchicine or NSAIDs prior to allopurinol and to over lap therapy to prevent precipitating flare. Allopurinol alone can cause an abrupt decrease in serum uric acid → breakdown and release of synovial urate crystal deposits → inflammation. Aim to decrease serum uric acid level below 300 µmol/L [5.1 mg/dL]. Do not start or stop allopurinol during an acute attack

#### SPECIFIC ENTITIES

**CALCIUM PYROPHOSPHATE DEPOSITION DIS EASE** (CPPD, pseudogout) associated with normal urate levels and chondrocalcinosis that are visible radiographically. Crystals appear rhomboid and

#### SPECIFIC ENTITIES (CONT'D)

have positive birefringence (blue when parallel to polarized light, yellow when perpendicular). Risk factors include old age, advanced osteoarthritis, neuropathic joint, gout, hyperparathyroidism, 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

### **Polyarticular Joint Pain and Fever**

#### NEJM 1994 330:11

#### **DIFFERENTIAL DIAGNOSIS**

#### **★RICE**★

#### RHEUMATOLOGIC

- SEROPOSITIVE SLE, rheumatoid arthritis
- **SERONEGATIVE** psoriatic arthritis, enteric arthritis, reactive arthritis
- VASCULITIS polymyalgia rheumatica, Wegener's granulomatosis, Behcet's disease, Still's disease

#### INFECTIONS

- BACTERIAL septic (Gonococci), meningococci, endocarditis, Lyme disease, Whipple's disease, mycobacteria
- VIRAL Parvovirus, rubella, HBV, HCV, HIV, EBV
- FUNGAL
- POST-INFECTIOUS/REACTIVE enteric infections, genitourinary infections, rheumatic fever, inflammatory bowel disease

# **CRYSTAL INDUCED** gout, pseudogout **ETC**

- MALIGNANCIES acute leukemia
- SARCOIDOSIS Lofgren's syndrome
- FAMILIAL MEDITERRANEAN FEVER
- POLYMYALGIA RHEUMATICA
- MUCOCUTANEOUS DISORDERS dermatomyositis, erythema nodosum, erythema multiforme, pyo derma qangrenosum, pustular psoriasis

#### CLINICAL FEATURES

#### **DISTINGUISHING FEATURES**

 TEMPERATURE >40°C [>104°F] Still's disease, bacterial arthritis, SLE

### CLINICAL FEATURES (CONT'D)

- FEVER PRECEDING ARTHRITIS viral arthritis, Lyme disease, reactive arthritis, Still's disease, bacterial endocarditis
- MORNING STIFFNESS RA, polymyalgia rheumatica, Still's disease, some viral/reactive arthritis
- MIGRATORY ARTHRITIS rheumatic fever, gonococ cemia, meningococcemia, viral arthritis, SLE, acute leukemia, Whipple's disease
- EPISODIC RECURRENCE palindromic rheumatism, Lyme disease, crystal induced arthritis, IBD, Whipple's dis ease, Familial Mediterranean fever, Still's disease, SLE
- PAIN DISPROPORTIONATELY GREATER THAN EFFUSION rheumatic fever, Familial Mediterranean fever, acute leukemia, AIDS
- EFFUSION DISPROPORTIONATELY GREATER THAN PAIN tuberculosis arthritis, bacterial endocarditis, IBD, qiant cell arteritis, Lyme disease
- SYMMETRIC SMALL JOINT SYNOVITIS RA, SLE, viral arthritis
- LEUKOCYTOSIS (>15x10<sup>9</sup>/L) bacterial arthritis, bacterial endocarditis, Still's disease, systemic vas culitis, acute leukemia
- LEUKOPENIA SLE, viral arthritis
- POSITIVE RHEUMATOID FACTOR RA, viral arthritis, tuberculoses arthritis, bacterial endocarditis, SLE, sarcoidosis, systemic vasculitis

#### INVESTIGATIONS

#### BASIC

 LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, uric acid, TSH, ESR, CRP, RF, anti CCP, Rheumatoid Arthritis 277

#### INVESTIGATIONS (CONT'D)

ANA, serologies (*Borrelia burgdorferi*, Strepto cocci, Parvovirus, HBV, HCV, HIV), c ANCA, urinalysis

- IMAGING CXR, X rays of affected joints SPECIAL
- 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 pharyn gitis, 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, methotrex ate, recombinant IL 1 receptor antagonist (anakinra)

### **Rheumatoid Arthritis**

#### DIFFERENTIAL DIAGNOSIS OF POLYARTHRITIS

#### **★RICE**★

#### RHEUMATOLOGIC (>6 weeks)

- SEROPOSITIVE ★PSSR★ Polymyositis, Palindro mic rheumatism, SLE, Scleroderma, Sjogren's syndrome, Rheumatoid arthritis
- VASCULITIS polymyalgia rheumatica, Wegener's granulomatosis, Behcet's disease, Still's disease

#### INFECTIONS (<6 weeks)

- BACTERIAL sepsis, endocarditis, Lyme disease, Whipple's disease, mycobacteria
- VIRAL Parvovirus, rubella, HBV, HCV, HIV
- FUNGAL
- POST-INFECTIOUS/REACTIVE enteric infections, genitourinary infections, rheumatic fever, inflammatory bowel disease

**CRYSTAL** gout, pseudogout, hydroxyapatite, basic calcium phosphate

#### **ETC**

- MALIGNANCIES leukemia
- SARCOIDOSIS Lofaren's syndrome
- FAMILIAL MEDITERRANEAN FEVER
- MUCOCUTANEOUS DISORDERS dermatomyositis, erythema nodosum, erythema multiforme, pyo derma gangrenosum, pustular psoriasis poly myalqia rheumatica

#### PATHOPHYSIOLOGY

#### CLASSIFICATION OF ARTHRITIS

• MONOARTHRITIS 1 joint involved

### PATHOPHYSIOLOGY (CONT'D)

- 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 car pal bones, subluxation at the wrist
- FEET MTP joint involved. Deformities include val gus of the ankle and hindfoot, pes planus, forefoot varus and hallux valqus, 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%)

278 Rheumatoid Arthritis

#### 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 glu cose), 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 ane mia 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, cuta neous ulceration, visceral arteritis)
- **OTHERS** amyloidosis

**CONSTITUTIONAL SYMPTOMS** fatigue (40%), fever (low grade), sweats, weight loss, myalgia

# DISTINGUISHING FEATURES BETWEEN INFLAMMATORY AND NON INFLAMMATORY ARTHRITIS

	Inflammatory	Non inflammator
Classic example	RA	OA
Morning stiffness	>1 h	+/
Resting	Worsens	Improves
Activity	Improves	Worsens
Synovitis, redness	+	
Fever, weight loss	+	
ESR, CRP, platelets	1	No change

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, ESR, CRP, RF (lgM), anti CCP (more speci fic), 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 rheu matoid 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** ( $\Omega$  3 and  $\Omega$  6 fatty acids). **Joint protection** (range of motion exercises, orthotics, splints). **NSAIDs** (anti inflammatory dose). **Intraarticular steroid injections** (if severe pain). **Patient education** 

DISEASE MODIFYING AGENTS OF RHEUMATOID DISEASE (DMARDs) single agent (methotrexate with folic acid, sulfasalazine, hydroxychloroquine, minocycline, cyclosporine, azathioprine, gold). Com bination triple therapy (methotrexate plus sulfasa lazine plus hydroxychloroquine). Selective pyrimi dine synthesis inhibitor (leflunomide). TNFα inhibitors (infliximab, etanercept, adalimumab). B cell inhibitor (rituximab, an anti CD20 monoclonal antibody). T lymphocyte activation inhibitor (aba tacept). Surgical intervention

#### SPECIFIC ENTITIES

**PALINDROMIC RHEUMATISM** episodic arthritis with one or more joints being affected sequentially for hours to days, and symptom free periods in

#### SPECIFIC ENTITIES (CONT'D)

between for days to months. May be anti CCP posi tive and occasionally progresses to other rheumatic disorders (RA, SLE). Treatment with hydroxychloro quine can be useful

# SJOGREN'S SYNDROME (KERATOCONJUNCTIVITIS SICCA)

- PATHOPHYSIOLOGY CD4 lymphocytic infiltration of salivary and lacrimal glands
- CAUSES 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 enlarge ment, dental caries), dyspareunia, arthralgia, arthritis, and constitutional symptoms. May be associated with Raynaud's phenomenon, cuta neous vasculitis, cerebritis, CNS vasculitis, stroke, and peripheral neuropathy
- INVESTIGATIONS quantitative lg (polyclonal lgG), RF, ANA, ENA (SS A, SS B). Check for secondary causes
- TREATMENTS symptomatic (artificial tears, pilocar pine 5 mg PO QID), hydroxychloroquine

**LOFGREN'S SYNDROME** a benign self limited form of sarcoidosis. Tetrad of erythema nodosum, hilar lymphadenopathy, arthritis (ankles and some times knees), and uveitis

#### SPECIFIC ENTITIES (CONT'D)

## RESPIRATORY DISEASES IN RHEUMATOID ARTHRITIS

- AIRWAY cricoarytenoid arthritis with central airway obstruction, bronchiectasis, obliterative bronchiolitis, chronic small airway obstruction
- PARENCHYMA pneumonia (particularly with immunosuppression), interstitial fibrosis, bronch iolitis obliterans with organizing pneumonia, rheu matoid nodules, rheumatoid pneumoconiosis, apical fibrobullous disease, drug related pneumo nitis and fibrosis (methotrexate, gold, penicilla mine, NSAIDs, cyclophosphamide, azathioprine, sulfasalazine)
- · VASCULAR pulmonary hypertension, vasculitis
- PLEURAL pleuritis, pleural effusion, pleura thickening

#### UNDIFFERENTIATED CONNECTIVE TISSUE DIS

**EASE** overlap syndrome with clinical features of two or more rheumatologic disorders (RA, SLE, Sjog ren's syndrome, scleroderma, inflammatory myopa thies) but does not fit the diagnostic criteria for any specific disorder

**MIXED CONNECTIVE TISSUE DISEASE** a specific overlap syndrome with clinical features of SLE, scler oderma, polymyositis, and antibodies to RNP. Char acteristically, Raynaud's phenomenon, myositis, and synovitis are present

### **Systemic Lupus Erythematosus**

#### PATHOPHYSIOLOGY

POPULATION typically affects women aged 15 45
AUTOIMMUNE REACTION antibody immune
complex deposition in kidneys (glomerulonephri
tis), autoantibodies against cell surface antigens
on hematopoietic progenitor cells (anemia, neutro
penia, thrombosytopenia), antiphospholipid anti
bodies (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 ×10<sup>9</sup>/L, lymphopenia <1.5x10<sup>9</sup>/L, thrombocytope nia <100x10<sup>9</sup>/L
- Excitation seizures, psychosis
- Serology ANA, anti dsDNA, anti Smith, antipho spholipid antibodies, false positive VDRL

#### PATHOPHYSIOLOGY (CONT'D)

Need ≥4 of 11 criteria (each rash counts as one criterion and ANA as a separate criterium) to make diagnosis. Note that many patients may not ever fulfill four criteria until several years into their disease course

#### CLINICAL FEATURES

**JOINT SYMPTOMS** symmetric non erosive polyar thritis 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, Lib man Sacks endocarditis

#### CLINICAL FEATURES (CONT'D)

- RENAL proteinuria or active sediment (sens 50%), glomerulonephritis
  - WHO CLASSIFICATION OF LUPUS NEPHRITIS
    - NORMAL (class I) asymptomatic
    - MESANGIAL PROLIFERATIVE (class II) mild hematuria or proteinuria
    - FOCAL PROLIFERATIVE (class III) nephritic syn drome, proteinuria
    - DIFFUSE PROLIFERATIVE (class IV) nephritic syndrome, nephrotic syndrome
    - MEMBRANOUS GLOMERULONEPHRITIS (class V) nephrotic syndrome
    - GLOMERULOSCLEROSIS (class VI) uremia
    - SEVERITY VI >IV >III >V >II >I, consider aggressive treatment for class III, IV
- GI mesenteric thrombosis and vasculitis, transa minitis/hepatitis. Corticosteroids could increase risk of peptic ulcer disease
- HEMATOLOGIC anemia of chronic disease, autoim mune hemolytic anemia, lymphopenia, thrombocytopenia
- NEUROLOGIC aseptic meningitis, transverse myeli tis, stroke, seizures, organic brain syndrome, psy chosis, depression, peripheral neuropathy
- DERMATOLOGIC photosensitivity (sens 50%), malar rash (nasolabial folds spared, sens 50%), discoid lupus (erythematous papules/plaques with central hypopigmentation, atrophic scarring involving scalp and exposed skin, sens 25%), mucosal ulcers (oral, vaginal, nasal septal), alopecia, livedo reticu laris, palpable purpura, Raynaud's

**SEROLOGIC** ANA (sens >99%), anti dsDNA (sens 40%), anti Smith (sens 25%), SSA/Ro, SSB/La, RNP, antiphospholipid antibody (sens 40%)

CONSTITUTIONAL SYMPTOMS fatigue, fever (high grade), lymphadenopathy, weight loss, myalgia LUPUS EXACERBATIONS typically with fatigue, arthritis, mucocutaneous, renal, neurologic, and/or dermatologic involvement. Individual patients usually have a fixed pattern of presentation. Precipi tants include UV exposure, medication non adher ence, infections, and pregnancy. Always consider other causes such as infections, medication side effects (steroids), and embolisms

#### INVESTIGATIONS

#### BASIC

- BLOOD TESTS CBCD, lytes, urea, Cr, ESR, CRP, ANA (sensitive), anti dsDNA (specific for SLE), C3, C4
- URINE TESTS urinalysis, urine protein to Cr ratio SPECIAL
- INFLAMMATORY WORKUP ENA (anti Smith, spc), anti Ro/La (especially in pregnancy, associated with neonatal lupus and congenital complete

#### INVESTIGATIONS (CONT'D)

heart block), antiphospholipid antibodies (antic ardiolipin antibodies, lupus anticoagulant), cryoglobulin

- INFECTIOUS WORKUP serologies (Parvovirus, HBV, HCV, EBV, CMV)
- ARTHROCENTESIS ★3C★ (Cell count with diff [>2000 WBC/mm³], Culture and Gram stain, Crys tal. Cannot make definite diagnosis of systemic lupus erythematosus from arthrocentesis)

#### MANAGEMENT

SYMPTOM CONTROL cutaneous lupus (sunscreen, hydroxychloroquine). Arthritis (NSAIDs, hydroxychloroquine, steroids, methotrexate). Nephritis and neuritis (steroids, cyclophosphamide, mycophenolate mofetil). Serositis (NSAIDs, steroids). Throm bocytopenia (steroids, IVIG, splenectomy). Avoid exogenous estrogen

TREAT UNDERLYING CAUSE rituximab

#### SPECIFIC ENTITIES

#### **DRUG INDUCED SYSTEMIC LUPUS**

- PATHOPHYSIOLOGY some drugs may trigger pro duction of autoantibodies (e.g. ANA) which may cause or precipitate drug induced lupus in suscep tible individuals
- CAUSES procainamide, hydralazine, quinidine, atenolol, anti TNFa (infliximab, etanercept), capto pril, carbamazepine, chlorpromazine, enalapril, ethosuximide, hydrochlorothiazide, isoniazid, lithium, methyldopa, minocycline, minoxidil, phe nytoin, primidone, statins, sulfasalazine, trimethadione
- CLINICAL FEATURES compared to systemic lupus, drug induced lupus has the following features: middle age presentation, no gender difference, no "blacks," acute onset, less cutaneous, renal, neurologic, and hematologic involvement, but equal joint, hepatic, and constitutional symptoms. Usually anti histone antibody positive, anti Smith negative, anti dsDNA negative and normal com plement 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, bleo mycin, vinblastine, interferon], tumors [lymphoma,

#### SPECIFIC ENTITIES (CONT'D)

carcinoid syndrome, pheochromocytoma], occlu sive arterial disease, hyperviscosity, hypothyroid ism, 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. Sec ondary 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, amlodipine 5 20 mg PO daily). Topical nitrates. ASA. Anticoagulate (if antipho spholipid 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 (Gl, lungs, renal, cardiac). There are four subtypes, including diffuse systemic sclerosis (progressive systemic sclerosis), limited systemic sclerosis ★CREST★ syndrome (Calcinosis, Ray naud's phenomenon, Esophageal dysmotility, Scler odactyly, 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 proxi mally, progressing from edematous to fibrotic to atrophic stage. Common signs include dilated capil lary loops, sclerodactyly, flexion contractures, hypo pigmentation, hyperpigmentation, "coup de sabre deformity", purse lip, telangiectasia), and Gl 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

#### SPECIFIC ENTITIES (CONT'D)

- DIAGNOSIS major criterion is sclerodermatous skin changes proximal to the MCP joints. Minor criteria include sclerodactyly, digital pitting scars, and bilateral pulmonary fibrosis. Tests include antibo dies to topoisomerase I (anti SCI 70) seen more in diffuse systemic sclerosis and antibody to centro mere seen more in CREST
- TREATMENTS Raynaud's (calcium channel block ers). GERD (proton pump inhibitor). Renal crisis (ACE inhibitors). Interstitial pneumonitis (steroids, azathioprine, cyclophosphamide). Pulmonary hypertension (endothelin antagonists [Bosentan])

#### **INFLAMMATORY MYOPATHIES**

- PATHOPHYSIOLOGY classified as polymyositis, der matomyositis, and inclusion body myositis
- ASSOCIATIONS dermatomyositis is associated with malignancy (GI, lung, ovarian, breast, lymphoma) in 6 45% of patients
- CLINICAL FEATURES proximal, symmetric, progres sive muscle weakness developing over weeks to months, may be associated with morning stiffness. Muscle pain is not common. Extramuscular mani festations include arthralgias, cardiac (conduc tion abnormalities, cardiomyopathy), respiratory (muscle weakness, aspiration, interstitial lung dis ease), skin (Gottron's papules [dorsal aspect of MCP and IP joints/elbows/knees], heliotrope rash (over upper eyelids with periorbital edema), V rash/shawl sign [erythematous rash over upper chest/back/shoulders], periungual telangiectasia, mechanic's hand [with darkened horizontal lines across lateral and palmar aspects of fingers/ hands]), and constitutional symptoms. Reflexes are usually normal
- DIAGNOSIS symmetric proximal weakness, eleva tion of muscle enzymes, EMG findings consistent with inflammatory myositis, muscle biopsy consis tent 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, azathiop rine, leflunomide, IVIG

#### DISTINGUISHING FEATURES BETWEEN STEROID MYOPATHY AND INFLAMMATORY MYOPATHIES Steroidmyopathy Inflammatory myopathies History Steroid use Other inflammatory myopathy symptoms Other steroid related symptoms Physical Neck flexor normal Neck flexor weaker Tests CK less often 1 CK often ↑, anti Jo1/anti Mi2 Ab **EMG** Normal Abnormal activity Stop steroid **Improves** Worsens

### **Seronegative Spondyloarthropathies**

#### DIFFERENTIAL DIAGNOSIS OF OLIGOARTHRITIS

#### **★RICE**★

#### RHEUMATOLOGIC (>6 weeks)

- SEROPOSITIVE ★PSSR★ Polymyositis, Palindro mic rheumatism, SLE, Scleroderma, Rheumatoid arthritis
- VASCULITIS polymyalgia rheumatica, Wegener's granulomatosis, Behcet's disease, Still's disease

#### INFECTIONS (<6 weeks)

- BACTERIAL sepsis, endocarditis, Lyme disease, Whipple's disease, mycobacteria
- VIRAL Parvovirus, rubella, HBV, HCV, HIV
- FUNGAL
- POST-INFECTIOUS/REACTIVE enteric infections, urogenital infections, rheumatic fever, inflam matory 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, pyo derma gangrenosum, pustular psoriasis poly myalgia rheumatica

#### CLINICAL FEATURES

### **CARDINAL FEATURES**

- **DISTRIBUTION** male preponderance, age 20 40
- SPONDYLOARTHROPATHY spondylitis, sacroiliitis, morning stiffness >30 min
- OLIGOARTHRITIS asymmetric, usually involving hands and below waist, morning stiffness >30 min
- ENTHESOPATHY inflammation at the sites of inser tion of ligaments, tendons, joint capsule, and fascia to bone, with both destruction and new bone for mation. 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, exten sion, 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)</li>
- EXTRARTICULAR CHANGES nail pitting, onycholy sis, psoriasis, tenosynovitis, dactylitis, synovitis, acute uveitis, aortic regurgitation, apical pulmon ary 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, anky losis (stiffness)
- **REACTIVE ARTHRITIS** history of urethritis/cervicitis/ diarrhea, eye involvement
- UNDIFFERENTIATED does not fit any of the above

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, ESR, CRP, urinalysis
- **IMAGING** X rays of affected joints (lumbosacral spine, peripheral)

#### SPECIAL

- INFECTIOUS WORKUP HIV serology (if suspect reactive arthritis), chlamydial PCR (if suspect reactive arthritis), stool culture (if suspect reactive arthritis)
- **HLA B27** association with seronegative spon dyloarthropathy (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/cer vicitis/ acute diarrhea (within 1 month prior to arthritis), alternating buttock pain, enthesopathy, sacroilii tis (sens 75%, spc 87%)

#### MANAGEMENT

**SYMPTOM CONTROL** physical therapy, NSAIDs, glucocorticoid injections

**TREAT UNDERLYING CAUSE** sulfasalazine, metho trexate, pamidronate, and anti TNF agents. Surgery

#### SPECIFIC ENTITIES

#### ANKYLOSING SPONDYLITIS (AS)

CLINICAL FEATURES spondylitis, sacroiliitis, morn ing 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 abnorm alities, and secondary amyloidosis. Imaging reveals bamboo spine (syndesmophytes), shiny corners (squaring and increased density anteriorly of ver tebral 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.])</li>
- RADIOLOGIC CRITERIA sacroiliitis with more than minimum abnormality bilaterally or unequivo cal abnormality unilaterally
- DIAGNOSIS one clinical plus one radiologic cri terion = definite AS; three clinical criteria or one radiologic criterion only = probable AS

#### **ENTEROPATHIC ARTHRITIS**

- PATHOPHYSIOLOGY 10 20% of IBD patients (more common in Crohn's than ulcerative colitis). May be first sign of IBD (especially if joint pain with anemia)
- CLINICAL FEATURES spondylitis, sacroillitis, morn ing stiffness, and large joint arthritis correlates with the activity of colitis. Other extraintestinal manifestations of IBD include fever, clubbing, uvei tis, iritis, anemia, jaundice (primary sclerosing cholangitis), aphthous ulcers (Crohn's mainly), arthritis, erythema nodosum, pyoderma gangreno sum, DVT, and amyloidosis

#### TREATMENTS

- TYPE I ARTHROPATHY acute, pauciarticular periph eral arthritis ± spondylitis and sacroillitis, asso ciated 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, azathiopr ine, 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, sacroillitis, morn ing stiffness, arthritis (distal DIP joints, asymmetric oligoarthritis of lower limbs, symmetric polyarthritis, arthritis mutilans), enthesitis (Achilles tendonitis, plantar fasciitis, tenosynovitis, dactylitis), nail changes (pits, onycholysis), pitting edema, and uveitis. Imaging reveals co existence of erosive changes and new bone formation in the distal joints with lysis of the terminal phalanges, fluffy periostitis, "pencil in cup" appearance, and the occurrence of both joint lysis and ankylosis in the same patient. Rheumatoid factor positive in 2 10%, CCP positive in 8 16%
- DIAGNOSIS requires one major and three minor criteria
  - MAJOR presence of musculoskeletal inflam mation (inflammatory arthritis, enthesitis, back pain)
  - MINOR skin psoriasis, nail lesions, dactylitis, negative rheumatoid factor, and juxtaarticular bone formation on X ray
- TREATMENTS methotrexate, sulfasalazine, lefluno mide, anti TNF agents

#### **REACTIVE ARTHRITIS**

#### **★Can't see, can't pee, can't climb a tree**★

- PATHOPHYSIOLOGY preceding/ongoing infectious disorders such as urethritis (Chlamydia), diarrhea (Shigella, Salmonella, Campylobacter, Yersinia) or HIV, usually within 6 weeks. Overall, 75% achieve remission within 2 years (about one third of them may experience intermittent relapses), and 25% develop chronic disease (with 5 10% developing ankylosing spondylitis)
- CLINICAL FEATURES spondylitis, sacroiliitis, morn ing stiffness, lower limb arthritis (asymmetric oli goarthritis of lower limbs), and enthesitis (Achilles tendonitis, plantar fasciitis, chest wall changes, and sausage fingers/toes). Other important findings include genital lesions (circinate balanitis with shallow painless ulcers on the glans or urethral meatus, urethritis, prostatitis), skin lesions (kerato derma 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 (aor tic regurgitation, conduction abnormalities). Plain film reveals fluffy erosions, periosteal spurs, and asymmetric syndesmophytes

284 Back Pain

### 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 cervi citis, or bilateral conjunctivitis (sens 85.5%, spc 96.4%), episode of arthritis, conjunctivitis, and ure thritis (sens 51%, spc 99%), episode of arthritis of more than 1 month, conjunctivitis, and urethritis (sens 48%, spc 99%)

#### SPECIFIC ENTITIES (CONT'D)

 TREATMENTS NSAIDs (pain control), sulfasalazine, anti TNF agents, methotrexate, azathioprine, leflunomide

#### **Related Topics**

Inflammatory Bowel Disease (p. 120) Psoriasis (p. 362)

### Back Pain NEJM 2005 353:4

#### **DIFFERENTIAL DIAGNOSIS**

#### MECHANICAL

- TRAUMA sprain, strain, fracture
- FRACTURE compression, traumatic
- SPONDYLOSIS disc, annulus, facet
- SPONDYLOLISTHESIS

#### INFLAMMATORY

- RHEUMATOLOGIC psoriatic arthritis, enteric arthritis, ankylosing spondylitis, reactive arthritis
- MALIGNANCY multiple myeloma, epidural metastasis, leptomeningeal metastasis
- INFECTIONS epidural abscess

#### REFERRED PAIN

- · GI pancreatitis, cholecystitis
- RENAL stones, pyelonephritis, abscess
- PELVIC
- AORTIC ANEURYSM RUPTURE

#### CLINICAL FEATURES

# RATIONAL CLINICAL EXAMINATION SERIES: WHAT CAN THE HISTORY AND PHYSICAL EXAMINATION TELL US ABOUT LOW BACK PAIN?

HISTORY "history of cancer, unexplained weight loss, pain duration >1 month, failure to improve with conservative therapy are all relatively specific for cancer pain. IDU or urinary infection suggests spinal infection. Back pain in young men raises possibility of ankylosing spondylitis. Failure to improve with rest is sensitive for systemic conditions. Sciatica or pseudoclaudication suggests neurological involve ment. 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,

### CLINICAL FEATURES (CONT'D)

**reflexes and sensory examination** of lower limbs should be done"

JAMA 1992 268:6

#### INVESTIGATIONS

#### BASIC

• IMAGING spine XR

#### SPECIAL

- **IMAGING** CT spine, MRI spine (if surgery), mye logram (gold standard but seldom used)
- MYELOMA WORKUP CBCD, lytes, urea, Cr, ESR, serum protein electrophoresis, urinary protein electrophoresis

#### Related Topics

Ankylosing Spondylitis (p. 283) Radiculopathy (p. 323)

Spinal Cord Compression (p. 228)

#### DIAGNOSTIC FEATURES

# DISTINGUISHING FEATURES BETWEEN INFLAMMATORY AND MECHANICAL BACK PAIN

Inflammatory Mechanical Age Younger Older Onset Insidious Abrupt Duration >3 months Shorter AM stiffness ++ Resting Worsens **Improves** Activity **Improves** Worsens Sacroiliac ioints ++

#### MANAGEMENT

SYMPTOM CONTROL pain control

**TREAT UNDERLYING CAUSE** flexion and extension exercises

Back Pain 285

#### SPECIFIC ENTITIES

SPINAL CORD COMPRESSION compression of spinal cord (upper motor neuron, usually above L1 level). Symp toms 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 distribu

#### SPECIFIC ENTITIES (CONT'D)

tion. The classic features are aching pain in the but tock 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 ver tebra on another, usually as a result of repeated stress on pars interarticularis. Symptoms include sciatica and low back pain, although it can also be asymptomatic

Disc/Root	Pain	Sensory	Weakness	Reflex
C4 5 (C5)	Medial scapula, lateral upper arm	Shoulder	Deltoid, supraspinatus, infraspinatus	Supinator
C5 6 (C6)	Lateral forearm, thumb, and index finger	Thumb and index finger	Biceps, brachioradialis, wrist extension	Biceps
C6 7 (C7)	Medial scapula, posterior arm, dorsum of forearm, third finger	Posterior forearm, third finger	Triceps, wrist flexion, finger extension	Triceps
C7 T1 (C8)	Shoulder, ulnar side of forearm, fifth finger	Fifth finger	Intrinsic hand muscles, thumb flexion, and abduction	None
L3 4 (L4)	Anterior thigh	Lateral leg to medial malleolus	Hip flexion, dorsiflexion, and inversion	Knee
L4 5 (L5)	Posterior lower limb	Lateral leg, dorsal foot including first web space	Hip extension and abduction, dorsiflexion, plantarflexion, and ankle eversion and inversion	None
L5 S1 (S1)	Posterior lower limb, often to ankle	Posterior leg Lateral foot	Hip extension and abduction, dorsiflexion, plantarflexion, and ankle eversion	Ankle
S2 S4	Sacral or buttock, radiate to posterior leg or perineum	Perineum (sacral paresthesia)	Bowel and bladder dysfunction	None

### SPECIFIC ENTITIES (CONT'D)

**DISC HERNIATION** prolapse of nucleus pulposus through the annulus, due to intervertebral pressure and degeneration of the ligamentous fibers. Occurs more commonly in younger patients. If the prolapsed material presses on a nerve root, may cause inflammation and sciatic symptoms. Over 95% of herniated discs affect the L4 5 or L5 S1 interspace. Most herniated discs resolve in 1 2 weeks with conservative treatment **SPINAL STENOSIS** 

- PATHOPHYSIOLOGY narrowing of the spinal canal, with compression of nerve roots → exerts pressure on venules around nerve roots → ischemic nerve injury causing back pain and neurologic symptoms
- CAUSES common causes include degenerative disc disease, osteoarthritis of facet joints with osteophyte and cyst formation, ligamentum flavum hypertrophy,

### SPECIFIC ENTITIES (CONT'D)

and spondylolisthesis. Laminectomy, spinal fusion, trauma, Cushing's syndrome, Paget's disease, and acromegaly are also associated with spinal stenosis

- CLINICAL FEATURES neurogenic claudication char acterized by worsening back and/or lower extre mity pain with walking, relieved with flexion, sit ting 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 mvelogram
- TREATMENTS pain control (acetaminophen, NSAIDs, opioids, lumbar epidural corticosteroid injections), decompression surgery with laminectomy and par tial facetectomy. Physiotherapy consultation

NEJM 2008 358:8

286 Osteoarthritis

Osteoarthritis NEJM 2007 357:14

#### DIFFERENTIAL DIAGNOSIS

#### PRIMARY OSTEOARTHRITIS

- GENERALIZED primary generalized, diffuse idio pathic skeletal hyperostosis
- ISOLATED nodal, hips, erosive

#### SECONDARY OSTEOARTHRITIS

- MECHANICAL post traumatic, post surgical
- NEUROPATHIC JOINTS diabetes, syphilis, spinal cord injury
- INFLAMMATORY RA, crystal arthropathies, infectious
- METABOLIC hemochromatosis, Wilson's disease, acromegaly, Paget's disease, Cushing's syn drome, ochronosis
- BLEEDING DYSCRASIAS hemophilic, warfarin use OSTEOARTHRITIS MIMICS inflammatory features and distribution should help to rule out inflammatory arthritis (seropositive, seronegative, crystal, infectious arthropathies). Important to try to distinguish from periarticular structures (tendonitis, bursitis)

#### PATHOPHYSIOLOGY

**ARTICULAR CARTILAGE** not due to wear and tear but involves increased activity of cartilage matrix formation and removal. As the repair effort becomes inadequate, metalloproteinases and collagenase cause degradation of cartilage and subsequent degeneration of surrounding soft tissues

**RISK FACTORS FOR PRIMARY OSTEOARTHRITIS** age, female, obesity, high bone mass, mechanical factors (previous joint injury, excessive varus, or valgus), smoking, genetics

### CLINICAL FEATURES

#### **SUBTYPES OF PRIMARY OSTEOARTHRITIS**

- GENERALIZED affects DIP (Heberden's nodes), PIP (Bouchard's nodes) and first CMC joints, hips, knees, and spine. More common in women
- ISOLATED NODAL affects DIP joints only. More common in women
- ISOLATED HIP affects hips only. More common in men
- EROSIVE affects DIP and PIP joints, with episodes of local inflammation, mucous cyst formation, and bony erosion resulting in joint deformity. Genetic predisposition. May mimic rheumatoid arthritis
- DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (DISH)
   affects spine mainly but peripheral joints may also
   be involved, with osteophytes connecting ≥4 ver
   tebrae. Also known as Forestier disease. X rays are
   diagnostic. May mimic ankylosing spondylitis

#### INVESTIGATIONS

**IMAGING** X ray of affected joints (joint space narrowing, marginal osteophytes, subchondral sclerosis, and cysts)

#### DIAGNOSTIC ISSUES

DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY OSTEOARTHRITIS primary osteoarthritis almost never involves the shoulders, elbows, ankles, MCP joints, or ulnar side of wrist. Should consider secondary osteoarthritis if unusual sites for primary osteoarthritis or widespread chondrocalcinosis ACR DIAGNOSTIC CRITERIA FOR HAND OSTEOAR THRITIS hand pain, aching, or stiffness and three or four of the following features (hard tissue enlargement of 2 or more of 10 selected joints [second and third DIP and PIP, first CMC], hard tissue enlargement of 2 or more DIP joints, fewer than 3 swollen MCP joints, deformity of at least 1 of 10 selected joints). Sens 94%, spc 87%

**ACR DIAGNOSTIC CRITERIA FOR HIP OSTEOAR THRITIS** hip pain and at least two of the following three features: ESR <20 mm/h, radiographic femoral or acetabular osteophytes, radiographic joint space narrowing. Sens 89%, spc 91%

#### MANAGEMENT

CONSERVATIVE MEASURES patient education, wei ght 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 OSTEOARTHRI

**TIS** usually isolated large joints. Knee OA may develop after meniscal tear, and shoulder OA may develop with long standing rotator cuff injury **HEMOCHROMATOSIS** affects second and third MCP

and shoulders mainly (see p. 420 for more details).

#### AVASCULAR NECROSIS/ASEPTIC NECROSIS

- PATHOPHYSIOLOGY damage to vasculature from mechanical interruption, thrombosis/embolism, vessel wall injury, or venous occlusion, leading to medullary infarction. Affects the femur head, tibial plateau, humeral head, and vertebrae more commonly
- ASSOCIATIONS \*ASEPTIC\* Alcohol, Steroids, Sepsis, Storage disease (Gaucher), Sickle cell disease, Emboli (fat, cholesterol), Post radiation, Trauma, Idio pathic, Connective tissue disease (SLE, rheumatoid arthritis, vasculitis), Cancer, hyperCoagulable states

Fibromyalgia 287

#### SPECIFIC ENTITIES (CONT'D)

- CLINICAL FEATURES joint pain. Have high index of suspicion, especially if prior use of high dose steroids
- DIAGNOSIS plain radiograph (initially appears nor mal), CT, bone scan. MRI is the most sensitive test

#### SPECIFIC ENTITIES (CONT'D)

 TREATMENTS stop offending agents. Avoid weight bearing. Pain control. Orthopedic consult for pos sible debridement, decompression, or joint replacement

### **Fibromyalgia**

### DIFFERENTIAL DIAGNOSIS OF DIFFUSE BODY PAIN

#### **FIBROMYALGIA**

MYOPATHY metabolic (hypothyroidism), drug induced, myofascial pain syndrome (more localized)

NEUROLOGIC multiple sclerosis

PSYCHIATRIC depression

### PATHOPHYSIOLOGY

### INCREASED PAIN PERCEPTION ASSOCIATIONS

irritable bowel syndrome, irritable bladder syndrome, chronic headaches, mood disorders (depression, anxi ety), sleep disorders

#### CLINICAL FEATURES

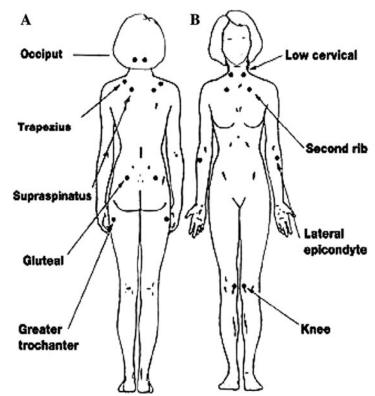
**GENERALIZED SYMPTOMS** diffuse soft tissue pain, sleep disturbances, fatigue

**SPECIFIC TENDER POINTS** ≥11/18 (occiput, ster nocleidomastoid, second rib, trapezius, supraspina tus, lateral epicondyle, gluteal, greater trochanter, medial fat pad of knees)

#### INVESTIGATIONS

#### BASIC

 LABS (usually normal) CBCD, lytes, urea, Cr, Ca, Mg, PO<sub>4</sub>, ESR, TSH, CK



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#### MANAGEMENT

# REASSURANCE AND PATIENT EDUCATION PROGRAMS

**LIFESTYLE** physical therapy/activity, sleep hygiene **MEDICATIONS** amitriptyline, muscle relaxants (cyclobenzaprine), SSRI, pregabalin

#### SPECIFIC ENTITIES

#### CHRONIC FATIGUE SYNDROME

 DIAGNOSTIC CRITERIA new onset unexplained per sistent or relapsing fatigue, exclude ongoing

#### SPECIFIC ENTITIES (CONT'D)

exertion, not alleviated by rest, substantial reduction in previous activities, and at least four of the following: self reported impairment in short term memory or concentration, sore throat, tender cervical or axillary nodes, muscle pain, multi joint pain without redness or swelling, headaches of a new pattern or severity, unrefreshing sleep, post exertional malaise lasting >24 h

TREATMENTS cognitive behavior therapy and graded exercise

#### **Vasculitis**

### NEJM 2003 349:2

#### DIFFERENTIAL DIAGNOSIS

PRIMARY VASCULITIDES Takayasu aortitis, giant cell/temporal arteritis, polyarteritis nodosa (PAN), microscopic polyangiitis (MPA), Churg Strauss syndrome, Wegener's granulomatosis SECONDARY VASCULITIDES (hypersensitivity)

#### **★VASCULITIS★**

- VARIOUS DRUGS
- AUTOIMMUNE SLE, rheumatoid arthritis, Behcet's disease, relapsing polychondritis
- SERUM SICKNESS penicillin
- CRYOGLOBULINEMIA
- ULCERATIVE COLITIS
- Low COMPLEMENT hypocomplementemic urticarial vasculitis
- INFECTIONS viral (HBV, HCV, HIV, CMV, EBV, Parvovirus B19), rickettsial
- TUMORS lymphoma, multiple myeloma
- IgA Nephropathy/Henoch—Schonlein purpura
- SMOKING-RELATED THROMBOANGIITIS OBLITER-ANS Buerger's disease

#### VASCULITIS MIMICS

- RHEUMATIC DISEASES SLE
- INFECTIOUS bacteremia, necrotic arachnidism
- INFILTRATIVE amyloidosis
- CANCER lymphoma
- CONGENITAL coarctation of the aorta, neurofibromatosis
- EMBOLI endocarditis, mycotic aneurysm, cho lesterol, atrial myxoma
- ETC fibromuscular dysplasia, granulomato sis/polymorphic reticulosis, ergotism, radia tion fibrosis, thrombocytopenia, malignant atrophic papulosis

#### PATHOPHYSIOLOGY

**MECHANISM** inflammation of vessel wall  $\rightarrow$  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, hyper sensitivity 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 blanch able), 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 meningococ cemia), 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, glomer ulonephritis, mononeuritis multiplex, myalgia/arthralgia/arthritis, abdominal/testicular pain, unex plained constitutional symptoms. Greater likelihood of vasculitis if combination

#### INVESTIGATIONS

#### BASIC

- BLOOD TESTS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, albumin, ESR, CRP, ANA, urinalysis
- IMAGING CXR

#### **SPECIAL**

- INFLAMMATORY WORKUP RF, C3, C4, p ANCA, c ANCA, cryoglobulins, CK, serum protein electrophoresis,
- INFECTIOUS WORKUP serologies (HIV, HBV, HCV, EBV, CMV, treponema pallidum, Borrelia buradorferi)
- FURTHER IMAGING GUIDED BY SYMPTOMS MR head, CT chest, abd, pelvis, angiogram
- BIOPSY OF AFFECTED ORGAN guided by symptoms (e.g. temporal artery, skin, kidney, Gl mucosa)

DIAGNOSIS BY ORG		IENT				<b></b>	
	Head (stroke, visual $\Delta$ )	Peripheral neuropathy	Lung (dyspnea, hemoptysis)	Kidneys (GN)	Abdomen (pain)	Skin (palpable purpura)	Others
akayasu aortitis	+						Cardiovas.
Giant cell arteritis	+						ESR++, PMR
olyarteritis nodosa		+			+	+	GI++
Nicroscopic polyangiitis			+	+	+		p-ANCA
legener's granulomatosis	±	+	+	+			Sinus, c-ANCA
hurg-Strauss syndrome			+	+		+	Asthma, eosinoph
enoch–Schonlein purpura					+	+	IgA
ehcet's disease	+					+	Oral ulcers
ryoglobulinemia		+		+		+	Cryoglobulii

#### MANAGEMENT

**PRIMARY VASCULITIDES** *prednisone* 1 mg/kg/day PO daily. *Cyclophosphamide* 2 mg/kg/day IV daily or 500 1000 mg/m² IV monthly

SECONDARY VASCULITIDES treat underlying cause

### SPECIFIC ENTITIES

### **TAKAYASU AORTITIS (PULSELESS DISEASE)**

- PATHOPHYSIOLOGY systemic vasculitis of the large arteries, typically the aorta and its branches with vessel occlusion causing MI, TIA, strokes, visual disturbances, and claudication
- ASSOCIATIONS young women of Asian or Mexican descent
- ACR DIAGNOSTIC CRITERIA age at disease onset <40
  years, claudication of extremities, decreased brachial
  artery pulse, systolic blood pressure difference
  >10 mmHg between arms, bruit over subclavian
  arteries or aorta, arteriogram abnormality (narrowing

#### SPECIFIC ENTITIES (CONT'D)

- 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 cri teria for diagnosis (sens 91%, spc 98%)
- **TREATMENTS** steroids, methotrexate, vascular sur gery, 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

#### SPECIFIC ENTITIES (CONT'D)

1 mg/month) every 4 weeks until tapered off. Use of prednisone greater than 15 mg decreases the diagnostic specificity. Relapse is frequent

#### **GIANT CELL ARTERITIS/TEMPORAL ARTERITIS**

- ASSOCIATIONS older age, polymyalgia rheumatica in 30 50%
- CLINICAL FEATURES systemic vasculitis of the large and medium arteries. This causes headache, amaurosis fugax, diplopia, jaw claudication, painful scalp nodules, and tender temporal artery. Extra cranial GCA involves aorta in 10 15% of cases
- ACR DIAGNOSTIC CRITERIA age >50, new onset headache, abnormal temporal artery, ESR

#### SPECIFIC ENTITIES (CONT'D)

- >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 methylpred nisolone 1 g IV daily ×3 days, then prednisone 80 mg PO daily and taper over time. Initiate ther apy before biopsy if high index of suspicion. Con sider methotrexate if steroid sparing therapy required. ASA 81 mg PO daily is recommended to reduce vascular complications

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE TEMPORAL ARTERITIS?  LR+  LR				
History	LR+	LK		
Jaw claudication	4.2	0.72		
Diplopia	3.4	0.95		
Temporal headache	1.5	0.82		
Any headache	1.2	0.7		
Unilateral visual loss	0.85	1.2		
Any visual symptom	1.1	0.97		
Vertigo	0.71	1.1		
Anorexia	1.2	0.87		
Weight loss	1.3	0.89		
Arthralgia	1.1	1		
Fatigue	1.2	0.94		
Fever	1.2	0.92		
Myalgia	0.93	1.1		
Polymyalgia rheumatica	0.97	0.99		
Physical				
Beaded temporal artery	4.6	0.93		
Prominent temporal artery	4.3	0.67		
Tender temporal artery	2.6	0.82		
Absent temporal artery pulse	2.7	0.71		
Any temporal artery	2	0.53		
Scalp tenderness	1.6	0.93		
Optic atrophy or ischemic optic neuropathy	1.6	0.8		
Any fundoscopic abnormality	1.1	1.0		
Synovitis	0.41	1.1		
Male gender	0.83			
White race	1.1			
Laboratory investigations				
Anemia	1.5	0.79		
ESR abnormal	1.1	0.2		
ESR >50 mm/h	1.2	0.35		
ESR >100 mm/h	1.9	0.8		
ADDDOLGIL # 1	OF 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1			

**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 (particularly the peroneal and tibial branches of sciatic nerve), orchitis, skin (palpable purpura, livedo reticularis, subcutaneous nodules, distal gangrene), GI (mesenteric vasculitis), renal (vasculitis but NO glomerulonephritis)
- ACR DIAGNOSTIC CRITERIA weight loss >4 kg since illness, livedo reticularis, testicular pain or tenderness, myalgias, weakness or leg 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

#### MICROSCOPIC 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 infil
   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 myeloperoxi dase), eosinophilia, and ↑ loE 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

#### BEHCET'S DISEASE

- PATHOPHYSIOLOGY systemic vasculitis of the large, medium, and small arteries, typically involving the oral mucosa, eyes, skin, and CNS
- CLINICAL FEATURES occurs more commonly along the Silk Route of Asia and Europe. Typically involves painful aphthous ulcers (gingival, tongue, buccal), eyes (iritis, anterior uveitis), skin (erythema nodosum, pseudofolliculitis, acneiform nodules), painful genital ulcers, joints (non deforming monoarthritis, sometimes oligo or polyarthritis), venous thrombosis (vena cava, portal, hepatic veins, extremities), and CNS (aseptic meningitis, meningoencephalitis, focal neurological deficits)
- DIAGNOSTIC CRITERIA oral aphthous ulcers recurring
   ≥3x over 1 year, plus two of the following: recurrent
   genital aphthous ulcers, eyes features, skin features,
   and positive pathergy testing at 24 48 h
- TREATMENTS steroids and others (lesion dependent)

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### **Approach to Serologies**

#### INFLAMMATORY MARKERS

# **ERYTHROCYTE SEDIMENTATION RATE (ESR)** (non specific)

- DISORDERS elevated in vasculitis such as temporal arteritis and polymyalgia rheumatica and almost all inflammatory disorders (rheumatologic, infectious, malignancy), anemia, renal disease, pregnancy, birth control pills, thyroid disease, and old age
- UTILITY associated with disease activity in tem poral 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 tem poral 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 endocar ditis. Somewhat elevated in other rheumatologic diseases (SLE, MCTD, polymyositis, sarcoidosis), pulmonary and hepatic diseases, infections, and malignancy. May also be positive in the normal elderly
- UTILITY seronegative rheumatoid arthritis does not have extraarticular findings. Does not correlate with disease activity

# **ANTICYCLIC CITRULLINATED PEPTIDES (CCP)** (very specific)

 UTILITY very useful for diagnosis of rheumatoid arthritis (sens 85%, spc 95%). For patients with elevated rheumatoid factor of >50 U/mL and fulfilling other criteria, rheumatoid arthritis is diag nosed without need for anti CCP. However, if rheu matoid factor <50 U/mL, consider anti CCP testing (suggests rheumatoid arthritis if positive)

### LUPUS

**ANTINUCLEAR ANTIBODIES (ANA)** (non specific but most sensitive test for SLE)

DISORDERS SLE (sens >99%), mixed connective tissue disease (sens >95%), Sjogren's syndrome (sens 75%), inflammatory myopathies (sens >75%), scleroderma (sens >60 90%), rheumatoid arthritis (sens 15 35%), and normal elderly

#### LUPUS (CONT'D)

- STAINING PATTERNS
  - RIM most specific, SLE
  - HOMOGENOUS SLE
- NUCLEOLAR scleroderma, CREST
- DIFFUSE non specific
- SPECKLED most common, least specific, con sider 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

# ANTI DOUBLE STRANDED DNA (most specific test for SLE)

- DISORDERS elevated in SLE (sens 20 30%, spc >95%) and chronic active hepatitis. Usually not elevated in drug induced lupus
- utility associated with lupus nephritis and disease activity in SLE (most useful for following disease)

#### ANTI SMITH (very specific)

- DISORDERS SLE. Usually not elevated in drug induced lupus
- **UTILITY** SLE (sens 30%, spc >95%). Associated with lupus nephritis

#### ANTI RNP

- **DISORDERS** SLE, mixed connective tissue disease
- UTILITY associated with milder SLE

#### **ANTI HISTONE**

 DISORDERS drug induced lupus (sens >90%, very spc), SLE (sens >50%)

#### C3, C4

- DISORDERS decreased in SLE, cryoglobulinemic vasculitis, Henoch Schonlein purpura
- UTILITY associated with lupus nephritis and dis ease 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 Sjog ren's syndrome, heart block in neonates with anti Ro positive mothers, cutaneous lupus rash, photosensitivity, and thrombocytopenia in SLE

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#### SJOGREN'S SYNDROME (CONT'D)

#### ANTI LA (SS B)

- **DISORDERS** Sjogren's syndrome (sens 40%), SLE (sens 10%)
- UTILITY associated with anti-Ro and benign course in SLE if no other autoantibody present except ANA

#### INFLAMMATORY MYOPATHIES

**ANTI JO 1** antibodies against t RNA histidyl synthetase

- DISORDERS polymyositis (sens 30%)
- UTILITY associated with deforming arthritis, 'mechanic's hands", Raynaud's, and pulmonary fibrosis in dermatomyositis and polymyositis

#### ANTI MI 2

- **DISORDERS** dermatomyositis (sens 5%)
- UTILITY associated with V sign, shawl sign, cuticular overgrowth, good response to therapy, and good prognosis

### INFLAMMATORY MYOPATHIES (CONT'D)

**ANTI SRP** antibodies against antisignal recogni tion protein

• DISORDERS dermatomyositis and polymyositis

#### VASCULITIS

**C ANCA** autoantibodies against proteinase 3. Con firm by testing for antiproteinase 3

• **DISORDERS** Wegener's granulomatosis (sens

**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%), micro scopic polyangiitis (sens 45%), polyarteritis nodosa (sens 15%), Wegener's granulomatosis (sens 10%)

Joint Examination	ination				2)-
	Inspection (SEADS <sup>a</sup> )	ROM (Active and	Palpation (SWAT <sup>b</sup> )	Special tests	•
Shoulder	Winging of scapulae	Passive) Abduction (180°) Adduction (50°) Flexion (180°) Extension (60°) Internal rotation (90°) External rotation (90°)	Clavicle, AC joint, coracoid process, acromion, spine of scapula, greater and lesser tuberosity of humerus, biceps tendon	Initial abduction against resistance (supraspinatus) External rotation against resistance (infraspinatus and teres minor) Internal rotation against resistance (subscapularis) Relocation and anterior release tests (shoulder instability) Biceps load I and II (labrum tear) Biceps tendonitis	
Hand and wrist	Boutonniere, Swan neck, subluxation @ MCP and wrist, ulnar deviation @ MCP, radial deviation @ carpus, rheumatoid nodules, Heberden's and Bourbard's nodes	Thumb flexion, extension, abduction, and adduction Finger flexion/extension Opposition Writt flexion/extension	Wrist Carpal joints MCP joints PIP joints DIP joints	Also examine C-spine and upper mino freurological resting)  Tinel's test, Phalen's test (carpel tunnel syndrome)  Finkelstein's test (de Querozain's tenosynovitis)  Hand grip strength and function (write)  Neurological testing of hand	
d d	Lumbar lordosis Gait <sup>c</sup>	Abduction (50°) Adduction (20°) Internal rotation (35°) External rotation (45°) Flexion (120°) Extension (20-30°)	ASIS Iliac crest SI joint Greater trochanter Ischial tuberosity	FABER test (groin pain=hip joint, buttock pain=Si joint) Thomas test (hip flexion contracture) Trendelenburg test (weakness of gluteus medius on standing side) Leg length discrepancy (true and false)	
Knee	Varus Valgus Genu recurvatum Baker cyst Gait³	Flexion (135°) Extension (10°) Eversion (10°) Inversion (10°)	Patella, tibial tuberosity Head of tibia/fibula Joint line tenderness Femoral condyles Bursa (suprapatellar, subpatellar, infrapatellar, anserine) Bulqe test, balloon test, patella tap	Anterior drawer test, Lachman test, pivot shift (anterior cruciate ligament)  Posterior drawer test (posterior crudate ligament)  Collateral ligaments  McMurray test, medial-lateral grind test (meniscal)	
Ankle and foot	Varus Valgus Achilles tendon Nalis, bunion Hallux valgus Metatarsus varus Pes planus	Donsiflexion (20°) Plantarflexion (50°) Subtala (joint— inversion and eversion (5°) Forefoot joints	Achilles tendon Maileolus Anterior talofibular ligament Deltriof ligament Calcaneus Base of MTP Calcaneus	Anterior drawer test Lateral/medial stability Subtalar complex stability Achilles tendon rupture	Joini Exar
<sup>a</sup> SEADS— <b>S</b> ymme <sup>b</sup> SWAT— <b>S</b> welling <sup>c</sup> Gait—heel strike	<sup>a</sup> SEADS—Symmetry/swelling, Erythema, Atrophy, Deformity, and Surgeries/scars b SWAT—Swelling/synovitis, Warmth, Anatomic landmarks, Tenderness c Gait—heel strike, foot flat (mid-stance), heel off (lift off), toes off (swing)	nity, and Surgeries/scars s., Tenderness toes off (swing)			піншиоп

Joint Examination 295

# RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE AN INSTABILITY OF THE SHOULDER OR A LABRUM LESION?

**POSITION FOR TESTING** shoulder  $90^{\circ}$  abducted and  $90^{\circ}$  externally rotated, elbow  $90^{\circ}$  flexed for all tests described below, with the exception of biceps load for which the shoulder is  $120^{\circ}$  abducted and maximally externally rotated and the elbow is  $90^{\circ}$  flexed

	Sens	Spc	LR+	LR
Clinical tests for shoulder instability				
Relocation test applying pressure to shoulder anteriorly causes relief	85%	87%	6.5	0.18
Anterior release releasing anterior pressure causes pain	92%	89%	8.3	0.09
Apprehension test applying pressure to shoulder posteriorly causes pain	88%	50%	1.8	0.23
Clinical tests for labral tears				
Biceps load I and II tests flexion of elbow against resistance causes pain	83%	98%	29	0.09
	90%	96%	26	0.11
Pain provocation of Mimori passive movement from maximally supinated to pronated causes pain	100%	90%	7.2	0.03
Internal rotation resistance strength internal rotation against resistance	88%	96%	25	0.12

**APPROACH** "best evidence supports the value of the relocation and anterior release tests for diagnosis of shoulder instability. Symptoms related to labral tears remain unclear. Most promising for establishing labral tears are currently the biceps load I and II, pain provocation of Mimori, and the internal rotation resistance strength tests"

JAMA 2004 292:16

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A TORN MENISCUS OR LIGAMENT OF THE KNEE?			
	LR+	LR	
Clinical tests for anterior cruciate ligament to	ear		
Anterior drawer test	3.8	0.30	
Lachman test	42	0.1	
Lateral pivot shift test			
Composite assessment	25	0.04	
Clinical tests for posterior ligament tear			
Composite assessment	21	0.05	
Clinical tests for meniscal tear			
McMurray test	1.3	0.8	
Joint line tenderness	0.9	1.1	
Joint effusion	5.7	0.7	
Medial lateral grind	4.8	0.4	
Apley apprehension test			
Composite assessment	2.7	0.4	

**APPROACH** "the complete examination for specific meniscal or ligamentous injuries of the knee performed much better than specific maneuvers, suggesting that synthesis of a group of examination maneuvers and historical items may be required for adequate diagnosis'

JAMA 2001 286:13

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### Notes

# **10** NEUROLOGY

### Section Editor: Dr. Brian Thiessen

### **Brain Tumors**

#### PATHOPHYSIOLOGY

#### CLASSIFICATION BY HISTOLOGY

- NEUROEPITHELIAL
  - GLIOMAS
    - ASTROCYTOMA (30%) pilocytic (grade 1), fibril lary (grade 2), anaplastic (grade 3), glioblas toma multiforme (grade 4, 20% of all brain tumors)
    - OLIGODENDROGLIOMA (4%) well differentiated, anaplastic, mixed; 50% have 1p19q co deletion
    - EPENDYMOMA (2%)
  - CHOROID PLEXUS TUMORS
  - NEURONAL AND MIXED NEURONAL-GLIAL TUMORS
  - PINEAL PARENCHYMAL TUMORS
  - EMBRYONAL TUMORS (1.7%) medulloblastoma, pineoblastoma, neuroblastoma, ependymo blastoma
- 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 melano sis, 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, epider moid 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 adeno matous 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** epige netic 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 contribut ing to increased effectiveness of treatment

MASS EFFECT tumors → vasogenic edema → direct compression of neurons causing demyelination and necrosis and specific neurological symptoms. Also increases intracranial pressure causing headache, nausea and vomiting, papilledema, and third nerve palsy, and herniation syndromes. Hydrocephalus may also occur with obstruction of third or fourth ven tricle 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), cog nitive dysfunction, visual spatial dysfunction, aphasia, N&V, altered level of consciousness

298 Brain Tumors

### 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, pro nator drift, Romberg sign

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, INR, PTT, albumin
- IMAGING MRI head, CT head
- BIOPSY open biopsy, stereotactic biopsy SPECIAL
- MR SPECTROSCOPY N acetylaspartate, choline, lactate
- FUNCTIONAL MR blood flow

#### PROGNOSTIC ISSUES

**PROGNOSIS FOR LOW GRADE GLIOMAS** median survival 7 8 years, 5 year survival 64%; median time to recurrence 4.5 years, median survival from recurrence 12 months

#### PROGNOSIS FOR GLIOBLASTOMA MULTIFORME

median survival 14 weeks with observation only, 20 weeks with resection, 36 weeks with radiation added, and 40 50 weeks with chemotherapy added

### PROGNOSTIC FACTORS FOR ANAPLASTIC ASTRO CYTOMA AND GLIOBLASTOMA MULTIFORME older age, poor Karnofsky performance status, degree

older age, poor Karnofsky performance status, degree of excision, neurologic deficits

MEDIAN SURVIVALS FOR OLIGODRENDROGLIOMAS

MEDIAN SURVIVALS FO	ROLIGODRENI	DROGLIOM/
Oligodrendroglioma	1p19q deletion	No 1p19o deletion
Low grade	15 years	5 years
High grade	5 10 years	2 years

### MANAGEMENT

**SYMPTOM CONTROL** seizure control (phenytoin, levetiracetam, carbamazepine, lamotrigine, cloba zam, valproate, topiramate), steroids may be used short term for cerebral edema with symptoms such as headaches, neurological deficits

#### **TUMOR CONTROL**

- ASTROCYTOMA
  - LOW GRADE (GRADE 2) maximal surgical debulk ing. Upfront radiation improves progressive free survival but not overall survival. Thus, it may be delayed in patients who are asymptomatic
  - ANAPLASTIC (GRADE 3) maximal surgical debulking, followed by radiation  $\pm$  chemother apy (PCV, temozolomide)
  - GLIOBLASTOMA MULTIFORME (GRADE 4) maximal surgical debulking, concurrent chemoradiation with temozolomide ×6 weeks, followed by

#### MANAGEMENT (CONT'D)

4 week break and then adjuvant temozolomide d1 5  $\alpha$ 28d  $\times$ 6

- LOW-GRADE OLIGODENDROGLIOMA
  - WITH 1P19Q DELETION resection. Chemother apy 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  $\pm$  che motherapy  $\pm$  radiation
  - without 1P19q DELETION resection, RT alone or concurrent chemoradiation with temozolo mide ×6 weeks, followed by 4 week break and then adjuvant temozolomide d1 5 q28d ×6
  - SALVAGE CHEMOTHERAPY FOR GLIOMAS nitro soureas, bevacizumab, etoposide, carboplatin, procarbazine
  - **EPENDYMOMA** resection  $\pm$  radiation. Palliative chemotherapy may be provided with recurrence
  - PRIMARY NEUROECTODERMAL TUMORS (medullo blastoma, supratentorial, pineoblastoma) resection plus craniosoinal radiation for low risk tumors may be curative. Add adjuvant che motherapy (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  $\geq$  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 Acute Stroke Syndromes 299

#### 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 fora men magnum compresses the medulla and upper spinal cord, resulting in rapid failure of vital functions

#### **BRAIN METASTASIS**

- PATHOPHYSIOLOGY occurs in 20 30% of patients, most commonly from lung, breast, melanoma, and primary unknown cancers. About 10× more fre quent than primary brain tumors. Found in cere bral hemispheres, cerebellum, and brain stem 80%, 15% and 5% of the time
- **TREATMENT** surgery plus radiation offers survival advantage over radiation alone, although <50%

#### SPECIFIC ENTITIES (CONT'D)

of brain metastases are resectable. Radiation reduces recurrence but does not improve survival

#### 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, par ticularly after combined methotrexate and radia tion administration

### **Acute Stroke Syndromes**

NEJM 2007 357:6 NEJM 2008 359:13 AHA/ASA Stroke Guidelines 2009

#### DIFFERENTIAL DIAGNOSIS

#### ISCHEMIC STROKE

- THROMBOTIC/INTRINSIC VESSEL DISEASE athero sclerosis, vasculitis, vasospasm, dissection, com pression, fibromuscular, hypercoagulable state
- EMBOLIC/REMOTE ORIGIN cardiogenic, artery, septic, air, fat, paradoxical
- GLOBAL ISCHEMIA MI, VT

#### **HEMORRHAGIC STROKE**

- INTRACEREBRAL VESSEL RUPTURE hypertension, trauma, bleeding diatheses, amyloid angiopa thy, illicit drug use, vascular malformation
- SUBARACHNOID VESSEL RUPTURE aneurysm rupture, vascular malformation, bleeding diatheses, trauma, amyloid angiopathy, illicit drug use (cocaine)

**STROKE MIMICS** (usually global rather than focal neurological symptoms) ★**DIMS**★

- DRUG INTOXICATION
- INFECTIONS
- INSANITY conversion disorder
- METABOLIC hypoglycemia, renal failure, hepa tic failure
- MIGRAINES
- SYNCOPE
- SEIZURES Todd's paralysis
- STRUCTURAL trauma, tumors, subdural hemorrhage

#### PATHOPHYSIOLOGY

#### **FIVE QUESTIONS**

1. Is the patient stable?

#### PATHOPHYSIOLOGY (CONT'D)

- 2. Is this a stroke?
- 3. Where is the stroke? Symptoms/signs, CT head
- What kind of stroke? Ischemic (thrombotic, embolic, global ischemic), hemorrhagic (intracer ebral, subarachnoid)
- 5. How to manage the patient? Thrombolytics?

#### PATHOPHYSIOLOGIC STROKE CLASSIFICATION

- THROMBOTIC STROKE
  - LARGE VESSEL STROKE most commonly due to atherothrombosis. Found at bifurcation of com mon 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
  - SMALL VESSEL STROKE (lacunar/penetrating ves sels) most commonly due to lipohyalinotic occlusion related to hypertension and occasion ally atheroma at the origin of vessels. Found at penetrating branches of the anterior, middle, and posterior cerebral and basilar arteries

#### · CARDIOAORTIC EMBOLIC STROKE

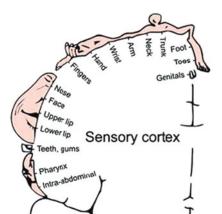
- CARDIAC SOURCES DEFINITE (antithrombotic ther apy generally used) LV thrombus, LA throm bus, rheumatic valve disease, artificial valve (mechanical, bioprosthetic), AF
- CARDIAC SOURCES DEFINITE (anticoagulation hazar dous) bacterial endocarditis, atrial myxoma
- CARDIAC SOURCES POSSIBLE mitral annular calci fication, left ventricular dysfunction, status post MI, LA spontaneous echo contrast, PFO, ASD, mitral valve strands

#### PATHOPHYSIOLOGY (CONT'D)

- 4. UNKNOWN SOURCE EMBOLIC STROKE
- 5. **OTHERS** dissection, moyamoya, primary thrombosis, cerebral mass

#### **RISK FACTORS FOR STROKE**

- THROMBOTIC age, smoking, diabetes, dyslipidemia, hypertension, family history, male, history of TIA
- EMBOLIC smoking, diabetes, dyslipidemia, hyper tension, family history, male, history of heart dis ease (valvular, AF, endocarditis)
- ICH hypertension, trauma, bleeding diatheses, illicit drugs, vascular malformations, blacks, Asians



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#### CLINICAL FEATURES

**TRANSIENT ISCHEMIC ATTACK** defined as an ischemic episode with full recovery within 24 h. Most TIAs last <5 min, while most ischemic attacks >1 h are associated with infarction. Risk of stroke in patients with TIA is 5% within 2 days and 10% within 90 days

#### PREDICTION OF STROKE RISK AFTER TIA

- ★ABCD2★ CRITERIA
  - **A**ge 1=age >60 years,
  - Blood pressure 1=hypertension at the acute evaluation >140/90 mmHg)
  - Clinical features 2=unilateral weakness,
     1 = speech disturbance without weakness
  - **D**uration 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 neces sary without another indication such as new onset atrial fibrillation

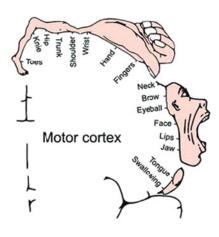
#### PATHOPHYSIOLOGY (CONT'D)

SAH illicit drugs, bleeding diatheses

**COMPLICATIONS OF STROKE** about 25% of patients can worsen during the first 24 48 h after stroke

- NEUROLOGIC cerebral edema, seizures, hemorrha gic transformation of infarction with or without hematoma, neurological deficits
- NON-NEUROLOGIC myocardial infarction, arrhyth mia, aspiration, pneumonia, DVT, pulmonary embolism, malnutrition, pressure sores, orthopedic complications, contractures

#### MAP OF MOTOR/SENSORY CORTEX



### **CLINICAL FEATURES (CONT'D)**

- MODERATE RISK (scores 4 5)=risk of stroke 4.1% at 2 days. Hospital observation justified in most situations
- HIGH RISK (scores 6 7)=risk of stroke 8.1% at 2 days. Hospital observation recommended

#### CLINICAL STROKE CLASSIFICATION

- ANTERIOR CEREBRAL ARTERY (embolic >thrombotic) motor and sensory deficit (leg >face, arm), frontal release signs (grasp, snout, root, and suckling reflexes), abulia, paratonic rigidity, gait apraxia, personality  $\Delta$
- MIDDLE CEREBRAL ARTERY (left dominant hemi spheric, embolic >thrombotic) aphasia, right hemiparesis, and sensory deficit (face, arm >leg), may be complete hemiplegia if internal capsule involved, right spatial neglect, right homonymous hemianopia, impaired right conjugate gaze
- MIDDLE CEREBRAL ARTERY (right non dominant hemi spheric, embolic >thrombotic) anosognosia, left motor and sensory deficit (face, arm >leg), left spatial neglect, left homonymous hemianopia, impaired left conjugate gaze

Acute Stroke Syndromes 301

#### 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, lan guage, 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 (thala
  mus), third nerve palsy, paresis of vertical eye

### CLINICAL FEATURES (CONT'D)

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), dysconju gate 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+	ĹR
5.5	0.39
LR+	Prob. stroke
0.14	1.5%
	≥10%
40	80%
	5.5 <b>LR+</b> 0.14

NIH STROKE SCALE level of consciousness (0=alert, 1=not alert, 2=obtunded, 3=unresponsive, level of consciousness questions (0=answers both correctly, 1=answers one correctly, 2=answers neither correctly), level of consciousness commands (0=performs both tasks correctly, 1=performs one task correctly, 2=performs neither task), gaze (0=normal, 1=partial gaze palsy, 2=total gaze palsy), visual fields (0=no visual loss, 1=partial hemianopsia, 2=complete hemianopsia, 3=bilateral hemianopsia), facial palsy (0=normal, 1=minor paralysis, 2=partial paralysis, 3=complete paralysis), left motor arm (0=no drift, 1=drift before 5 s, 2=falls before 10 s, 3=no effort against gravity, 4=no movement), right motor arm (0=no drift, 1=drift before 5 s, 2=falls before 10 s, 3=no effort against gravity, 4=no movement), right 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  $\rightarrow$  prehospital assessment  $\rightarrow$  in hospital assessment  $\rightarrow$  if likely stroke, assess with NIH stroke score, perform neuroimaging and laboratory tests to exclude stroke mimics  $\rightarrow$  begin stroke treatment. "The accurate determination of stroke subtype requires neuroimaging to distinguish ischemic from hemorrhagic stroke. Early mortality increases among those with any one of impaired consciousness, hemiplegia, and conjugate gaze palsy (LR+ 1.8, LR 0.36)"

JAMA 2005 293:19

#### **Related Topics**

CT Head (p. 333)

Dysphagia (p. 112)

#### CLINICAL FEATURES (CONT'D)

# RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE A CLINICALLY IMPORTANT CAROTID BRUIT?

	Sens	Spc	LR+
Ability of carotid bruits to indicate carotid stenosis in symptomatic patients			
TIA patients with >50% stenosis	29%	88%	2.4
Anterior circulation TIA patients with 75 99% stenosis	76%	76%	3.2
Anterior circulation TIA patients with 70 99% stenosis	62%	61%	1.6

**APPROACH** "although the presence of a carotid bruit in a patient with carotid territory TIA/stroke increases the probability that the underlying stenosis is high grade (and therefore amenable to endarterectomy), the accuracy of this physical finding is low. Accordingly, carotid bruit cannot be used to rule in or rule out surgically amenable carotid artery stenosis in symptomatic patients. Asymptomatic preoperative bruits are not predictive of increased risk of perioperative stroke. However, they may be harbingers of transient postoperative cognitive and behavioral abnormalities"

JAMA 1993 270:23

#### CLINICAL FEATURES (CONT'D)

#### **CLINICAL CLUES TO DIAGNOSIS**

- THROMBOTIC stuttering progression with periods of improvement. Lacunes develop over hours or at most a few days; large artery ischemia may evolve over longer periods. May have neck bruit or prior TIAs
- EMBOLIC sudden onset with deficit maximal at onset. Clinical findings may improve quickly. Can be precipitated by getting up at night to urinate, or sudden coughing or sneezing
- ICH gradual progression over minutes to hours.
   May be precipitated by sex or physical activities
- SAH abrupt onset, severe headache, focal brain dysfunction less common. May be precipitated by sex or other physical activity

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, troponin, CK, PTT, INR, AST, ALT, ALP, bilirubin, total chol, TGL, LDL, HDL, homocysteine, ESR
- IMAGING CT head without contrast, MRI head (more sensitive than CT head in detecting acute ischemic stroke), angiogram (CT, MR, contrast), carotid dopplers, echocardiogram (TEE >TTE)

#### **SPECIAL**

- ECG ST depression, QT prolongation, inverted T. prominent U waves
- EEG if seizures
- TOXICITY SCREEN

#### DIAGNOSTIC AND PROGNOSTIC ISSUES

**DOMINANT HEMISPHERE** the left hemisphere is dominant (language functions) in 95% of right handed and 70% of left handed individuals

CT HEAD gold standard, but relatively insensitive in detecting acute and small cortical or subcortical infarc tions, especially in the posterior fossa. Early signs (within 6 h) of MCA infarction include hyperdense middle cerebral artery sign (thrombus or embolus in

#### DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

first portion of MCA), **loss of gray white differentia tion in the cortical ribbon** (especially at the lateral margins of the insula), or lentiform nucleus and **sul cal effacement.** Hypodense lesions may not appear until after 24 h. They become more hypodense overtime

**MORTALITY RATE** 30 day mortality post ischemic stroke is 10 17%

**PROGNOSTIC MARKERS** age, degree of neurolo gical deficit (NIH stroke scale), extent of stroke on CT, fever

#### MANAGEMENT

ACUTE ABC, O2, IV, do not treat blood pressure unless extreme (hypertensive encephalopathy or >220/120 mmHg, then labetalol 40 80 mg IV g10min or 200 400 mg PO BID until BP <185/110 mmHg). Thrombolytics (if within 4.5 h of onset of ischemic stroke, see below; alteplase 0.9 mg/kg IV). Anticoagula tion is not indicated unless embolic stroke with obvious cardiac source (e.g. atrial fibrillation) or dissec tion (to be initiated 7 10 days after stroke). ASA 160 325 mg PO daily (if thrombolytics given, may start ASA after first 24 h. For long term secondary prophylaxis. consider clopidogrel, ASA/persantine, or dipyrida mole if cannot tolerate or failed ASA). If SAH, consider nimodipine. Neurology or neurosur gery consult. Early mobilization/rehabilitation with multi disciplinary team management (e.g. swallowing assessment, physiotherapy, occupa tional therapy). Monitor complications and treat other cardiovascular risk factors

#### TREATMENT ISSUES

#### THROMBOLYSIS

 INCLUSION clinical diagnosis of ischemic stroke, age 18 80 years, onset of symptoms within 4.5 h, measurable neurological deficit, stroke symptoms present for at least 30 min with no significant improvement before treatment Acute Stroke Syndromes 303

#### 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, Gl/GU bleed <21 days, arterial puncture in non compressible site <7 days, combination of previous stroke and DM, oral anticoagulant treat ment, 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 Ml/post MI pericarditis, persistent hyperten sion ≥185/110), labs (platelet <100 × 10³/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

#### TREATMENT ISSUES (CONT'D)

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 out come in 52.4% compared to 45.2% in non treated patients, with an increased risk of intracranial hemorrhage, but no effect on mortality

	ION FOR ISCHEMIC STROKE/TIA	
Condition	Primary prophylaxis	Secondary prophylaxis
Hypertension	Anti HTN 20%	Anti HTN 28%
Hyperlipidemia	Statins	Statins
Atrial fibrillation	ASA 20 30%	ASA 20 30%
	Coumadin 60%	Coumadin 60%
Post MI	ASA 31%	ASA
Post stroke	No needed if no previous stroke	ASA 30%
		Clopidogrel 43%
		ASA/persantine 43%
The percentages in this t	able represent relative risk reduction	

CRITERIA FOR CAROTID ENDARTERECTOMY				
Carotid stenosis	Symptomatic	Asymptomatic		
≥70%	Yes (NNT 6.3)	Yes for men with stenosis $\geq$ 60% only (NNT 33)		
50 69%	Yes for men only (NNT 22)			
<50%	No	No		
AND I I I I I I I I I I I I I I I I I I I				

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

LESION2		
	Upper motor neuron	Lower motor neuron
Inspect	Atrophy after long term	Atrophy and fasciculations
Tone	Spasticity	Flaccidity
Strength	Upper limbs flexors >extensors pronation >supination Lower limbs extensors >flexors	Nerve root/peripheral nerve distribution
Reflex	Increased with clonus Babinski upgoing	Decreased Babinski downgoing
Pronator drift	Present	Absent

#### SPECIFIC ENTITIES (CONT'D)

#### APHASIA (LANGUAGE IMPAIRMENT)

- TESTING PHRASES
  - COMPREHENSION WITHOUT REPLY "Touch your chin, then your nose, then your ear"

#### SPECIFIC ENTITIES (CONT'D)

- COMPREHENSION WITH ANSWERS "Do you put your shoes on before your socks?"
- FLUENCY "Describe your daily activities."
- NAMING "Name this object." (e.g. pen)
- REPETITION "No ifs, ands, or buts."

SPECIFIC ENTITIES (CONT'D)						
DISTINGUISHING FEATURES BETWEEN						
DIFFERENT TYPES OF APHASIA  Wernicke Broca's Global						
Comprehension	No	Normal	No			
Fluency	Normal	No	No			
Naming	No	No	No			
Repetition	No	no	No			
Others Contralat.						
sensory/						
		motor $\Delta$				

#### DYSARTHRIA (SPEECH IMPAIRMENT)

- DYSARTHRIA speech disorder resulting from dis turbances in muscular control that affect res piration, articulation, phonation, resonance, or prosody
- DYSPHONIA voice disturbance in parameters of vocal quality, pitch, or intensity

Types of dysarthria	Quality
Spastic (hemispheric	Harsh, strained voice
stroke cranial	Low pitch voice
nerves LMN)	

SPECIFIC ENTITIES (CONT'D)				
Types of dysarthria	Quality			
Hyperkinetic (basal	Harsh, strained voice			
ganglia lesion)	Low pitch voice			
	Voice stoppages			
Hypokinetic	Hoarseness			
(Parkinson's)	Low volume			
Ataxic (cerebellar lesion)	Explosive, scanning speech			
Flaccid	Breathy, nasal, low volume			
(cranial nerves VII, IX, X)	Wheezing			

#### PRIMITIVE REFLEXES

- **GRASPING REFLEX** deep pressure over palmar sur face results in grasp response
- **SUCKLING REFLEX** insertion of an object into mouth results in sucking motion
- ROOTING REFLEX gentle stroking of cheek results in mouth turning toward that side
- **SNOUT REFLEX** gentle pressure over the nasal phil trum results in puckering of lips
- GLABELLAR TAP REFLEX repeated tapping forehead produces persistent blinking

Cra	Cranial Nerve Examination					
CN	Nucleus location	Skull exit	Abnormalities			
1	Olfactory tract	Cribriform plate	Sensory smell (coffee, vanilla, peppermint)			
II	Thalamus	Optic foramen	Sensory visual acuity and color, visual fields, blind spot, fundoscopy Reflex pupillary reflex (afferent)			
III	Midbrain	Superior orbital fissure <sup>b</sup>	Motor ptosis and eye deviated downward and outward. Poor medial elevation and accommodation <sup>d</sup> Reflex pupillary reflex (efferent) Parasympathetic pupillary dilation <sup>d</sup>			
IV	Midbrain	Superior orbital fissure b	Motor patient tilts head to contralateral side, vertical diplopia worst looking to one side and down			
V	Principal Pons Spinal Medulla Mesencephalic Pons/ midbrain Motor Pons	V1 superior orbital fissure <sup>b</sup> V2 foramen rotundum V3 foramen ovale	Sensory light touch, pain and temperature over V1, V2 and V3 <sup>e</sup> Motor wasting of temporal and masseter muscles, weakness of jaw movement  Reflex corneal reflex (afferent) and jaw jerk (afferent and efferent)			
VI VII <sup>a</sup>	Pons Motor, solitary, superior salivatory Pons	Superior orbital fissure <sup>b</sup> Motor internal acoustic meatus <sup>c</sup> and stylomastoid foramen Taste stylomastoid foramen	Motor crossed eyes, impaired lateral gaze Sensory numbness around the ear canal and altered taste (anterior 2/3 of tongue) Motor difficulty raising eye brows, closing eyes, frowning, blowing out cheeks and showing teeth. Altered speech ('Pa Pa Pa") and hyperacusis Reflex Corneal reflex (efferent) Parasympathetic lacrimation and saliva production <sup>f</sup>			

Cranial Nerve Examination 305

	Cra	nial Nerve Examina	ation (Cont'd)				
	CN	Nucleus location	Skull exit	Abnormalities			
VIII Vestibular, cochlear medulla			Internal acoustic meatus <sup>c</sup>	Sensory whispering, Rinne's test, Weber's test.  Dix Hallpike maneuver (if vertigo). Check for nystagmus			
	IX	Nucleus ambiguous, inferior salivatory,	Jugular foramen	Sensory sensation of palate, taste (posterior 1/3 of tongue)			
		solitary medulla		Motor uvula and palate movement. Speech ('Ka Ka Ka"), coughing, swallowing			
	V	M. d	1 . 1 . 6	Reflex gag reflex			
	X	Nucleus ambiguous, dorsal motor vagal, solitary medulla	Jugular foramen	Sensory sensation of palate  Motor uvula and palate movement. Speech ('Ka  Ka Ka,' hoarseness), coughing, swallowing			
				Reflex gag reflex			
	XI	Nucleus ambiguous medulla Spinal accessory cervical cord	Jugular foramen	Motor weakness with shrugging shoulders and rotating head against resistance			
XII <sup>a</sup> Medulla			Hypoglossal canal	Motor tongue wasting and fasciculations, tongue deviation (toward affected side). Altered speech ("La La La")			

<sup>&</sup>lt;sup>a</sup> **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

- <sup>b</sup> CAVERNOUS SINUS LESIONS (tumor, aneurysm, and thrombosis) may lead to III, IV, V1 and VI palsies
- <sup>c</sup> CEREBELLOPONTINE ANGLE LESIONS (acoustic neuroma, glomus tumor) may lead to V1 3, VII, and VIII palsies
- <sup>d</sup> **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)
- <sup>e</sup> 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 (syringo bulbia, PICA infarction). Loss of light touch but not pain/temperature suggests pathology of pontine nuclei (tumor, vascular lesion)
- f FACIAL (VII) NERVE LESIONS for details on localization, please refer to p. 307

#### SPECIFIC ENTITIES

#### VISUAL FIELD DEFECTS

- MONOCULAR VISUAL LOSS lesion is located before optic chiasm (optic nerve, eye pathology)
- BITEMPORAL HEMIANOPIA lesion is at the optic chiasm. The pituitary gland lies below the optic chiasm. An adenoma may compress the optic chiasm inferiorly, causing superior bitemporal quadranopsia and eventually complete bitemporal hemianopia
- HOMONYMOUS HEMIANOPIA lesion is located post optic chiasm
- FORMAL VISUAL FIELD TESTING Goldman perimeter

## SPECIFIC ENTITIES (CONT'D)

## OCULAR FINDINGS IN HYPERTENSION AND DIABETES

- HYPERTENSION see p. 57
- DIABETES see p. 337

### **Related Topics**

Diplopia (p. 306) Dysarthria (p. 304)

Facial Droop (p. 307)

Ptosis (p. 318)

SPECIFIC ENTITIES (CON	T'D)		·		
DISTINGUISHING FEA	TURES BETWEEN PAPILLEDE	MA, OPTIC ATROPHY, A	ND OPTIC NEURITIS		
Paj	oilledema	Optic atrophy	Optic neuritis		
Etiology ↑ IC	TP	Neuritis	Multiple sclerosis		
Tur	nors Hypertension	Glaucoma			
		Congenital			
Symp Hea	ndaches	↓ vision	↓ vision		
N&	I, ↓ level of consciousness	↓ color	↓ color		
Foo	al deficits		Eye pain		
Optic disc Swe	Optic disc Swollen optic disc Gray wh Disc margins obscured		Swollen optic disc		
Dis					
Other signs Flai	Flame hemorrhages \( \preceq \ ac		↓ acuity		
Cot	ton wool spots	↓ color vision	↓ color vision		
↑ b	lind spot	↓ pupil reflex	↓ pupil reflex		
			↑ blind spot		
MEDULLARY SYNDRO	MES				
	Medial (Dejerine synd	rome) Lateral (Wall	enberg syndrome)		
Artery supply	Anterior spinal artery		ior cerebellar artery		
Cranial nerve (ipsilatera	'		V		
cramar retre (ipsilateral)		*	•		
		, ,	IX, X dysphagia, hoarseness, altered taste		
		Sympathetic			
Motor (contralateral)	UMN weakness	None			
Sensory (contralateral)	↓ vibration, propriocept	ion   pain and ter	mperature		
Cerebellum (ipsilateral)		Affected	·		

## **Diplopia**

### DIFFERENTIAL DIAGNOSIS

**BINOCULAR DIPLOPIA** (resolves with one eye closed, suggestive of ocular misalignment)

- CRANIAL NERVES III, IV, VI palsy, internuclear ophthalmoplegia
- RECTUS MUSCLES myasthenia gravis, trauma MONOCULAR DIPLOPIA (persists with one eye closed, suggestive of intrinsic eye disease)
- CORNEA deformity, keratoconus
- LENS cataract, displaced lens

EVERACELL AR EVE MOVEMENTS

RETINA macular scarring

#### PATHOPHYSIOLOGY

EXTRAOCOLAR ETE MOVEMENTS						
Muscle	Nerve	Movement				
Superior rectus	III	Upward				
Inferior rectus	III	Downward				
Lateral rectus	VI	Lateral				
Medial rectus	III	Medial				
Superior oblique	IV	Downward medial				
Inferior oblique	III	Upward medial				

### CLINICAL FEATURES

HISTORY determine whether diplopia resolves with one eye closed, which direction diplopia is worse, whether separation of images occur vertically, horizontally, or obliquely, whether any head position makes diplopia better, and whether diplopia is worse at distance (typically VI palsy) or near (typically med ial 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 abra sion, cataract, ptosis (III nerve palsy, myasthenia gravis), eyelid retraction (thyroid ophthalmopathy), and extraocular eye movements (each eye individu ally, 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)

Bell's Palsy 307

## 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 longitudi nal fasciculus (MLF), which connects the ipsilateral VI nucleus with the contralateral III nucleus
- **CAUSES** multiple sclerosis (bilateral), brain stem infarc tion (unilateral), infections, malignancy, metabolic
- CLINICAL FEATURES horizontal eye movement with weak adduction of the ipsilateral eye and abduc tion nystagmus of the contralateral eye

## **Bell's Palsy**

## NEJM 2004 351:13

## CAUSES OF FACIAL DROOP

**CENTRAL** (upper motor neuron) stroke **PERIPHERAL** (lower motor neuron)

- PONS infarction, glioma, multiple sclerosis
- CEREBELLOPONTINE ANGLE acoustic or facial neu roma, meningioma, cholesteatoma, lymphoma, aneurysm, sarcoidosis
- INTERNAL AUDITORY CANAL PROXIMAL TO OR INVOL-VING GENICULATE GANGLION Bell's palsy, Ramsay Hunt syndrome (VZV), acoustic or facial neuroma
- DISTAL TO INTERNAL AUDITORY CANAL AND GENICU-LATE GANGLION Bell's palsy, temporal bone frac ture, 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 inner vated by both cerebral hemispheres, while the lower facial muscles are only innervated by the contralateral cerebral hemisphere. Thus, an upper motor neuron lesion would spare the upper face, while a lower motor neuron lesion would lead to ipsilateral upper and lower facial weakness

#### CLINICAL FEATURES

## DISTINGUISHING FEATURES BETWEEN UPPER AND LOWER MOTOR NEURON FACIAL NERVE LESIONS

Central (stroke) Peripheral (Bell's palsy)
Lesion Contralateral cortex or corticobulbar Ipsilateral facial nerve nucleus or facial

fibers nerve

Upper facial muscles Furrows present No furrows
Can close eves Cannot close eves

Lower facial muscles Unable to show teeth Unable to show teeth

Hemiplegia (same side as palsy)

Salivation, taste, and Normal

lacrimation

<sup>a</sup> 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

Other findings

#### 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 paraly sis after 1 week of treatment

## DIAGNOSTIC AND PROGNOSTIC ISSUES FOR BELL'S PALSY

**Hyperacusis** 

Varies depending on lesion location<sup>a</sup>

**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

308 Multiple Sclerosis

#### MANAGEMENT OF BELL'S PALSY

**TREAT UNDERLYING CAUSE** prednisone 1 mg/ kg PO  $\times$ 7 days (given within 3 days of onset). For severe facial weakness, consider valacyclovir 1 g PO TID  $\times$ 7 days. Surgical decompression (only if documented 90% nerve degeneration by electroneurography)

#### SPECIFIC ENTITIES

RECURRENT OR BILATERAL FACIAL PALSY Guil lain 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 mea tus may be present. Taste often affected

## **Multiple Sclerosis**

#### **DIFFERENTIAL DIAGNOSIS**

**INFLAMMATORY DISEASES** Devic's neuromyeli tis (neuromyelitis optica, combination of optic neuritis and cervical myelopathy), acute dissemi nated encephalomyelitis, SLE, PAN, Sjogren's, Beh cet's disease, granulomatosis angiitis, paraneoplas tic encephalomyelopathies

**INFECTIONS** Lyme neuroborreliosis, neurosyphi lis, HIV, HTLV 1, PML (JC virus)

GRANULOMATOUS DISEASES sarcoidosis, Wege ner granulomatosis, lymphomatoid granulomatosis DISEASES OF MYELIN adult metachromatic leu kodystrophy, adrenomyeloleukodystrophy

**OTHERS** vitamin B12 deficiency, Arnold Chiari malformation, spinocerebellar disorders

#### PATHOPHYSIOLOGY

**MULTIPLE SCLEROSIS** autoimmune demyelina tion 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 relap sing remitting period
- PROGRESSIVE—RELAPSING relapsing course, but with overall progression following each relapse

**EXACERBATIONS** new neurological deficit or reap pearance/worsening of old deficit that lasts longer than 24 h and is not due to fever or other systemic process **PSEUDO EXACERBATIONS** transient fluctuations in neurological function due to concomitant illness (e.g. UTI), heat, or exertion that typically resolve with removal of precipitant

#### CLINICAL FEATURES

**CRANIAL NERVES** optic neuritis (afferent pupillary defect), diplopia (internuclear ophthalmoplegia, especially if bilateral), trigeminal neuralgia, other cranial nerves

#### CLINICAL FEATURES (CONT'D)

SENSORY (most common) paresthesia, dysesthesia, hyperesthesia. Pain syndromes include trigeminal neuralgia, Lhermitte's sign (lightening bolt radiating down neck with flexion), dysesthetic pain, back pain, visceral pain, and painful tonic spasms. May be migra tory (contralateral, ascending). Other sensory changes include useless hand syndrome (loss of discriminatory function and proprioception), "cold water" trickling feeling along limb, and pseudoathetosis (loss of sen sory 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 pro cessing, memory loss, and difficulties with abstract concepts and complex reasoning

**FATIGUE, DEPRESSION** 

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, Ca, Mg, PO<sub>4</sub>, CK, quantitative lg, ANA, ENA
- IMAGING MRI head/spine (sens 90%)
- LUMBAR PUNCTURE with CSF IgG index and oli goclonal 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  $\geq 2$  attacks, with clinical or laboratory evidence of  $\geq 2$  CNS lesions. The newer McDonald criteria incorporate MRI evidence of multiple sclerosis for diagnosis (lesions disseminated by time and space)

Seizures 309

#### DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

**PROGNOSIS** most patients initially in relapsing remit ting 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 RE MITTING MULTIPLE SCLEROSIS >2 exacerba tions/year, motor/cerebellar exacerbations, older age at onset (greater than 40 years), residual motor/cerebellar deficits 6 months following attack, moder ate disability within 5 years, number of lesion of MRI GOOD PROGNOSTIC FACTORS IN RELAPSING RE MITTING MULTIPLE SCLEROSIS initial presenta tion optic neuritis, purely sensory disorder, normal MRI

#### MANAGEMENT

## **EXACERBATIONS** methylprednisolone

500 1000 mg IV daily  $\times$ 3 5 days. **Plasma exchange IMMUNOTHERAPY**  $\star$  **ABCR** $\star$  drugs **A**vonex (interferon  $\beta$  1a 30  $\mu$ g IM weekly), **B**etaseron

#### MANAGEMENT (CONT'D)

(interferon  $\beta$  1b 250  $\mu$ g SC q2days), Copaxone (glatir amer acetate 20 mg SC daily), Rebif (interferon  $\beta$  1a 22 44  $\mu$ g SC three times a week). Natalizumab (monoclonal antibody against leukocyte  $\alpha$ 4 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 sec ondary progressive disease

**SYMPTOM CONTROL fatigue** (*amantadine* 100 mg PO BID), **spasticity** (physiotherapy, baclofen, tizanidine, benzodiazepines), **hyperreflexic bladder** (fluid restriction, timed voiding, oxybutynin, pro pantheline, imipramine, intermittent catheterization)

#### **Related Topics**

Cranial Nerve Lesions (p. 304) Orthostatic Hypotension (p. 312)

## **Dementia**

See DEMENTIA (p. 378)

## **Delirium**

See DELIRIUM (p. 380)

#### Seizures

NEJM 2008 359:2

## **DIFFERENTIAL DIAGNOSIS**

#### UNPROVOKED EPILEPTIC SEIZURES

- **PRIMARY EPILEPSIES** absence, generalized tonic clonic, juvenile myoclonic
- STRUCTURAL stroke (infarction), head trauma, brain tumors, neuro degenerative disorders
- INFECTIONS encephalitis
- **CONGENITAL** neuronal migration errors and cor tical dysgenesis, vascular malformations

#### PROVOKED EPILEPTIC SEIZURES

 DRUGS withdrawal (benzodiazepine, alcohol), overdoses (methanol, ethylene glycol, TCAs), illicit drug use (cocaine, amphetamines, LSD)

## DIFFERENTIAL DIAGNOSIS (CONT'D)

emotional trauma

- METABOLIC hypoglycemia, non ketotic hyper glycemia, hyponatremia, hypocalcemia, uremia, hypoxia (cerebral anoxia), hyperthyroidism
- INFECTIONS meningitis, febrile seizures
- OTHERS arrhythmia, acute intermittent porphyria
   PSYCHOGENIC NON EPILEPTIC (PSEUDOSEI-ZURES) stressful psychological conflicts, major

**SEIZURE MIMICS** syncope, TIA, migraine, benign positional vertigo, hypoglycemia, sleep disorders (sleep apnea, narcolepsy/cataplexy, night terrors, nightmares, nocturnal myoclonus), periodic paraly sis, breath holding spells

310 Seizures

#### 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 conscious ness) temporal, e.g. automatisms
- GENERALIZED SEIZURES (loss of consciousness) tonic clonic, clonic, tonic, myoclonic, absence, or atonic

## PATHOPHYSIOLOGY (CONT'D)

#### TYPES OF EPILEPSIES

- LOCALIZATION RELATED frontal lobe, temporal lobe, parietal lobe, occipital lobe
- GENERALIZED juvenile absence epilepsy, juvenile myoclonic epilepsy, infantile spasms

COMPLICATIONS OF SEIZURES aspiration pneu monia, 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

DISTINGUISHI	NG FEATURES BETWEEN SEIZURES AND SYNCO	PE
	Generalized seizures	Vasovagal syncope
Past history	Seizures, head injury, stroke, tumor	No strong history
Pre event	Awake or sleep	Usually upright
	No warning	Usually warning
	Aura	Lightheaded
Event	Vocalization at onset	No vocalization
	Tonic clonic convulsions	Occasional clonic movements, hypotonia
		Pale
	Cyanotic/gray	Incontinence occasionally
	Incontinence frequent	Tongue biting rare (tip)
	Tongue biting (side)	Less commonly injured
	Frequent injuries (fall on face, #, dislocations)  Longer ↓ level of consciousness	Short ↓ level of consciousness
Post event	Confused, tired, sleepy	Alert
	Muscle ache	Diaphoretic

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, Ca, Mg, PO<sub>4</sub>, AST, ALT, ALP, bilirubin, albumin, CK, tropo nin, 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 pri mary 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 panence phalitis, 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 investiga tions (ABG, CBCD, lytes, Cr, glucose, Mg, Ca, PO<sub>4</sub>, toxic screen, antiepileptic drug level), glucose if hypoglyce mia (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 Seizures 311

#### 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 (lor azepam 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, carbamaze pine, valproate). If alcohol withdrawal (add thiamine 100 mg IV/PO daily, multi vitamin 1 tab IV/PO daily) LONG TERM MANAGEMENT valproic 200 500 mg or 10 15 mg/kg PO daily, increase dose by 250 500 mg/week, typical daily dose is 750 2000 mg; lamotrigine 25 mg PO daily, increase dose by 25 mg/week, typical daily dose is 100 400 mg; topiramate 25 50 mg PO daily, increase by 25 50 mg/week, typical daily dose is 200 400 mg; levetiracetam 250 500 mg PO daily, increase dose by 250 500 mg/week, typical daily dose 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 (load ing dose may be given for quicker effect), typical daily dose is 200 400 mg; gabapentin 300 mg daily BID, increase dose by 300 600 mg/week, typical daily dose is 1800 3600 mg; pregabalin 75 150 mg PO daily, increase dose by 75 150 mg/week, typical daily dose is 150 300 mg

**PSYCHOSOCIAL ASPECTS** loss of independence, employment, insurance, self esteem, and ability to drive

**DRIVING ISSUES** recommendations vary from region to region. Check with driving authority for specific restrictions and legal requirements. If single unprovoked seizure, usually no driving restrictions are needed as long as EEG and imaging are normal. If >1 unprovoked seizure, consider 6 12 months of seizure free interval before re instating driver's license (varies with jurisdiction). Some places may also restrict driving for 6 months after antiepileptic dose adjustments. More stringent rules may exist for commercial drivers

#### TREATMENT ISSUES

**FIRST TIME SEIZURE** if no structural lesion, no physical findings, and normal EEG, usually do not need to start antiseizure medications. Risk of

#### TREATMENT ISSUES (CONT'D)

recurrence after first seizure is 30 60%. Risk after second seizure is 80 90%

#### **ANTIEPILEPTIC CHOICES**

- BROAD-SPECTRUM ANTIEPILEPTIC DRUGS in decreas ing order of efficacy, include valproic acid, lamo trigine, topiramate, levetiracetam, and zonisamide. These antiepileptic medications represent reason able first line therapy for most seizure types
- NARROW-SPECTRUM ANTIEPILEPTIC DRUGS include carbamazepine, phenytoin, gabapentin, tiaga bine, oxcarbazepine, and pregabalin. These med ications are effective against partial seizures with or without secondarily generalized features, but have limited activity against primary general ized seizures

	P	C	٧	В	L	G	Т	Ε
Tonic clonic	+	+	1	+	+	$\pm$		
Absence			+					1
Status	+			+				
Partial	+	1	+	+		$\pm$	+	
Myoclonic			+	+				

Key: P=phenytoin, C=carbamazepine, V=valproate, B=phenobarbital, L=lamotrigine, G=gabapentin, T=levetiracetam or topiramate, E=ethosuximide, 1=drug of choice, +=possible use, ±=adjunct use

**STOPPING ANTIEPILEPTICS** consider stopping anticonvulsants after a seizure free period of 2 5 years. Relapse is 26 63% within 1 2 years after with drawal. Risk factors for recurrence include abnormal EEG before or during withdrawal, abnormal neurolo gic findings, frequent seizures before remission, and mental retardation

**DRUG OR TOXIN INDUCED SEIZURES** top five drug induced etiologies include isoniazide, theophyl line, oral hypoglycemic agents, carbon monoxide, and bupropion. Supportive management for theo phylline induced, carbon monoxide induced, and bupropion induced seizures. Treat isoniazide induced seizures with pyridoxine; hypoglycemic sei zures with glucose  $\pm$  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) 312 Syncope

## Syncope

#### DIFFERENTIAL DIAGNOSIS

#### **★SVNCOPE**★

**SITUATIONAL** micturition, defecation, coughing, laughing

VASOVAGAL painful, emotional stimulus, head turning

**NEUROGENIC** vestibular stroke, seizures, auto nomic insufficiency

#### CARDIOGENIC

- conduction VT, AV block/Stokes Adams, pro longed QT, carotid sinus hypersensitivity (shav ing, tight collars)
- VALVULAR aortic stenosis, mitral stenosis, pul monary stenosis, tricuspid stenosis
- VASCULAR pulmonary hypertension, pulmonary embolism
- PERICARDIAL tamponade
- MYOCARDIAL myocardial infarction, hyper trophic cardiomyopathy

# ORTHOSTATIC PSYCHOGENIC ETC drugs

#### CLINICAL FEATURES

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

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

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

#### INVESTIGATIONS

## BASIC

- LABS CBCD, lytes, Cr/urea, CK, troponin
- IMAGING CXR, echocardiogram, carotid dop plers, CT head
- OTHERS ECG, 24 h Holter

#### INVESTIGATIONS (CONT'D)

#### SPECIAL

- **EEG** if suspect seizures
- STRESS TEST
- TILT TABLE TEST to confirm vasovagal syncope

#### MANAGEMENT

ACUTE ABC, 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 deci sions. If patient has any of 5 risk factors ★ CHESS★ CHF history, Hct <30, ECG abnormality, SBP <90 mHg, or 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 → exces sive peripheral venous pooling → decreased venous return → compensation with cardiac hypercontractile state → activation of mechanor eceptors (and this is seen by brain as hypertension like) causing paradoxical reflex bradycardia and drop in peripheral vascular resistance → decreased output to brain → syncope
- CLINICAL FEATURES pre syncope symptoms may include weakness, light headedness, diaphoresis, visual blurring, headache, nausea, and feeling warm or cold. Syncope lasts about 30 s to 5 min. Recovery is rapid with minimal postictal state
- DIAGNOSIS tilt table test (spc 90%), implantable loop recorders
- TREATMENTS lie down if pre syncope, adequate fluids and salt intake, SSRI (paroxetine 20 mg PO daily), vasoconstrictor (midodrine 2.5 10 mg PO TID), permanent cardiac pacing if recurrent

#### NEJM 2005 352:10

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

#### NEUROGENIC ORTHOSTATIC HYPOTENSION

 PATHOPHYSIOLOGY standing leads to pooling of blood (500 1000 mL) in legs → decreased venous Migraine Headaches 313

#### 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 resis tance and cardiac output. In orthostatic hypoten sion, 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, strenu ous exercises, high temperature, and meals

- CAUSES see autonomic neuropathy for more details (p. 327)
- CLINICAL FEATURES pre syncope symptoms may include weakness, light headedness, diaphoresis, visual blurring, headache, nausea and feeling warm or cold. Syncope lasts about 30 s to 5 min. Recovery is rapid with minimal postictal state

#### SPECIFIC ENTITIES (CONT'D)

- DIAGNOSIS SBP drop of ≥20 mmHg or DBP drop of ≥10 mmHg during first 3 min of standing, or a head up tilt on tilt table. Autonomic failure may be assessed by heart rate variability testing
- TREATMENTS gradual staged movements with postural changes, exercises, increase salt/fluid intake, elastic stockings, and minimize antihypertensive medication use. Medications include fludrocortisone 0.05 0.1 mg PO daily, midodrine, pseudoephedrine, ephedrine, DDAVP, and potentially pyridostigmine

NEJM 2008 358:6

#### **Related Topics**

Arrhythmia (p. 39)

Dizziness (p. 315) Falls (p. 382)

Stroke (p. 299)

Valvular Heart Disease (p. 47)

## **Migraine Headaches**

NEJM 2002 346:4; NEJM 2006 354:2

#### DIFFERENTIAL DIAGNOSIS OF HEADACHES

**VASCULAR** (primary) migraine, cluster, tension, medication overuse

**INFECTIONS** meningitis, encephalitis

**STRUCTURAL hemorrhage** (subarachnoid, epi dural, subdural, intracerebral), **thrombosis** (ischemic stroke, cerebral vein), **tumor**, **trauma** 

## DIFFERENTIAL DIAGNOSIS OF HEADACHES (CONT'D)

**OTHERS** sinusitis, temporal arteritis, pseudotu mor 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 ≤2 criteria)

	LIV!	-11	
Chronic headache features suggestive of serious intracranial abnormality requirin	g neuroimag	jing	
Cluster type headache	11	0.95	
Abnormal findings on neurologic examination	5.3	0.71	
Undefined headache	3.8	0.66	
Headache with aura	3.2	0.51	
Headache aggravated by exertion or a Valsalva like maneuver	2.3	0.7	
Headache with vomiting	1.8	0.47	

**APPROACH** "the presence of 4 simple historical features can accurately diagnose migraine. Headaches may be classified as new headache, acute thunderclap headache, or chronic headache. Neuroimaging may be done for new headaches at the discretion of physician. All acute thunderclap headaches should be investigated with neuroimaging and lumbar puncture. Chronic headaches with high risk features above should be investigated with neuroimaging. No clinical features were useful in ruling out significant pathologic conditions"

JAMA 2006 296:10

314 Migraine Headaches

#### CLINICAL FEATURES (CONT'D)

ALARM SYMPTOMS (suggesting secondary causes) "thunderclap headache," progressive head ache 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 dura tion of each episode as well as frequency are particularly important in making the diagnosis. Char acterize headaches (location, nature, intensity, radia tion, alleviation, and aggravation), precipitants (stress, food, physical activity), and any associated neurological symptoms. Consider temporal arteritis (jaw claudication, visual changes, temporal scalp ten derness) in the elderly, past medical history, current medications (especially headache medications)

**PHYSICAL** vitals. Neurological examination including visual fields and fundoscopy. Remember to check temporal arteries in the elderly

#### INVESTIGATIONS

## **BASIC**

- LABS CBCD, lytes, urea, Cr, ESR (temporal arter itis), INR, PTT
- IMAGING CT head, MRI head SPECIAL
- LUMBAR PUNCTURE

#### DIAGNOSTIC ISSUES

## INTERNATIONAL HEADACHE SOCIETY MIGRAINE CRITERIA

- 1. At least 5 attacks
- 2. Episodic attacks lasting 4 72 h
- Any 2 of unilateral pain, throbbing, moderate or severe intensity, pain aggravated by physical activity
- 4. Any 1 of N&V, photophobia, and phonophobia
- 5. Exclude secondary causes

## MANAGEMENT OF MIGRAINE HEADACHES

SYMPTOM CONTROL regularity in life activities (sleep, eat, exercise), first line agents (acetaminophen 650 mg PO q4h, ibuprofen 400 800 mg PO q6h), second line agents (dihydroergotamine 0.5 1 mg IV, setorolac 30 mg IV, sumatriptan 50 mg PO or 6 mg SC, naratriptan, rizatriptan, eletriptan, zolmitriptan), antie metics/dopamine antagonists (metoclopramide 10 mg IV, prochlorperazine 10 mg IV + 500 mL NS). Consider adding dexamethasone 10 2 5 mg IV or IM  $\times$ 1 with standard acute migraine therapy for patients in ER or clinic to reduce rate of early headache recurrence PROPHYLAXIS indicated if patient has  $\geq$ 3 attacks per month, severe prolonged attacks, or when poor

## MANAGEMENT OF MIGRAINE HEADACHES (CONT'D)

response to abortive medications. Choices include **tricyclic antidepressants** (*amitriptyline* 25 300 mg PO qhs, *desipramine* 25 200 mg PO qhs, nortripty line), **β blockers** (atenolol, propranolol, metoprolol, and nadolol), **anticonvulsants** (valproic acid, topir imate, gabapentin), **calcium channel blockers** (verapamil, flunarizine), **serotonin antagonists** (cyproheptadine, methysergide), **botulinum toxin** 

#### SPECIFIC ENTITIES

CHRONIC DAILY HEADACHES any headaches > 15 days per month for > 3 months. Risk factors include obesity, history of frequent headache (>1 per week), caffeine consumption, and overuse of acute head ache 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 mod erately severe, bilateral (band like), usually stress related. Treatments include stress reduction, tricyclic antidepressants for prophylaxis, and pain control PRN **CLUSTER HEADACHES** chronic daily headaches with up to 8x 1 h attacks each day lasting 4 8 weeks each episode, with 1 3 episodes per year. Extremely severe, mostly periorbital or temporal. Associated with autonomic symptoms (tearing, rhinorrhea), Horner syndrome (Horton headache), and motor restlessness **HYPNIC HEADACHES** chronic daily (only happens

**HEMICRANIA CONTINUA** constant exacerbations of severe headaches ('ice pick" pain), unilateral, cra nial autonomic symptoms. By definition, responsive to indomethacin

during sleep), moderately severe, bilateral

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 tran sient visual changes, papilledema and sometimes sixth nerve palsy
- DIAGNOSIS MRI/MRV (to exclude other causes such as cerebral vein thrombosis), lumbar punc ture with ↑ opening pressure (>250 mmH<sub>2</sub>O)
- TREATMENTS weight loss, NSAIDs for pain, furose mide, acetazolamide 250 mg PO QID, lumboperi toneal shunting, optic nerve sheath fenestration, serial neuro ophthalmologist follow up

Dizziness and Vertigo 315

## Meningitis

See MENINGITIS (p. 241)

## **Dizziness and Vertigo**

#### **DIFFERENTIAL DIAGNOSIS**

#### **VERTIGO**

- CENTRAL vertebrobasilar insufficiency, vertigi nous migraine (9%), multiple sclerosis, cerebel lopontine angle tumor, cerebellar hemorrhage, subclavian steal
- PERIPHERAL benign positional vertigo (30%), acute labyrinthitis/vestibular neuronitis (3%), acute recurrent peripheral vestibulopathy, Meniere's disease (6%), cholesteatoma drugs (aminoglycoside, phenytoin), acoustic neuroma, herpes zoster oticus, deep sea diving

#### DIFFERENTIAL DIAGNOSIS (CONT'D)

#### SYNCOPE/PRE SYNCOPE/ORTHOSTATIC HYPO TENSION see SYNCOPE (p. 312)

**IMBALANCE** spastic gait (infarction), apraxic gait (normal pressure hydrocephalus, frontal lobe dementia, Alzheimer's), ataxia gait (cerebellar dis order), shuffling gait (Parkinson's disease), sensory ataxia gait (decreased proprioception), Trendelen burg gait (proximal muscle weakness), steppage gait (impaired dorsiflexion)

**VAGUE DIZZINESS/LIGHT HEADEDNESS** panic attacks, hyperventilation, multisensory dizziness

## CLINICAL FEATURES

### RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE VERTIGO?

	PPV	NPV	LR+	LR	
History					
Positive head hanging maneuver plus either vertigo or vomiting	85%	68%	7.6	0.6	
predict peripheral vertigo					
Absence of vertigo or age >69 or presence of neurological deficit	40%	88%	1.5	0.3	
predict serious causes of dizziness					

**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 head edness, 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

- FI FCTRONYSTAGMOGRAPHY WITH CALORIC TESTING
- SYNCOPE WORKUP ECG, 24 h holter
- AUDIOMETRY

Peripheral

More sudden

Shorter duration

More severe

#### DIAGNOSTIC ISSUES

#### **DISTINGUISHING BETWEEN CENTRAL AND PERIPHERAL VERTIGO**

Central

Onset More gradual

Nystagmus Purely horizontal, vertical, rotational

Not inhibited by fixation onto object

Persists for a longer period

N&V Varies

Others Severe imbalance

Other non auditory cranial nerve

symptoms usually present

Tinnitus, hearing loss

Usually horizontal and rotational

Inhibited by fixation of eyes onto object

Tullio's phenomenon (nystagmus and vertigo

caused by loud noises at a particular frequency)

SPECIFIC ENTITIES (CONT'D)
 TREATMENTS may improve with canalith repositioning maneuvers (e.g. Epley maneuver). Usually

#### **MIGRAINOUS VERTIGO**

 CLINICAL FEATURES vertigo (typically minutes to hours, sporadically), photophobia, sonophobia, headache

#### **BRAIN STEM/LABYRINTH TIA**

• PATHOPHYSIOLOGY embolic/thrombotic phenomenon

self limited and resolves over months

- CLINICAL FEATURES vertigo (minutes to hours, sporadically), usually other neurological deficits such as facial sensory loss, diplopia, dysarthria, dysphagia, weakness, or numbness
- DIAGNOSIS CT head, MRI head

#### MÉNIÈRE'S DISEASE

- PATHOPHYSIOLOGY endolymphatic hydrops → distension of the labyrinthine system, compressing the perilymphatic spaces
- CLINICAL FEATURES vertigo (typically hours, spora dically), N&V, sensorineural hearing loss, tinnitus and aural fullness
- DIAGNOSIS 2 spontaneous episodes of vertigo (>20 min each), audiometric confirmation of sen sorineural hearing loss, tinnitus/aural fullness
- **TREATMENTS** betahistine, hearing aid use, intraco chlear gentamicin injection

## **ACUTE LABYRINTHITIS/VESTIBULAR NEURONITIS**

- PATHOPHYSIOLOGY labyrinthitis/vestibular neuro nitis secondary to viral infection
- CLINICAL FEATURES vertigo (typically days, spora dically) that may be precipitated by change in position (labyrinthitis) or spontaneous (vestibular neuronitis), severe N&V

## DIAGNOSTIC ISSUES (CONT'D)

MRI HEAD used to rule out acoustic neuroma, pos terior fossa tumors, stroke, or demyelinating disease. Indications include unexplained asymmetric sensori neural hearing loss with retrocochlear features, sud den and unexplained complete unilateral vestibular loss, or other brain stem signs or symptoms

## Related Topic

Syncope (p. 312)

## MANAGEMENT

SYMPTOM CONTROL benzodiazepines (diaze pam 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/epi sode, multiple episodes per day) usually precipi tated 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)

Hearing Impairment 317

## **Hearing Impairment**

#### DIFFERENTIAL DIAGNOSIS

SENSORINEURAL (inner ear to cortex) CVA, presbycusis, multiple sclerosis, Meniere's dis ease, 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?

THIS PATIENT HAVE HEARING IMPAIRMENT?				
	LR+	LR		
History				
Asking patients whether they have hearing impairment	2.5	0.13		
Hearing handicap inventory for the elderly (screening version) score of ≥8	3.8	0.38		
Physical				
Inability to perceive whispering	6.1	0.03		
Weber test	1.6 1.7	0.70 0.76		
Rinne test	2.7 62	0.01 0.85		
Investigations				

**APPROACH** "elderly individuals who acknowl edge they have hearing impairment require audio metry, while those who reply no should be screened with the whispered voice test. Individuals who per ceive the whispered voice require no further testing, while those unable to perceive the voice require audiometry. The Weber and Rinne tests should not be used for general screening"

Not passing the audioscope

test

JAMA 2006 295:4

0.07

#### CLINICAL FEATURES (CONT'D)

RINNE TEST 256 Hz tuning fork on mastoid pro cess, when vibration no longer heard, placed in line with external meatus. If can still hear (air conduction > bone conduction), either normal or sensorineural loss on that side. If cannot hear any more (bone conduction >air conduction), conductive hearing loss on that side

**WEBER TEST** 256 Hz tuning fork on bridge of 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. Hear ing amplifier** (stethoscope, electronic)

TREAT UNDERLYING CAUSE audiology and/or ENT consult

318 Myasthenia Gravis

## **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 ACETYLCHO LINE RECEPTOR leads to decreased neurotransmis

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),

#### CLINICAL FEATURES (CONT'D)

limb weakness, shortness of breath, symptoms better with rest and worse with prolonged use, past medical history (malignancy, trauma), medications

PHYSICAL vitals, pulmonary examination, mea sure palpebral fissure at rest and after upward gaze for 30 s, extraocular eye movements, orbicu laris oculi weakness (cannot bury eye lashes). Peek sign is positive when palpebral fissure can be seen after patient tries to gently close the eye lids), voice changes, assess for weakness of neck flexor, del toids, hip flexors, finger/wrist extensors, and foot dorsiflexors with repeated challenges. Sensory examination should be normal and reflexes should demonstrate fatigability

SPECIAL TESTS FOR MYASTHENIA GRAVIS ice test (improvement of ptosis with palpebral fissure increase of 2 mm after applying ice over eyelid for 2 min), sleep test (improvement of ptosis with palpebral fissure increase of 2 mm after resting in dark room for 30 min), curtain sign, lid twitch sign, cover uncover test (examiner covers one eye as patient fixates on a distant object. Observe for deviation of the uncovered eye during lateral and then upward gazing. With extraocular weakness, the uncovered eye will drift)

RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE MYASTHENIA GRAVIS?		
	LR+	LR
History		
Food in mouth after swallowing	13.0	0.70
Speech becoming unintelligible during prolonged speaking	4.5	0.61
Physical		
Peek sign	30	0.88
Ice test	24	0.16
Sleep test	53	0.01
Special tests		
Edrophonium test	15	0.11

**APPROACH** 'the presence of speech becoming unintelligible after prolonged periods and peek sign may be useful in confirming the diagnosis of myasthenia gravis, though their absence does not rule it out. The ice test, sleep test, and response to anticholinesterase agents (especially the edrophonium test) are useful in confirming the diagnosis, and reduce the likelihood when results are negative. A positive test result should prompt acetylcholine receptor antibody testing and specialist referral for electrophysiologic tests and should help confirm the diagnosis in patients who have negative results for the acetylcholine receptor antibody panel"

JAMA 2005 293:15

# DISTINGUISHING FEATURES BETWEEN HORNER'S SYNDROME AND THIRD NERVE PALSY Horner's syndrome Third nerve palsy Ptosis Partial. Never complete Partial or complete

Ptosis Partial. Never complete
Pupil size Constricted
Pupil asymmetry Worse in darkness
Pupil reflex Normal
Others Anhydrosis

Enophthalmos
Absent ciliospinal reflex
Heterochromia

Dilated Worse in light Sluggish or absent

Affected eye downward and outward

Ataxia 319

## 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</li>
- ANTIBODIES anti acetylcholine receptor anti body (sens 80 90%, very high spc), muscle spe cific receptor tyrosine kinase antibody
- SINGLE FIBER EMG WITH/WITHOUT REPETITIVE STIMULATION

#### MANAGEMENT OF MYASTHENIA GRAVIS

**MYASTHENIA GRAVIS** pyridostigmine 30 mg PO q3 6h. Thymectomy (controversial if no thymoma). Other treatments include corticosteroids, azathiopr ine, cyclosporine, mycophenolate, plasmapheresis, IVIG

**MYASTHENIC CRISIS** ICU admission, treat any pre cipitating infection, discontinue any anticholinester ase agents, correct electrolyte abnormality, monitor

#### MANAGEMENT OF MYASTHENIA GRAVIS (CONT'D)

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

#### **Related Topics**

Horner's Syndrome (p. 13) Thymoma (p. 189)

## Ataxia

#### DIFFERENTIAL DIAGNOSIS

#### **CEREBELLAR ATAXIA**

- HEMISPHERES/POSTERIOR LOBE SYNDROME (intention tremor, dysmetria, dysdiadochokinesia, slurred speech)
- SUPERIOR VERMIS/ANTERIOR LOBE SYNDROME (trun cal and gait ataxia) alcoholism and thiamine deficiency
- FLOCCULONODULAR LOBE SYNDROME (dysequili brium, 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

H&N

Motor

## DISTINGUISHING FEATURES BETWEEN CEREBELLAR DISORDER AND TABES DORSALIS (see p. 244)

Inspection Normal cognition Dementia if neurosyphilis

Ataxic speech
Nystagmus Argyll Robertson pupils

Scanning speech Optic atrophy Explosive speech

Hypotonia, dysmetria, dysdiadochokinesia, heel shin test, pendular reflexes Heel shin test

Absent reflexes (Westphal's sign)

Extensor plantar

**320** Parkinson's Disease

#### CLINICAL FEATURES (CONT'D)

Sensorv

## DISTINGUISHING FEATURES BETWEEN CEREBELLAR DISORDER AND TABES DORSALIS (see p. 244)

#### Cerebellar ataxia

Normal

Gait Truncal ataxia

Wide based gait

Romberg Positive with eyes closed and open

## CLINICAL FEATURES (CONT'D)

staggering), rebound (outstretched arms swing easily when pushed), pronator drift (upward), trun cal ataxia (Romberg's test shows unsteadiness with eyes both open and closed)

**Tabes dorsalis** 

Slap foot gait

Wide based gait

| vibration and proprioception

Positive with eyes closed only

#### INVESTIGATIONS

IMAGING CT/MR head

#### MANAGEMENT

TREAT UNDERLYING CAUSE

## CLINICAL FEATURES (CONT'D)

**HISTORY** characterize ataxia (truncal or limb, tim ing, progressive), speech changes, vision changes, incoordination, falls, headaches, nausea and vomit ing, weight loss, past medical history (alcohol use, stroke, multiple sclerosis, malignancy, Wilson's dis ease), medications, family history

**PHYSICAL** nystagmus, ataxic speech ("British constitution," explosive in volume, scanning), hypo tonia, dysdiadochokinesia, finger to nose test (dysmetria), heel shin test, pendular reflex, wide based stance, ataxic gait (wide based and

## **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 pos tural reflexes

#### **HYPERKINETIC**

- DYSTONIA/ATHETOSIS sustained muscle contraction, causing twisting and repetitive move ments/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, pur poseless movements. Ballismus is large ampli tude, proximal chorea, e.g. Huntington's chorea
- **PSEUDOATHETOSIS** chorea type movements sec ondary 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 exten sion of big toe
- RESTLESS LEG SYNDROME abnormal sensation in legs, especially at night
- ALIEN LIMB complex non volitional movements (reaching, grasping)
- TICS rapid, non rhythmic movement or sound on background of normal activity
- STEREOTYPY tardive dyskinesia
- AKATHISIA motor activity from voluntary effort to relieve uncomfortable sensation, mainly in daytime
- PHANTOM DYSKINESIA amputees
- HEMIFACIAL SPASM unilateral contraction of facial muscles involving eyelids, cheek, and corner of mouth
- STARTLE DISEASE OR HYPEREKPLEXIA, STIFF-PERSON SYNDROME continuous isometric contractions of somatic muscles

## PATHOPHYSIOLOGY

PARKINSONISM ★TRAP★ any 2 of Tremor, Rigidity, Akinesia/bradykinesia, and Postural instability.

Parkinson's Disease 321

#### PATHOPHYSIOLOGY (CONT'D)

Parkinson's disease is primary or idiopathic parkin sonism. Secondary or acquired parkinsonism may be due to head trauma, cerebrovascular disease, drugs, or hydrocephalus

**PARKINSONISM PLUS SYNDROMES** progressive supranuclear palsy, multiple system atrophy, Lewy body dementia, cortico basal ganglionic degeneration

#### CLINICAL FEATURES

#### PHYSICAL EXAMINATION FOR PARKINSON'S DIS

**EASE** resting tremor (4 6/s), rigidity, bradykinesia, micrographia, dementia, stare (reduced blink rate), mask face (hypomimia), glabellar tap, drooling, dys arthria, difficulty getting up from chair, postural instability, difficult with heel to toe walking, shuffling gait, and en bloc turn. Associated with disordered sleep, constipation, pain, and depression

#### CLINICAL FEATURES (CONT'D)

# DISTINGUISHING FEATURES BETWEEN PHYSIOLOGIC AND PSYCHOGENIC MOVEMENT DISORDERS

- HISTORY abrupt onset, static course, spontaneous remissions (inconsistency over time), obvious psychiatric disturbance, multiple somatizations, healthcare works, pending litigation or compensa tion, secondary gain
- PHYSICAL inconsistent character of movement (amplitude, frequency, distribution, selective disabil ity), 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 pla cebo, remission with psychotherapy

RATIONAL CLINICAL EXAMINATION	N SERIES: DOES THIS PATIENT	HAVE PARKINSON'S DISEASE?
	LR+	LR
History		
Tremor	1.3 17	0.24 0.60
Rigidity	1.3 4.5	0.12 0.93
Difficulty rising from chair	1.9 5.2	0.39 0.58
Loss of balance	1.6 6.6	0.29 0.35
Shuffling gait	3.3 15	0.32 0.50
Difficulty opening jars	6.1	0.26
Difficulty turning in bed	13	0.56
Micrographia	2.8 5.9	0.30 0.44
Physical		
Tremor	1.3 1.5	0.47 0.61
Rigidity	0.5 2.8	0.38 1.6
Bradykinesia	0.4 0.9	1.67 3.7
Heel to toe difficulties	2.9	0.32
Glabellar tap	4.5	0.13

**TESTING** glabellar tap (percussion of forehead for  $\sim$ 20 times. Normally blinking stops after 5 10 times. Persistent blinking suggests positive Myerson sign), **bradykinesia maneuvers** (tapping finger, twiddling like motor, pinching and circling, tapping with heel)

**APPROACH** "a combination of tremor, rigidity, bradykinesia, loss of balance, shuffling gait, micrographia, difficulty with turning in bed, opening jars, and rising from a chair should raise suspicion of Parkinson's disease. On examination, the diagnostic value of the classic combination of tremor, rigidity, bradykinesia is limited. Useful signs include the glabellar tap, difficulty walking heel to toe and rigidity"

JAMA 2003 289:3

DISTINGUISHING FEATURES BETWEEN VARIOUS TREMORS			
	Parkinson	Essential	Cerebellar
Tremor	Resting	Postural (action)	Intention (action)
Hertz	4 6	5 9	3 5
Head direction	Up down ("yes")	Side to side ("no')	None
Legs involved	Yes	Rare	Yes
Effect of alcohol	No change	Improved	No change

322 Parkinson's Disease

#### CLINICAL FEATURES (CONT'D)

#### CHARACTERIZING MOVEMENT DISORDERS

- SPEED slow (dystonia, athetosis, dystonic tics), moderate (chorea, tremor, asterixis), quick (myo clonus, 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, mus cle/nerve biopsy, lumbar puncture, genetic test ing (CAG repeats), and smear for acanthocytes if suspect Huntington's disease
- INFLAMMATORY WORKUP ESR, CRP, ANA, ENA, RF, ANCA, C3, C4, lupus anticoagulant, antiphospho lipid antibody, antistreptolysin O
- MALIGNANCY WORKUP quantitative immunoglo bulin, serum protein electrophoresis
- ENDOCRINE WORKUP TSH, PTH
- METABOLIC WORKUP copper, 24 h urinary cop per, vitamin B12, ceruloplasmin, RBC folate, lac tate pyruvate

#### MANAGEMENT

#### TREAT UNDERLYING CAUSE

- SINEMET carbidopa/levodopa 25/100 25/250 mg PO TID. Combined use with entacapone can lead to more sustained levodopa levels. See NEJM 2008 359:23 for details
- DOPAMINE AGONISTS bromocriptine 5 10 mg PO BID, pramipexole, ropinirole, pergolide. Ineffective in patients unresponsive to levodopa

#### MANAGEMENT (CONT'D)

- COMT and MAO B inhibitors entacapone 200 mg with each dose of levodopa, rasagiline 0.5 1 mg PO daily
- ANTICHOLINERGICS benztropine 0.5 2 mg PO BID
- AMANTADINE amantadine 200 300 mg PO daily
- APPROACH Sinemet should be first line therapy for most patients because of its effectiveness. COMT/MAO B inhibitors or dopamine agonists may be used in combination with Sinemet or as first line agent alone for young patients. Anticho linergics 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 dvskinesia

#### SYMPTOM MANAGEMENT

- GENERAL education, support, exercise, speech
- NAUSEA domperidone is safe as it does not cross the blood brain barrier. Avoid antidopaminergic medications such as metoclopramide and phe nothiazines (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

#### Type Pathology Spastic gait Upper motor neuron lesion (stroke)

Scissor gait Bilateral upper motor neuron disease

Apraxic/magnetic gait Frontal lobe (NPH, stroke) Radiculopathy 323

## SPECIFIC ENTITIES (CONT'D)

Type Pathology

Shuffling gait Extrapyramidal lesion (Parkinson's)

Broad based gait Cerebellar vermis

Ataxic gait Cerebellar anterior (alcohol)

Unsteady, sensory ataxia gait Posterior column (Tabes dorsalis, B12 deficiency, Friedreich's ataxia)

Trendelenburg gait (waddling) Hip adductor muscle weakness (gluteus medius)

Steppage gait Foot drop (peroneal nerve palsy)

#### **Related Topics**

Dementia (p. 378)

Orthostatic Hypotension (p. 312)

## Radiculopathy

NEJM 2005 353:4

#### PATHOPHYSIOLOGY

FORAMINAL ENCROACHMENT OF THE SPINAL NERVE usually due to a combination of decreased disc height and degenerative changes of the unco vertebral joints anteriorly and zygapophyseal joints posteriorly

#### **COMMONLY AFFECTED NERVE ROOTS**

- **CERVICAL REGION** C7 (70%) and C6 (20%) are the most commonly affected nerve roots
- LUMBOSACRAL REGION L5 and S1 (>90% combined) are the most commonly affected nerve roots

#### Related Topics

Back Pain (p. 284)

Peripheral Neuropathy (p. 327)

Spinal Cord Compression (p. 228)

### CLINICAL FEATURES

**HISTORY** characterize neck or back pain. Paresthe sia, radiation of pain, and weakness over specific nerve root distribution, any associated neurological symptoms. Ask about red flags (fever, chills, unex plained weight loss, unremitting night pain, previous cancer, immunosuppression, and IDU) which may suggest tumor or infections

**SPURLING'S SIGN** reproduction of symptoms (e.g. pain radiating down arm) with extension and lateral rotation of neck toward affected side followed by compressive force to the top of the head suggests cervical radiculopathy and may facilitate localization. Despite popularization in physical examination books

## CLINICAL FEATURES (CONT'D)

and modest diagnostic utility (LR+ 3.6), Spurling's test should probably *not* be performed. In patients with rheumatoid arthritis, cervical malformations, or metastatic diseases, this test risks serious injury to the spine

#### INVESTIGATIONS

**IMAGING** spine X ray (low sens), CT spine, MR spine (especially if suspect myelopathy, red flags, progressive neurologic deficits, no improvement for 4 6 weeks)

**EMG AND NERVE CONDUCTION STUDY** 

## TREATMENT OF CERVICAL RADICULOPATHY

NON SURGICAL acetaminophen, NSAIDs, opioids, corticosteroid injections, cervical traction, exercise SURGICAL indicated if myelopathy or a combina tion 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 neuro pathy), imbalance, sphincter disturbances (late find ing, urinary urgency/frequency initially, then reten tion 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

**324** Radiculopathy

## DERMATOMES C2 C3 C3 C4 T4 T5 T4 T5 T6 T7 T6 **T7 T8** T8 T9 T9 C6 55 53 L3 52 51

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MYOTOMES		
Root	Muscles	
C3,4,5	Diaphragm	
C5	Deltoid (shoulder abduction)	
C6	Biceps and brachioradialis (elbow flexion), radial wrist extensors (wrist extension)	
C7	Triceps (elbow extension), ulnar wrist extensors (wrist extension), wrist flexors, finger extensors	
C8	Intrinsic muscles of hand	
T1	Intrinsic muscles of hand	
T2 12	Chest wall and abdominal muscles	
L2	lliopsoas (hip flexion)	
L3	Quadriceps (knee extension), adductor longus (hip adduction)	
L4	Quadriceps (knee extension), tibialis anterior (dorsiflexion and inversion)	

MYOTOMES (CONT'D)		
Root	Muscles	
L5	Extensor hallucis longus ( <b>big toe extension</b> ), tibialis posterior (planterflexion and eversion), gluteus medius (hip abduction)	
S1	Gluteus maximus (hip extension), gastrocnemius, soleus, peroneus longus (plantar flexors, eversion)	
S2,3,4	Bowel, bladder, sexual organs, anal other pelvic muscles	

BRACHIAL PLEXUS		
Nerve	Root/origin	Muscle function
Dorsal scapular	C <b>5</b> /root level	Rhomboids (retracts scapula)
Long thoracic	C <b>5</b> 67/root	Serratus anterior (scapula abduction)
Suprascapular	C <b>5</b> 6	Supraspinatus (arm abduction)
	Upper trunk	Infraspinatus (arm external rotation)
Lateral anterior	C6 <b>7</b>	Pectoralis major (arm adduction, internal rotation)
thoracic	Upper, middle	
	trunk	
Medial anterior	C <b>8</b>	Pectoralis major (arm adduction, int. rotation)
thoracic	Lower trunk	Pectoralis minor (protracts scapula)
Subscapular	C <b>5</b> 6	Subscapularis (arm adduction)
	Posterior cord	Teres major (arm extension, ext. rotation)
Thoracodorsal	C <b>7</b> 8	Latissimus dorsi (arm extension, adduction, internal
	Posterior cord	rotation)
Axillary	C <b>5</b>	Deltoid (arm abduction)
	Posterior cord	Teres minor (arm external rotation)
Musculo cutaneous	C <b>5</b> 6	Biceps (forearm flexion)
	Lateral cord	Brachioradialis (supination)
Median	C5 <b>67T1</b>	See tables below
	Anterior cord	
Radial	C <b>678</b>	See tables below
	Posterior cord	
Ulnar	C <b>8T1</b>	See tables below
	Lateral cord	

MUSCLE NERVE FUNCTION CORRELATION			
Muscle	Innervation	Function	
Tibialis anterior	Deep peroneal n. (L4 <b>L5</b> S1)	Inversion, dorsiflexion	
Tibialis posterior	Tibial n. ( <b>L4</b> L5)	Inversion, planterflexion	
Peroneus longus	Superficial peroneal n. (L5 <b>S1</b> )	Eversion, planterflexion	
Peroneus brevis	Superficial peroneal n. (L5 <b>S1</b> )	Eversion, planterflexion	

DIFFEREN				
DIFFEREN	FIATING BETWEEN NERVE ROOT AND PERIPHERAL	NERVE LESIONS		
C6 VS. M	EDIAN NERVE LESION			
	C6	Median nerve (C6 T1)		
Sensory	Palmer surface of 1 <sup>st</sup> 2 <sup>nd</sup> fingers Lateral surface of arm/forearm	Palmer surface of 1st lateral 4th fingers		
Motor	Biceps, brachioradialis, forearm pronators Wrist extensors	<b>★LOAF★</b> Lateral lumbricals (1 <sup>st</sup> and 2 <sup>nd</sup> ), <b>O</b> pponens pollicis (opposition), <b>A</b> bductor pollicis brevis (abduction of thumb), <b>F</b> lexor pollicis brevis (flexion of thumb/fingers)		
Reflex	Biceps, brachioradialis	None		

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#### DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT'D)

#### **C7 VS. RADIAL NERVE LESION**

**C7** 

Palmer surface of 3rd finger

Sensory

Dorsal surface of arm/forearm

Motor

Wrist extensors and flexors

Finger and thumb extensors

Reflex Triceps Radial nerve (C5 T1)

Dorsal surface of 1st lateral 4st fingers

Dorsal surface of arm/forearm

Triceps (normal if high lesion)

Wrist extensors

**Brachioradialis** 

Fingers and thumb extensors

Triceps (normal unless high lesion)

Brachioradialis

## C8/T1 VS. ULNAR NERVE LESION

C8/T1

Palmar and dorsal surface of 4th and 5th fingers Sensory

Medial surface of arm and forearm

Lumbricals (3<sup>rd</sup>, 4<sup>th</sup>), interossei Motor

5<sup>th</sup> finger opposition, abduction, and flexion.

Thumb adductor

LOAF muscles (median n.) Wrist flexion and abduction

Triceps (radial n.)

Reflex Triceps Ulnar nerve (C8T1)

Palmar and sometimes dorsal surface of 4th and

5<sup>th</sup> fingers

Lumbricals (3<sup>rd</sup>, 4<sup>th</sup>), interossei

5<sup>th</sup> finger opposition, abduction and flexion.

Thumb adductor

None

## L3 VS. OBTURATOR NERVE LESION

Thigh/knee and medial leg Sensory

Hip adduction Motor Knee extension

Reflex Knee, adductor Obturator nerve (L34)

Medial thigh/knee

Hip adduction

Adductor

## L4 VS. FEMORAL NERVE LESION

L4

Sensory Lateral leg to medial malleolus

Motor Knee extension

Reflex

Dorsiflexion (deep peroneal n.)

## L5 VS. PERONEAL NERVE LESION

Lateral leg, dorsal foot including first web Sensory

Motor Dorsiflexion and eversion

Great toe dorsiflexion

Knee flexion

Planterflexion and inversion (tibial n.)

Hip abduction (sup. gluteal n.)

Femoral nerve (L234) Lateral leg to medial malleolus

Knee extension

Hip flexion

Knee

## Common peroneal n. (L45S1)

Lateral leg, dorsal foot including first web space

Dorsiflexion (deep peroneal n.) and eversion

(superficial peroneal n.)

Great toe dorsiflexion

Peripheral Neuropathy 327

## DIFFERENTIATING BETWEEN NERVE ROOT AND PERIPHERAL NERVE LESIONS (CONT'D)

#### **S1 VS. SCIATIC NERVE LESION**

S1

Sensory Lateral foot including 5<sup>th</sup> toe

Motor Planterflexion

Toe flexion

Hip abduction and extension

Reflex Ankle

For the nerve root/peripheral nerve lesions tables above,

**BOLD**=highlights differences between nerve root and peripheral nerve lesions

REFLEXES complete peripheral nerve lesions will lead to complete areflexia, while complete nerve root

lesions will only lead to partial reduction of reflexes

#### SPECIFIC CONSIDERATIONS

DISTINGUISHING FEATURES BETWEEN MEDIAN NERVE LESION, ULNAR NERVE LESION, AND T1 RADICULOPATHY these lesions can be differen tiated by testing two muscles: abductor pollicis brevis is supplied by the median nerve (i.e. supinate hand,

#### SPECIFIC CONSIDERATIONS (CONT'D)

Sciatic nerve (L4 S3)

Lower leg and foot

inversion

**Knee flexion** 

Ankle

point thumb toward ceiling, test power by pushing thumb down), while first dorsal interosseous is sup plied by the ulnar nerve (i.e. test power of index finger abduction)

Planterflexion and eversion, dorsiflexion and

LesionAbductor pollicis brevis1st dorsal interosseousT1 radiculopathyWeakWeakMedian nerveWeakSparedUlnar nerveSparedWeakNOTE: 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 lgA, lgG, lgM
  - INFECTIOUS sepsis, HIV, Lyme
  - METABOLIC diabetes, uremia
  - VITAMIN DEFICIENCY malabsorption
  - **DRUGS** cisplatin, taxanes, vincristine, isonia zid, nucleoside analogue
- DEMYELINATING Guillain Barre, neoplastic (car cinoma, lymphoma, MGUS IgM), drugs (taxanes), chronic inflammatory demyelinating polyradi culoneuropathy

## CLINICAL FEATURES

**DIFFERENTIATING SITE OF MEDIAN NERVE INJURY** if lesion at carpal tunnel, LOAF muscles affected. If lesion at or above the elbow, there may be lateral forearm wasting and the index finger held in extension (Benediction sign)

## CLINICAL FEATURES (CONT'D)

**DIFFERENTIATING** SITE OF ULNAR NERVE INJURY low lesion (below the wrist) characterized by marked hand clawing (because of unopposed flexor digitorum profundus flexion of DIPs). High lesions have subtle clawing, termed ulnar paradox

## INVESTIGATIONS

#### BASIC

 LABS CBCD, lytes, urea, Cr, glucose, ESR, serum protein electrophoresis, vitamin B12, ANA, TSH, urinalysis

#### SPECIAL

- EMG AND NERVE CONDUCTION STUDY
- NERVE/MUSCLE BIOPSY
- LUMBAR PUNCTURE

## MANAGEMENT

TREAT UNDERLYING CAUSE diabetic (glucose control), lymphoma/myeloma (chemotherapy)

SYMPTOM MANAGEMENT tricyclic antidepres sants (desipramine 10 50 mg qhs), gabapentin (300 mg PO daily ×1 day, then 300 mg PO BID

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#### 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, amyloido sis, hypothyroidism, rheumatoid arthritis, diabetes mellitus, pregnancy, and mucopolysaccharidosis. Bilateral disease suggests a systemic condition

#### SPECIFIC ENTITIES (CONT'D)

- DIAGNOSIS nerve conduction studies (sens 49 84%, spc 95 99%) should be done if inade quate response to conservative therapy (changes in the workplace, nighttime neutral splints), thenar atrophy, or if the diagnosis is unclear
- TREATMENTS activity modifications, wrist splint ing, NSAIDs, corticosteroid injections (success 49 81%, recurrence 50 86%), carpel tunnel release (success 75 99%)

### SPECIFIC ENTITIES (CONT'D)

**RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE CARPEL TUNNEL SYNDROME? KATZ HAND DIAGRAM classic** (tingling of at least two of digits 1 3. The classic pattern permits symptoms in the 4<sup>th</sup> and 5<sup>th</sup> digits, wrist pain, and radiation of pain to wrist, but not symptoms on the palm/dorsum of the hand), **probable** (same symptom pattern as classic, except palmer symptoms are allowed unless confined solely to the ulnar aspect), **possible**, **unlikely** 

	LR+	LR
History		
Classic/probable Katz diagram	2.4	0.5
Age >40	1.3	0.5
Nocturnal paresthesia	1.2	0.7
Bilateral symptoms	1.4	0.7
Physical		
Hypalgesia (↓ pain sensation) in the median nerve territory	3.1	0.7
Abnormal vibration	1.6	0.8
Weak thumb abduction strength	1.8	0.5
Thenar atrophy	1.6	1.0
Square wrist sign	2.7	0.5
Closed fist sign	7.3	0.4
Flick sign	21.4	0.1
Tinel's sign	1.4	0.8
Phalen's sign	1.3	0.7

**APPROACH** "Katz hand symptom diagrams, hypalgesia, and thumb abduction strength testing are helpful in establishing diagnosis of carpel tunnel syndrome"

JAMA 2000 283:23

#### SPECIFIC ENTITIES (CONT'D)

#### **AUTONOMIC NEUROPATHY**

 CAUSES autonomic failure may be secondary to peripheral neuropathy associated with diabetes, cancer (paraneoplastic), amyloidosis, cachexia, HIV, Guillain Barre syndrome, Lambert Eaton syn drome, other inflammatory/infectious conditions, or due to primary disorders such as Parkinson's disease, Shy Drager syndrome (multiple system atrophy with autonomic failure), Lewy body dementia, and multiple sclerosis

	Sympathetic dysfunction	Parasympathetic dysfunction
Vitals	Orthostatic hypotension	Tachycardia
Skin	Warm and moist	Cool and dry

SPECIFIC ENTITIES (CONT'D)		
	Sympathetic dysfunction	Parasympathetic dysfunction
H&N	Horner's	Dry eyes + mouth Dilated pupil
Heart	No respiratory variation	
GI/GU		Constipation Distended bladder Impotence
MSK, gait	Postural instability	

## Related Topics Diabetic neuropathy (p. 337) Radiculopathy (p. 323)

#### SPECIFIC ENTITIES

#### GUILLAIN BARRE SYNDROME (GBS)

- PATHOPHYSIOLOGY precipitants (Campylobacter jejuni, pper respiratory tract infections, possibly flu shots) → acute inflammatory demyelinating polyradiculoneuropathy 2 4 weeks later → reach nadir of symptoms 2 4 weeks (25% require mechanical ventilation) → recovery weeks to months
- CLINICAL FEATURES fine paresthesias in toes and fingertips → weakness in lower/upper extremities → potential autonomic dysfunction (50%), cranial nerves, respiratory muscle involvement. Areflexia. Low/mid back pain common
- SUBTYPES four subtypes include demyelinating (acute inflammatory demyelinating polyradi culoneuropathy), axonal motor (acute motor axonal

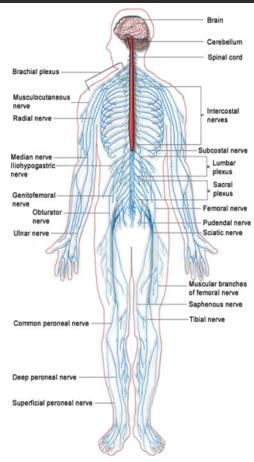
#### SPECIFIC ENTITIES (CONT'D)

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 /V/G 0.5 1 g/kg IV daily, plasma exchange. ICU admission with respiratory support if FVC <20 mL/kg, maximum inspiratory pressure <30 cmH<sub>2</sub>O, maximum expiratory pressure <40 cmH<sub>2</sub>O, rapid progression <7 days, cranial or autonomic involvement

**MONONEURITIS MULTIPLEX** simultaneous/ sequential involvement of noncontiguous nerve trunks (multiple nerve infarcts due to a systemic vasculitis)

#### PERIPHERAL NERVES



PERIPHERAL NERVES (CONT'D)			
MONONEUROPATHIES			
Nerve (origin)	Pathophysiology	Signs and symptoms	Comments
Axi ary nerve (C5–6)	Lesion usua y near shou der joint	Motor: weakness of shou der abduction,	
	Affects de toid and teres minor	shou der atrophy	
		Sensory: deficit simi ar to C5 esion	
Subscapu ar nerve (C5–6)	Lesion usua y at suprascapu ar notch of scapu a	Motor: weakness of atera rotation of arm	
	Affects supraspinatus and infraspinatus	Sensory: intact	
Long thoracic nerve (C5–7)	Affects serratus anterior	Motor: winging of the scapu a Sensory: infact	
Radia nenze (C5_T1)	lesion using v at spira groove of humanis	Motor: wrist drop weakness of finger and	Saturday night na sy (actite compression) is
	Affects brachioradia is, triceps, wrist, finger and	thumb extensors	frequent cause
	thumb extensors	<u>r</u> a	Cheira gia paresthetica (entrapment of
		4" fingers, dorsa surface of arm/forearm	superficia branch of radia nerve to dorsum of hand)
Posterior interosseous	Lesion usua y at the Arcade of Foshse	Motor: finger drop, wrist re ative y spared	
branch of radia nerve (C7–8)	Affects finger and thumb extensors	Sensory: intact	
U nar nerve (C8–T1)	Lesion usua y at cubita tunne or u nar groove	Motor: weakness of finger adduction,	
	at the e bow	abduction and thumb adduction (Froment's	
	Affects u nar f exor of the wrist, ong f exors of	sign), c aw-hand and interosseous atrophy	
	4"-5" digits and intrinsic hand musc es	Sensory: changes in both dorsa and pa mer surfaces of $4^{th}$ and $5^{th}$ fingers. May have pain	
		over median proxima forearm (cubita	
		tunne ).	
	:	Tests: Tine sign positive	
U nar nerve (C8–T1)	More dista esion usua y at media base of pa m	Motor: weakness of finger adduction and abduction. nterosseous atrophy	Cyc ist's pa sy
	Affects intrinsic hand musc es on y	Sensory: changes in pa mer surface of 4 <sup>th</sup> and	
		5 <sup>th</sup> fingers on y	
		Tests: Tine sign negative	

PERIPHERAL NERVES (CONT'D)	()		
MONONEUROPATHIES			
Nerve (origin)	Pathophysiology	Signs and symptoms	Comments
Median nerve (C6–T1)	Lesion at carpa tunne	Motor: weakness, pain, numbness and ting ing	Carpe tunne syndrome
	Affects abductor po icis brevis, proxima	over thumb, 2 <sup>nd</sup> and 3 <sup>rd</sup> fingers	
	musc es inc ude forearm pronator, ong finger, and thumb fexors	Sensory: changes in pa mer surface of 1 <sup>st</sup> - atera 4 <sup>th</sup> fingers	
		Tests: sauare wrist sian, c osed fist sian, F ick	
		sign, Tine sign and Pha en sign	
Anterior interosseous	Lesion usua y just be ow the e bow	Motor: weakness of pinch, pain in vo ar forearm	
branch of median nerve (C7–T1)	Affects ong f exors of thumb and index and midd e fingers	Sensory: intact	
Femora nerve (L2–4)	Lesion usua y proxima to inguina igament	Motor: buck ing of knee, absent knee jerk, weak	Post-femora catheterization or pe vic surgery
	Affects i iopsoas (hip f exor) and quadriceps	anterior thigh musc es with atrophy.	with retroperitonea hematoma, diabetes
	femoris (knee extensor)	Obturator nerve (hip adduction) not affected	me itus
		Sensory: changes in atera eg to media	
		ma eo us	
Latera femora cutaneous	Latera femora cutaneous Lesion usua y at inguina igament	Motor: intact	Mera gia paresthetica (entrapment of atera
branch of femora nerve		Sensory: dysesthetic hyperpathia of atera	cutaneous femora nerve to antero atera
(L2-3)		thigh (burning)	aspect of thigh)
Obturator nerve (L3-4)	Lesion usua y at pubis or intrape vic	Motor: weakness of hip adduction	
	Affects thigh adductors	Sensory: deficit of media thigh	
Sciatic nerve (L4–S3)	Lesion usua y near sciatic notch	Motor: severe ower eg and hamstring	Overdose victims
	Affects hamstring musc es, hip abductor and a	weakness, f ai foot, difficu ty wa king	
	musc es be ow the knee	Sensory: changes in ower eg and foot	
Tibia nerve (L5–S2)	Lesion usua y at tarsa tunne or near media	Motor: weak toe f exors	Tarsa tunne syndrome
	ma eo us	Sensory: pain and numbness of so e	
	Affects ca f musc es (proxima y), toe f exor, and		
	other intrinsic foot musc es		
Peronea nerve (L4–S1)	Lesion usua y at neck of fibu a	Motor: weakness of foot eversion and foot drop Cross- eg pa sy	Cross- eg pa sy
	Affects dorsif exors of toes and foot and	Sensory: deficit simi ar to L5 esion	
	evertors of foot		

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## **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, hypocal cemia, hypophosphatemia, hyponatremia, hyper natremia, 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 Guil lain Barre, myeloma, amyloidosis, diabetes
- NEUROMUSCULAR JUNCTION myasthenia gravis, botulism, Eaton Lambert, organophosphate poisoning
- MUSCLES myopathies (see above)

## **Related Topics**

Critical Illness Weakness (p. 89) Dermatomyositis (p. 279) Eaton Lambert Syndrome (p. 319) Myasthenia Gravis (p. 318)

#### CLINICAL FEATURES

#### APPROACH TO CLINICAL DIAGNOSIS

- 1. FUNCTIONAL VS. TRUE MUSCLE WEAKNESS?
  - if functional, consider cardiopulmonary disease, arthritis, anemia, cachexia from malignancy or chronic disease, depression, deconditioning, fibromyalgia
  - if true muscle weakness, proceed to 2

#### 2. GENERALIZED VS. LOCALIZED MUSCLE WEAKNESS?

- if generalized, consider myasthenia gravis, long standing periodic paralysis, advanced disuse atrophy from prolonged bed rest, or advanced muscle wasting from malignancy
- if localized, proceed to 3

#### 3. ASYMMETRIC VS. SYMMETRIC MUSCLE WEAKNESS?

- if asymmetric, consider disease of central or peripheral nervous system (stroke, spinal cord injury, demyelinating disorders, com pression neuropathy, mononeuropathy/ neuritis), disuse atrophy, myasthenia gravis
- · if symmetric, proceed to 4
- 4. DISTAL VS. PROXIMAL MUSCLE WEAKNESS?
  - if distal, consider peripheral neuropathy, myasthenia gravis, motor neuron disease
  - if proximal, consider myopathies (see differ ential diagnosis), myasthenia gravis, Duch enne muscular dystrophy

#### MRC MUSCLE STRENGTH GRADING

0=no contraction

1=flicker

2=possible only with gravity eliminated

3=against gravity only

**4**=power decreased but muscle contraction possi ble against resistance

5=normal power resistance

**MUSCLE STRENGTH** preserved in patients with cachexia despite advanced generalized muscle atro phy. In contrast, patients with true muscle weakness due to myopathy generally have normal muscle bulk at time of presentation

**MUSCLE TENDERNESS** usually not associated with one of the causes of true muscle weakness, except for infectious myopathies, certain drug induced myopathies, thyroid myopathy, and inherited metabolic myopathies

### INVESTIGATIONS

#### BASIC

 LABS CBCD, lytes, urea, Cr, Ca, Mg, PO<sub>4</sub>, CK, aldolase, LDH, AST, ALT, ANA, ANCA, HBV/HBC serology, cryoglobulin, RF, TSH

#### INVESTIGATIONS (CONT'D)

#### SPECIAL

- EMG AND NERVE CONDUCTION STUDY
- MUSCLE BIOPSY
- POLYMYOSITIS/DERMATOMYOSITIS WORKUP anti Jo 1 and 2, anti SRP (signal recognition particle), anti Mi2

#### MANAGEMENT

## REHABILITATION TREAT UNDERLYING CAUSE

#### SPECIFIC ENTITIES

#### CRITICAL ILLNESS NEUROMUSCULAR DISORDERS

- CRITICAL ILLNESS POLYNEUROPATHY muscle weak ness and atrophy, ↓ deep tendon reflexes, ↓ per ipheral sensation to light touch and pin prick. Associated with sepsis, systemic inflammation
- DELAYED REVERSAL OF NEUROMUSCULAR BLOCKADE non depolarizing neuromuscular blocking agents (pancuronium, vecuronium) in susceptible patients

#### SPECIFIC ENTITIES (CONT'D)

- CRITICAL MYOPATHY muscle weakness and atro phy. Muscle damage second degree to sepsis and multi system organ failure
- MYOPATHY ASSOCIATED WITH COMBINED USE OF STEROID AND NEUROMUSCULAR BLOCKING AGENT muscle weakness and atrophy, ↓ deep tendon reflexes

#### AMYOTROPHIC LATERAL SCLEROSIS (ALS)

- PATHOPHYSIOLOGY combined upper and lower motor neuronal degeneration 

   → spread to involve multiple myotomes in multiple regions (bulbar, cervical, and lumbosacral). No sensory deficit
- CLINICAL FEATURES upper motor neuron signs (hyperactive reflexes, extensor plantar responses), lower motor neuron signs (muscle weakness, atro phy, 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), degen erative 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. Cal
  cification will usually be punctate and have no
  mass effect
- GRAY—WHITE DIFFERENTIATION the junction of gray matter and white matter adjacent to the cortex and the basal ganglia should be well defined. Poor delineation should raise suspicion of cerebral edema if the finding is global or acute infarction if the finding is localized
- MIDLINE SHIFT

**VENTRICLES AND SUBARACHNOID SPACES** (sulci and cisterns) difficulty with visualization of the basal cisterns may indicate increased intracranial pressure and possibly brain herniation. Hyperdensity (white) within the subarachnoid spaces and the dependent portions of the ventricles suggests subarachnoid hemorrhage

**DURA AND SUBDURAL SPACE** check for subdural hemorrhage in subdural window (crescent like), especially along the edges of the intracranial cavity

**BONE AND AIR SPACES** check for fractures in bone window and fluid in sinuses

#### APPROACH TO CT HEAD (CONT'D)

**SKIN AND SUBCUTANEOUS TISSUES** check for swelling of extracranial soft tissues in subdural window

#### HEAD CT FINDINGS IN THE ELDERLY

**SMALL VESSEL DISEASE** diffuse brain atrophy, hypodense periventricular white matter due to glio sis, 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

## HEAD CT FINDINGS IN STROKE (CONT'D)

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 hypo dense 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

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## Notes

Notes Notes

## Notes

## 11 ENDOCRINOLOGY

Section Editor: Dr. Laurie Mereu

## **Diabetes Mellitus**

## Canadian Diabetes Association Guidelines 2008

#### CLASSIFICATION

**TYPE 2 DIABETES** insulin resistance and a rela tive or absolute insulin deficiency

**GESTATIONAL DIABETES** glucose intolerance diagnosed during pregnancy

## OTHER SPECIFIC TYPES

- GENETIC DEFECTS OF  $\beta$  CELL FUNCTION
- GENETIC DEFECTS IN INSULIN ACTION
- OTHER GENETIC SYNDROMES ASSOCIATED WITH DIABETES
- DISEASES OF THE PANCREAS cystic fibrosis, hemo chromatosis, neoplasia, pancreatitis, pancreatectomy
- ENDOCRINOPATHIES acromegaly, Cushing's syn drome, glucagonoma, hyperthyroidism, pheochromocytoma
- INFECTIONS
- UNCOMMON FORMS OF IMMUNE-MEDIATED DIABETES
- DRUG OR CHEMICAL INDUCED atypical antipsycho tics, corticosteroids, nicotinic acid, pentamidine, phenytoin, protease inhibitors, thiazides

## PATHOPHYSIOLOGY

## CHRONIC COMPLICATIONS OF DIABETES

- MACROVASCULAR DISEASE patients with diabetes have a 2 4× ↑ in cardiovascular complications (coronary artery disease, stroke/TIA, peripheral vascular disease)
- RETINOPATHY
  - BACKGROUND microaneurysms, dot and blot hemorrhages, hard exudates
  - PRE-PROLIFERATIVE soft exudates, macular edema, intra retinal microvascular abnormality
  - PROLIFERATIVE increased new vessels around the optic disc, vitreous hemorrhage, detached retina, neovascular glaucoma
- NEPHROPATHY glomerular basement membrane thickening, 
   † glomerular pressure, microalbumi nuria, overt proteinuria, nephrotic range protei nuria, end stage renal disease

#### PATHOPHYSIOLOGY (CONT'D)

- NEUROPATHY (50% of all patients)
  - MONONEUROPATHY cranial (III most commonly sparing pupil, IV, VI, VII), peripheral (median, ulnar, peroneal)
  - MONONEURITIS MULTIPLEX combination of mul tiple mononeuropathies
  - DISTAL SYMMETRIC POLYNEUROPATHY most common with classic stocking glove distribution. Progressive loss of distal sensation due to axonal loss, followed by motor weakness and motor axonal loss. May be associated with Charcot's feet
  - PROXIMAL SYMMETRIC POLYNEUROPATHY (polyradicu lopathy) diabetic radiculoplexopathy or amyo trophy, usually involving L2 4 roots causing painful proximal weakness in knee extension, hip flexion, and, importantly, hip adduction (obturator nerve involvement, distinguishing feature from femoral neuropathy)
  - AUTONOMIC NEUROPATHY postural hypotension, gastroparesis, constipation, diarrhea, erectile dys function, atonic bladder, hypoglycemia unaware ness, hyperhidrosis of upper extremities, anhidro sis of lower extremities, dry skin

#### REASONS WHY BLOOD SUGAR FLUCTUATES

- LIFESTYLE diet (quantity/quality, timing), exercise
- BLOOD SUGAR TESTING accuracy, timing
- NEUROPATHY hypoglycemic awareness, gastroparesis
- ILLNESS infections, stress
- . INSULIN injection site, technique, dose
- DECREASED INSULIN REQUIREMENT renal failure, Addison's
- MEDICATIONS interactions
- OTHER ENDOCRINE CAUSES OF HYPERGLYCEMIA Cush ing's, pheochromocytoma, hyperthyroidism

**PRECIPITATING FACTORS FOR DKA** sepsis, acute abdomen, myocardial infarction, insulin omission, new onset diabetes

#### **CLINICAL FEATURES**

**HISTORY duration** and **type** of diabetes, **diabetic control** (frequency of monitoring, hypoglycemia,

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#### CLINICAL FEATURES (CONT'D)

hyperglycemia, previous HbA1C, previous DKA, prior hospitalization), **treatment** (insulin, oral hypoglyce mic agents, healthy eating guidelines, exercise, edu cation), **acute complications** (polyuria, polydipsia, blurred vision, numbness, weight loss, fatigue), **chronic complications** (see previous section). Risk factors for heart disease (hyperlipidemia, hyperten sion, smoking, family history of early cardiac events, obesity)

**PHYSICAL** height, weight, BMI, vitals, fundi (dia betic 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), gang rene (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, tem perature, capillary refill, Buerger's test, ankle/bra chial index
- NEUROLOGICAL 10 g sensory filament, vibration, glove and stalking sensory loss (light touch, pain, temperature), power (dorsiflexion, plantar flexion), ankle reflex

## INVESTIGATIONS

#### BASIC

 LABS glucose, lytes, anion gap, osmolality, ketones, creatinine, urea, HbA1C, fasting lipids, ALT, ALP, CK, TSH, C peptide, urine albumin to creatinine ratio

#### SPECIAL

ANTIBODIES insulin antibody, GAD65 antibody, islet cell antibody

#### **Related Topics**

Autonomic Neuropathy (p. 328) Coronary Artery Disease (p. 26) Gastroparesis (p. 113) Gestational Diabetes (p. 413) Osteomyelitis (p. 248) Peripheral Neuropathy (p. 327) Peripheral Vascular Disease (p. 54)

#### DIAGNOSTIC ISSUES

## DIAGNOSTIC CRITERIA FOR DIABETES

	rasting bs	GTT (75 g, 2nr)
Normal	<5.6 mmol/L	<7.8 mmol/L
	[<100 mg/dL]	[<140 mg/dL]
Impaired	5.6 6.9 mmol/L	
Fasting	[100 125 mg/	
Glucose	dL]	
Impaired		7.8 11.0 mmol/L
Glucose		[140 199 mg/
Tolerance		dL]
Diabetes*	≥7.0 mmol/L	$\geq$ 11.1 mmol/L
	[≥126 mg/dL]	[≥200 mg/dL]

GTT (75 a 2hr)

GTT=glucose tolerance test

\*random glucose ≥11.1 mmol/L [≥200 mg/dL] accompanied by classical symptoms (polyuria, polydipsia, unexplained weight loss) also sufficient for diagnosis

#### FACTITIOUS LABORATORY ABNORMALITIES

DKA itself may cause  $\uparrow$  WBC,  $\downarrow$  Na, and  $\uparrow$  amylase, which should correct with resolution of DKA

#### ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS

# ACUTE ABC, O<sub>2</sub>, 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)
- NINSULIN give 0.1 units/kg of regular insulin IV push, then 0.1 units/kg/h (mix 25 units of regular insulin in 250 mL D5W. One unit of insulin is equal to 10 mL of drip). Titrate insulin drip against anion gap. If anion gap still ↑, increase the rate (see table on next page). Try to keep glucose between 10 and 15 in first day. As anion gap falls, decrease insulin drip. Switch to SC insulin when (1) anion gap normalized, (2) insulin requirements reasonable, (3) patient hun gry, and (4) only in AM (to facilitate monitoring over the course of the day). Ensure overlap of SC insulin with insulin infusion by at least 1 h
- GLUCOSE once serum glucose is less than 15 mM, add glucose to IV fluids (e.g. D5NS, D5½NS). If patient is euvolemic and serum sodium is normal or high, D5½NS should be used
- BICARB if pH <6.9, may be beneficial to give 1 2 amps of HCO<sub>3</sub> over 1 2 h. If pH 6.9 7.0, giving HCO<sub>3</sub> is optional. If pH >7.0, giving HCO<sub>3</sub> is not necessary

## ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS (CONT'D)

- PHOSPHATE no indication for replacement in the acute setting unless there is severe cardiac or respiratory depression
- LABS obtain hourly ABGs, lytes, bicarb, anion gap,

## ACUTE MANAGEMENT OF DIABETIC KETOACIDOSIS (CONT'D)

glucose, serum osmolality, ketones. Cerebral edema is a concern (particularly in children) if osmolality/sodium parameters are corrected too quickly

## TREAT PRECIPITATING FACTOR(S)

N EXAMPLE	Hour 1	Hour 2	Но	urs 3-4	Hours 5-8	Hours 8-24
Hydration  IV #1  NS or ½ NS  ± potassium replacement	11 NS (i.e. 15–20 mL/kg/h) Use ½NS if corrected Na >145 mmol/L (for every 10 mmol/L[182 mg/dL] ↑ in blood glucose, correct Na by ↑ 3 mmol/L)	500 mL/h NS	500 mL/h N	S	250 mL/h NS When glucose <15 mmol/L [-227 mg/dl], change IV to D5½ NS @ 250 mL/h (if corrected sodium is low, use D5NS). If glucose -15 mM [-270 mg/dL], bu AG still 1, run D10W at 80 mL/h so that IV insulin can be	125–250 mL/h D5½ NS
Insulin IV #2	Bolus 0.1 units/kg regular IV insulin (e.g. 7 units for 70 kg)	Continue IV insulin  Expect a glucose fall of			270mg/d], decrease IV to 2-4 units/h, is cleared; use following scale:	After ketoacidosis has cleared, switch to SC insu in and thenstop IV
Mix 25 units	Then 0.1 un ts/kg/h initia ly	5 mmol/h [90 mg/dL/h]	Glu	cose		insu in
reg insulin in	following bolus (e.g. 5-10		mM	ma/dL	Insulin drip	
250 ml D5W (1 unit =10 mL)	units/h) Hold for 2 h if hypotensive or	Titrate insulin against AG. Double dose f poor response	<5 5.1–10	<90 91–180	Stop and recheck in 1 h Decrease by 1 un ts/h	Usua ly keep IV insulin for first day; do not stop overnight
	K <3.5 mEq/L	A drop in glucose >3-	10.1-15 15.1-20 20.1-24	181-270 271-360 361-437	No change Increase by 1 units/h Increase by 2 units/h	overnight
	Target glucose 10– 15 mmol/L	5 mmol/h [>54- 90 mg/dL/h] increases risk of cerebral edema (mostly in children		>438 rops by more to 5 units/h and c	Increase by 3 units/h and call MD han 5 mM [90 mg/dL] in 2 h, decrease	
Potassium replacement (when voiding)	Serum potassium Potassium replacement	<3 mEq/L, give 40 mEq/h	3-	-4 mEq/L, give 30 mEq/h	4-5 mEq/L, give 20 mEq/h	5–6 mEq/L, give 10 mEq/h
Laboratory	Baseline: glucose, β-OH- butyrate, ABG, urinalysis, CBCD, electrolytes, Cr,	Glucose (C/S), lytes (VBG)	Glucose (C/	S), lytes (VBG	Glucose (C/S) hourly, lytes (VBG), PO <sub>4</sub>	Glucose (C/S) q1-2h
	PO <sub>4</sub> , Mg, ± lipase, CXR, cultures, troponin, ECG	ABGs if pH <7.0	ABGs if pH	<7.0		lytes q4-8h
Alkaline	Rarely indicated unless severe acidosis (pH <6.9) with incipient circulatory collapse  Dose 50-100 mEq. NaHCO <sub>2</sub> in k:NS over 30-60 mins  Extra potassium may be needed wit bicarbonate therapy  Consider if serum phosphorus <0.65 mmol/L (<2.0 mg/dL) and give if serum phosphorus <0.35 mmol/L (<1.1 mg/dL)  2.5-8 mmol/M   R-25 mg/dL  (1 mmol. of phosphate = 31 mg of elemental phosphorus)  (=0.1 mL of KPO <sub>2</sub> in 1 NaCl over 61, 30 mM PO <sub>2</sub> 44 mEq k)					
replacement						
Phosphate replacement						
General measures	Make flow sheet (ABG's, gluc AG, ±O <sub>2</sub> , urine output), q1h v		be if unconscio c monitor wher			urine for 4 h

#### SPECIFIC ENTITIES

### NON KETOTIC HYPEROSMOLAR HYPERGLYCEMIA

- PATHOPHYSIOLOGY occurs in patients with type 2 diabetes
- CLINICAL FEATURES characterized by profound dehydration, increased osmolar state, severe ele vation 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

#### SPECIFIC ENTITIES (CONT'D)

glucose should drop by no more than 3 mEq/l/h. Lower insulin requirement compared to DKA. Mortality 10 20%

## 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</li>
- 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

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### LONG TERM MANAGEMENT (CONT'D)

reductase inhibitor ( $\downarrow$  LDL), bile acid sequestrants ( $\downarrow$  LDL), nicotinic acid ( $\downarrow$  triglycerides,  $\downarrow$  LDL,  $\uparrow$  HDL but may  $\uparrow$  glucose)

- DIABETIC CONTROL aim for HbA1C of less than 7.0% in all patients. A target HbA1C of ≤6.5% may be considered in selected patients. Fasting and before meals glucose should be 4.0 7.0 mmol/L [73 126 mg/dL]. The 2 h 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 gly cemic control of patients with type 1 diabetes reduces retinopathy, nephropathy, and neuropa thy. 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 vig orous aerobic physical activity and resistance exer cise 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 assess ment 5 years after the diagnosis as long as they are aged 15 or greater. Eye exams may be done annually after that. All patients should have an annual assessment of neuropathy including the diabetic foot exam. Amitriptyline, gabapentin, or pregabalin may be used for painful neuropathy. Domperidone, metoclopramide, erythromycin, or cisapride (beware long QT) may be used for gastroparesis
- FAT REDUCTION (lose 5 10 kg) all patients should follow healthy eating guidelines and try to attain an ideal body weight. See OBESITY ISSUES (p. 403)
- GET GOING TO QUIT SMOKING! there are many different options for patients, including nicotine gum, nicotine inhaler, Nicoderm patch, Bupro pion SR, and varenicline. Smoking cessation classes
- SCREENING FOR CARDIOVASCULAR DISEASE patients should have the following tests done at baseline if they meet any of the following criteria:
  - ECG if age >40, have had diabetes for >15 years, or if they have hypertension, proteinuria, reduced pulses or vascular bruits. ECG should be repeated every 2 years in patients of high car diovascular risk

### LONG TERM MANAGEMENT (CONT'D)

- EXERCISE ECG STRESS TEST angina, atypical chest pain, dyspnea, abnormal ECG, peripheral artery disease, carotid bruits, transient ischemic attack, and stroke
- stress MIBI individuals with an abnormal ECG (LBBB or ST T wave changes) or who cannot exercise
- REVASCULARIZATION prompt revascularization vs medical therapy for stable ischemia seems to have similar outcomes (death and major cardiovascular events)

# ORAL HYPOGLYCEMIC AGENTS

BIGUANIDES (↓ hepatic glucose production, ↑ tissue sensitivity) metformin 500 850 mg PO TID; adverse effects include GI upset and lactoacidosis; contraindi cations 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 cardiovas cular 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) repagli nide 0.5 4 mg PO TID ac meals; adverse effects include hypoglycemia

**SULFONYLUREA** († pancreatic insulin release) *gli clazide* 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 PEPTI DASE 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 postpran dial control; weight neutral; long term adverse effects are not yet known

GLUCAGON LIKE PEPTIDE 1 (GLP 1) ANALO GUES exenatide 5 10  $\mu g$  SC BID 30 min before meals. Causes dose dependent and glucose dependent insulin secretion, delays gastric emptying, promotes weight loss, and suppresses glucagon. Long term adverse effects are unknown. Nausea is a common adverse effect and pancreatitis has been reported

Principles of Insulin Use 341

# **Principles of Insulin Use**

NEJM 2005 352:2

### STARTING INSULIN FOR NEW PATIENTS

### **CALCULATE TOTAL DAILY DOSE**

- STABLE NEW PATIENTS the total daily requirement is 0.5 units/kg of insulin per day SC in divided dosages
- MULTIPLE DAILY INJECTIONS all diabetic patients should be encouraged to be on this regimen to achieve good control; 20% of total insulin should be given before breakfast, lunch, and supper as rapid or regular, 40% of total insulin dose should be given as basal insulin at bedtime using NPH, Lantus, or 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 Levemir

### SPECIAL CONSIDERATIONS

- DELAY DOSE patients may need to delay their insulin intake at times (e.g. if they were NPO for procedures). For every hour delay in giving NPH, subtract 10% of dose
- RENAL FAILURE insulin is renally excreted, thus its dose must be reduced in patients with renal failure
- METFORMIN AND INSULIN consider the use of met formin in conjunction with insulin in type 2 dia betics to increase insulin sensitivity and decrease insulin requirements
- THIAZOLIDINEDIONES AND INSULIN avoid using thia zolidinediones (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 hypo
  glycemia. Consider use of cardioselective β
  blocker agents in diabetics

### REGULAR INSULIN DOSE ADJUSTMENT PRINCIPLES

**INSULIN ADJUSTMENTS** understanding the phar macokinetics 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 Insulin type/action Rapid acting (clear)

Onset: 10 15 min Peak: 1 1.5 h Duration: 3 5 h Short acting (clear) Onset: 30 min

Peak: 2 3 h Duration: 6.5 h

Onset: 1 3 h Peak: 5 8 h Duration: up to 18 h

Long acting basal insulin analogues (clear) Onset: 90 min Duration: up to 24 h

Intermediate acting (cloudy)

Premixed

Premixed regular insulin NPH (cloudy) Premixed insulin analogues (cloudy)

# Trade names

Humalog (insulin lispro) NovoRapid (insulin aspart) Humulin R Novolin ge Toronto

Humulin N Novolin ge NPH

Insulin detemir (Levemir) Insulin glargine (Lantus) Humulin 30/70 Novolin ge 30/70 Novolin ge 40/60 Novolin ge 50/50 Humalog Mix 25 Humalog Mix 50 Novo Mix 30

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### SAMPLE SLIDING SCALE TEMPLATE

#### INSULIN SLIDING SCALE

Glucometer QID with insulin SC QID					
Blood sugar	Regular or rapid insulin SC TID ac meals	NPH or basal insulin SC qhs			
0–4	give juice, call MD	give juice, call MD			
4.1-6					
6.1-8					
8.1-10	Individualized	Individualized			
10.1–12	dosing	dosing			
12.1–16					
16.1–18					
18.1-20					

Notify MD Notify MD NOTE: dose of insulin varies depending on individual patient. For insulin requiring patients, total daily dose is 0.5 units/kg/day; 20% of this dose to be given as regular or Rapid with meals and 40% to be given as bedtime NPH or basal insulin

### TREATMENT ISSUES

# LOCAL COMPLICATIONS OF INSULIN INJECTION

lipoatrophy (human insulin), lipohypertrophy (animal insulin), edema, itching, pain or warmth at injection site, scar tissue

### TREATMENT ISSUES (CONT'D)

### LONG TERM COMPLICATIONS OF INSULIN USE

weight gain and risk of hypoglycemia. Possible asso ciation between long acting insulin and malignancy has been raised; however, further studies are required

# Hypoglycemia

### **DIFFERENTIAL DIAGNOSIS**

**↓ GLUCOSE, ↓ INSULIN, AND ↓ C PEPTIDE** alco holism, sepsis, adrenal insufficiency, panhypopitui tarism, liver failure, HF, renal failure, anorexia, inborn errors of metabolism, drugs (β blockers, salicylates, haloperidol)

**↓ GLUCOSE,** ↑ **INSULIN, AND ↓ C PEPTIDE** exo genous insulin, insulin autoantibodies

**GLUCOSE,** ↑ **INSULIN, AND** ↑ **C PEPTIDE** drugs (sulfonylurea, meglitinide, pentamidine, quinine) β cell tumor (insulinoma, islet cell hyperplasia nesidioblastosis)

# PATHOPHYSIOLOGY

DEFINITION OF **HYPOGLYCEMIA** glucose <2.5 mM [<45 mg/dL]

REACTIVE HYPOGLYCEMIA hypersecretion of insulin postprandially

CLINICAL PEARL the most common reason for a patient to have a low glucose is too much insulin or exposure to oral hypoglycemic agents. However, in patients without diabetes who are presenting with hypoglycemia, it is important to rule out alcoholism, severe sepsis, adrenal insufficiency, and panhypopi tuitarism. Insulinoma is rare and should be a diagno sis of exclusion. Always consider surreptitious use if no obvious cause found, especially if there is possibi lity of access to diabetic drugs

### CLINICAL FEATURES

SYMPTOMS sweating, palpitations, tachycardia, dizziness, blurred vision, mental deficits, altered level of consciousness

### CLINICAL FEATURES (CONT'D)

WHIPPLE'S TRIAD hypoglycemia, symptoms of hypoglycemia, reversal of symptoms with glucose

### INVESTIGATIONS

### BASIC

• LABS Whenever the glucose is found to be low, serum glucose, insulin, C peptide, and proinsulin should be sent along with a spot urine for sulfo nylurea 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 diag nosis of insulinoma if spontaneous hypoglycemic episodes are infrequent. Consult endocrinology
- THIN CUT CT OF PANCREAS WITH PANCREATIC ANGIO-**GRAM** 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 g1h to ensure glucose is recovering

TREAT UNDERLYING CAUSE pancreatic ade noma (resection. If unresectable cancer, consider diazoxide or octreotide)

Hypothyroidism 343

# **Hypothyroidism**

### DIFFERENTIAL DIAGNOSIS

### PRIMARY HYPOTHYROIDISM

- THYROIDITIS Hashimoto's, subacute, postpar tum, irradiation
- IATROGENIC radioactive I<sup>131</sup>, 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 hyper tension, hypothermia, cool and dry skin, vitiligo, orange skin (from carotonemia), carpel tunnel syn drome, hair thinning, periorbital edema, anemia, goi ter, pleural effusion, pericardial effusion, proximal myopathy, pseudo myotonia, delayed relaxation phase of the reflexes, edema (non pitting)

### INVESTIGATIONS

#### BASIC

LABS TSH

### **SPECIAL**

- . ANTI TPO ANTIBODIES AND ANTITHYROGLOBULIN
- ANTIBODIES Hashimoto's

# DIAGNOSTIC ISSUES

**TSH** is all that is required to make a diagnosis. Free T4 and free T3 are not done in the setting of hypothyroidism. If you suspect secondary hypothyr oidism from panhypopituitarism, then measuring TSH along with free T4 is warranted. In sick euthyroid, the thyroid is okay but abnormal lab parameters may occur because the patient is medically unwell. Free T3 will be low due to decreased conversion of free T4 to free T3

INTERPRETATION				
	TSH	fT4	fT3	
Subclinical hypothyroidism	1	N	N	
Primary hypothyroidism	1	1	1	
Secondary hypothyroidism	$\downarrow$	1	1	

### DIAGNOSTIC ISSUES (CONT'D)

Sick euthyroid syndrome Secondary or tertiary hypothyroidism, nephrotic syndrome, anticonvulsants (phenytoin, carbamazepine), and some sick euthyroid syndrome

### MANAGEMENT

MYXEDEMA COMA ABC,  $O_2$ , IV. Levothyroxine 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' dis ease, type 1 diabetes, myasthenia gravis, Addison's, Sjogren's, pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis

**SICK EUTHYROID SYNDROME** in sick and euthyr oid patients! Secondary to hypothalamic pituitary axis disruption, with  $\downarrow$  T4 $\rightarrow$ T3 conversion. Mildly altered N/ $\uparrow$ / $\downarrow$  TSH, N/ $\downarrow$  total T4,  $\downarrow$  fT3,  $\uparrow$  rT3. Thyroid replacement is not needed. Repeat TSH when acute illness resolved

# **Related Topic**

Hypothyroidism in Pregnancy (p. 414)

# Hyperthyroidism

NEJM 2007 358:24

## DIFFERENTIAL DIAGNOSIS

### PRIMARY HYPERTHYROIDISM

- GRAVES' DISEASE (diffuse toxic goiter) most common cause of hyperthyroidism
- TOXIC NODULAR GOITER/TOXIC MULTINODULAR GOI-TER most common in elderly
- THYROIDITIS subacute thyroiditis, silent thyroiditis, Hashimoto's thyroiditis ("Hashitoxicosis'), postpartum thyroiditis, radiation induced thyroiditis, drug induced thyroiditis (lithium, amiodar one, 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 simi lar 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, psy chosis, agitation, confusion, anxiety, goiter, dyspnea, palpitations, diarrhea, amenorrhea, weight loss, med ications, family history

PHYSICAL vitals (tachycardia, atrial fibrillation, tachypnea, systolic hypertension, fever), systolic flow murmur, systolic pleuro pericardial scratch (Means Lerman scratch), thyroid acropachy (club bing, Graves' only), onycholysis (Plummer's nails), palmar erythema, tremor, warm and moist skin ('vel vet skin"), stare, exophthalmos (Graves' only), prox imal myopathy, hyperreflexia, pretibial myxedema (Graves' only), splenomegaly

- GOITER present along with thyroid bruits in Graves'. Thyroid enlargement may be found in other types of hyperthyroidism as well
- GRAVES' OPHTHALMOPATHY protrusion of eyes from the orbits. Features include upper and lower lid retraction, lid lag and stare, ophthalmoplegia, diplopia, conjunctivitis, chemosis, corneal ulcera tion, optic atrophy, loss of vision. Check visual acuity and visual fields

# CLINICAL FEATURES (CONT'D)

# CLASSIFICATION OF GRAVES' OPHTHALMOPATHY ★NO SPECS★

### Class Findings

0 No symptoms or signs

Only symptoms of ocular irritation

(dryness, grittiness)

II **S**oft tissue involved (periorbital edema)

III **P**roptosis

IV Extraoccular muscle involved

(ophthalmoplegia) **C**orneal involvement

VI Sight loss

٧

**THYROID STORM** may be precipitated by anes thetics, surgery, systemic illness (especially sepsis). Clinical manifestations include fever, CNS (delirium), CVS (tachycardia, hypotension), and/or GI (vomiting, jaundice, diarrhea, † LFT) symptoms. The presence of thyrotoxicosis along with dysfunction in 2 of 4 sys tems 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 cri cothyroid 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 pal pation (LR+ 0.15 if normal exam, LR+ 1.9 if 1  $2 \times$  size, LR+ 25 if  $>2 \times$  size)"

JAMA 1995 273:10

# INVESTIGATIONS

# **BASIC**

 LABS TSH, fT4, fT3, TSH receptor antibody (Graves'), anti TPO antibody (Hashimoto's, Graves'), thyroglobulin (\perp if factitious), ESR (\(\gamma\) in thyroiditis), CBCD, ALT, AST, ALP, bili Solitary Thyroid Nodule 345

### INVESTIGATIONS (CONT'D)

### SPECIAL

- THYROID SCAN diffuse homogeneous increased iodine uptake suggests Graves' disease, multi focal uptake suggests toxic multinodular goiter, increased single focus suggests toxic adenoma, while decreased global uptake suggests thyroi ditis or factitious hyperthyroidism
- RADIOACTIVE IODINE UPTAKE normal 2 h uptake = 6 10%; <1% suggests thyroiditis, 1 6% sug gests iodine exposure, >10% suggests Graves', toxic nodule, or toxic multinodular goiter

## DIAGNOSTIC ISSUES

# THYROID HORMONE LEVELS AND INTERPRET ATION

	TSH	fT4	fT3
Subclinical hyperthyroidism	$\downarrow$	N	N
Primary hyperthyroidism	$\downarrow$	1	1
T3 thyrotoxicosis	$\downarrow$	N	1
Secondary hyperthyroidism	↑/N	1	1

### MANAGEMENT

**THYROID STORM** ABC, O<sub>2</sub>, IV. *Propylthiouracil* 1000 mg PO/NG stat, then 300 mg PO q6h. *lodide 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 hyperthyr oidism 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
- RADIOIODINE I<sup>131</sup> ABLATION for Graves', multinod ular goiter and toxic adenoma. Only give once the thyroid levels have been stabilized. Must discon tinue antithyroid drugs 3 7 days in advance. With hold 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** inhi bits thyroid hormone synthesis *and* peripheral con version 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 typi cally leads to hyperthyroidism initially as the thyroid cells lyse, then a period of hypothyroidism before recovering to euthyroid state

### **Related Topic**

Hyperthyroidism in Pregnancy (p. 414)

# **Solitary Thyroid Nodule**

# NEJM 2004 351:17

# DIFFERENTIAL DIAGNOSIS

**BENIGN** (95%) colloid nodule, cyst, thyroiditis, benign follicular neoplasm

**MALIGNANT** (5%) thyroid carcinoma (papillary, follicular, medullary, anaplastic)

# CLINICAL FEATURES

### RISK FACTORS FOR THYROID CANCER

 HIGH RISK family history of medullar thyroid car cinoma 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 com pression (dysphagia, dysphonia, hoarseness, dys pnea, cough)

# INVESTIGATIONS

#### BASIC

- LAB TESTS TSH
- IMAGING U/S guided FNA

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### 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 thyroi dectomy 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 can cer, proceed to surgery. Otherwise, U/S guided FNA  $\rightarrow$  if malignant or suspicious, proceed to surgery. If benign, no treatment necessary with clinical follow up only → repeat thyroid U/S in 6 12 months; alternatives include surgery. If non diagnostic FNA, repeat FNA

# **Pituitary Tumors**

NEJM 2003 349:21

# DIFFERENTIAL DIAGNOSIS OF PITUITARY TUMORS **FUNCTIONAL** prolactinoma is the most com

mon, 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 func tional 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

**SYMPTOMS** bitemporal hemianopsia (loss of per ipheral vision), hormone deficiencies or excess and mass effect (\*GO LOOK FOR THE ADENOMA PLEASE★ A compressive pituitary adenoma will

## CLINICAL FEATURES (CONT'D)

affect hormone production in this order: 

GH, 
LH and FSH, ↓ TSH, ↓ ACTH, and ↑ Prolactin)

**PROLACTINOMA IN** ♀ infertility, oligomenorrhea, galactorrhea

PROLACTINOMA IN ♂ erectile dysfunction, infertility FSH/LH ADENOMA asymptomatic/mass effect

# INVESTIGATIONS

# BASIC

- LABS prolactin, IGF 1 (simpler than GH to inter pret), 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 (Cush ing's syndrome

## DIAGNOSTIC ISSUES

MRI PITUITARY should be done for all patients with elevated prolactin to check for any hypothala mic pituitary tumors, unless they are on a medication classically known to cause hyperprolactinemia

MACROADENOMA (>1 cm [0.4in]) should investi gate anterior pituitary function (IGF 1, LH, FSH, TSH, ACTH, prolactin, AM cortisol, freeT4, estrogen, pro gesterone, AM testosterone), and formal visual field testing

Polyuria 347

### MANAGEMENT

**PROLACTINOMA dopamine agonists** (bromocrip tine 2.5 10 mg PO daily, cabergoline 0.25 1 mg PO 2/ week). **Transsphenoidal resection** (only if visual field compromise). Indications for treatment of pro lactinoma include infertility, galactorrhea, hypogo nadism and macroadenoma

**ACROMEGALY transsphenoidal resection** (pre ferred). See SPECIFIC ENTITIES below for details

CUSHING'S DISEASE transsphenoidal resection.
See p. 350 for details

**TSH SECRETING transsphenoidal resection** (first line but rarely cures). **Octreotide** 

**LH/FSH SECRETING transsphenoidal resection** (if tumor growth causes symptoms). **Bromocriptine** (10% response rate)

**NON FUNCTIONAL transsphenoidal resection** (if tumor growth causes symptoms)

# SPECIFIC ENTITIES

### ANTERIOR PITUITARY DEFICIENCY

- CAUSES infiltration (tumor, sarcoidosis), infection (TB, actinomycosis), infarction (Sheehan's), autoim mune hypophysitis, inherited, irradiation
- CLINICAL FEATURES growth failure, deficient or absent lactation, hypogonadism, hypothyroidism, and adrenal insufficiency. In pituitary apoplexy may have severe headache and visual disturbance
- TREATMENTS dexamethasone, surgery

# POSTERIOR PITUITARY DEFICIENCY

 CAUSES infiltration (tumor, sarcoidosis), infection (TB), infarction (Sheehan's), irradiation, iatrogenic (neurosurgery)

# SPECIFIC ENTITIES (CONT'D)

- CLINICAL FEATURES diabetes insipidus
- TREATMENTS desmopressin/DDAVP see diabetes insipidus (p. 347) for more details

#### ACROMEGALY

- PATHOPHYSIOLOGY usually due to excessive growth hormone secretion by pituitary adenoma
- CLINICAL FEATURES vitals (hypertension), large, doughy, spade like hands, increased ring, glove, shoe, and hat size, increased sweating, osteoar thritis (DIP, PIP, CMC, wrists), carpal tunnel syn drome, proximal muscle weakness, course facial features, frontal bossing, bitemporal hemianop sia, 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, tes ticular 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 (pre ferred, 5 20% recurrence). Irradiation of pitui tary. Octreotide (long acting analogue of soma tostatin). Bromocriptine

NEJM 2006 355:24

# **Polyuria**

# DIFFERENTIAL DIAGNOSIS

**OSMOTIC DIURESIS** ( $\sim$ 3 L/day, urine osmo $\sim$ 500 mOsm/kg) glucose, urea, mannitol

**WATER DIURESIS** ( $\sim$ 20 L/day, urine osmo <100 mOsm/kg)

- NEPHROGENIC DIABETES INSIPIDUS chronic kidney disease, hypercalcemia, hypokalemia, lithium, demeclocycline
- CENTRAL DIABETES INSIPIDUS granulomatous infiltration (sarcoidosis, TB, histiocytosis X), trauma (closed head injury, neurosurgery), tumor (craniopharyngioma, metastatic breast cancer, metastatic lung cancer)
- PSYCHOGENIC POLYDIPSIA

**SALINE DIURESIS** (∼3 L/day, urine osmo ~300 mOsm/kg) post ATN, post obstructive

### PATHOPHYSIOLOGY

**DEFINITION OF POLYURIA** urine >3 L/day

# INVESTIGATIONS

#### BASIC

 LABS lytes, urea, Cr, glucose, osmolality (if dia betes insipidus, >290 mOsm/kg), urine lytes, urine osmolality (if diabetes insipidus, <275 mOsm/kg)</li>

# **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 des mopressin/DDAVP SC causes concentration of the urine in central DI but not nephrogenic. Measure urine osmolality 30min, 60min, and 120 min after.
 † in urine osmolality by 50% suggests central DI

348 Adrenal Incidentaloma

### MANAGEMENT OF DIABETES INSIPIDUS

TREAT UNDERLYING CAUSE central diabetes insipidus (desmopressin DDAVP 5 40 µg/day nasal

# MANAGEMENT OF DIABETES INSIPIDUS (CONT'D)

or 0.05 1.2 mg/day PO or 1 2  $\mu$ g SC/IV/day. Note the risk of hyponatremia)

# Adrenal Incidentaloma

NEJM 2007 356:6

### **DIFFERENTIAL DIAGNOSIS**

### BENIGN

- **FUNCTIONAL TUMOR** Cushing's, Conn's (primary hyperaldosteronism), pheochromocytoma
- NON-FUNCTIONAL TUMOR

#### MALIGNANT

- FUNCTIONAL TUMOR Cushing's, aldosterone secreting, pheochromocytoma, adrenocortical carcinoma
- NON-FUNCTIONAL TUMOR, METASTASES lung, breast, Gl, renal, melanoma

### PATHOPHYSIOLOGY

**SYMPATHETIC RESPONSE** adrenal medulla pro duces 85% epinephrine and 15% norepinephrine. Epinephrine has equal effect on  $\alpha$  and  $\beta$  receptors. Norepinephrine acts mainly on  $\alpha$  receptors

- ACTIVATION OF  $\alpha$  RECEPTORS peripheral vasocon striction, mydriasis, and sweating
- ACTIVATION OF  $\beta$  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 (AlI, 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 obe sity, thin extremities, acne, emotional and cognitive changes, opportunistic infections, altered reproduc tive function, hirsutism. Typical symptoms and signs of Cushing's may be minimal or absent with ectopic ACTH production. Hypokalemic alkalosis may be the only obvious initial finding
- SYMPTOMS OF PHEOCHROMOCYTOMA episodic spells of palpitations, pallor, tremor, headache, diaphoresis

## CLINICAL FEATURES (CONT'D)

- **SYMPTOMS OF CONN'S** hypokalemia, hypertension
- SYMPTOMS OF ADRENOCORTICAL CARCINOMA andro gen secretion leading to virilization, severe hirsut ism, acne, amenorrhea
- PAST MEDICAL HISTORY particularly lung, breast, gastrointestinal, and renal cell cancer or mela noma, smoking history

**PHYSICAL** vitals (tachycardia, paroxysmal or sus tained hypertension, orthostatic hypotension), pallor, tremor, thin skin, proximal muscle weakness, hyper tensive retinopathy, moon face, plethora, acne, hir sutism, supraclavicular and dorsocervical fat pad, supraclavicular lymphadenopathy, left ventricular hypertrophy, central obesity, abdominal masses

# INVESTIGATIONS

### BASIC

- LABS cortisol and ACTH, 24 h urine cortisol and creatinine, DHEAS androstenedione, testosterone, plasma renin and aldosterone, lytes urea, creati nine, 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 INCIDEN

**TALOMA** 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 (gluco corticoid, 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

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# DIAGNOSTIC ISSUES (CONT'D)

- ADRENOCORTICAL CARCINOMA irregular, heteroge neous 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, para thyroid 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, palpita tions, cold sweats. ★10% tumor★ 10%

# SPECIFIC ENTITIES (CONT'D)

incidental, 10% bilateral, 10% extra adrenal, 10% malignant, 10% recurrence, 10% in children, 10% familial (MEN, VHL)

- **DIAGNOSIS** 24 h urinary metanephrine and creatinine
- TREATMENTS volume repletion (reduce postural hypotension from adrenergic blockage). α Block ade (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 hyperaldos teronism) can be due to adrenal adenoma or hyperplasia. Secondary hyperaldosteronism can be due to 

  renin from edematous states, dehydra tion, diuretics, and renal artery stenosis
- CLINICAL FEATURES hypertension, 
   ↓ K
- DIAGNOSIS ↓ renin and ↑ aldosterone for Conn's, ↑ renin and ↑ aldosterone for secondary hyperal dosteronism
- TREATMENTS for unilateral Conn's amenable to surgery, consider adrenalectomy. Otherwise, con sider medical therapy (spironolactone 12.5 100 mg PO BID or amiloride 5 10 mg PO daily)

# **Adrenal Insufficiency**

# DIFFERENTIAL DIAGNOSIS

PRIMARY (Addison's disease)

- AUTOIMMUNE
- INFECTIONS TB, histoplasmosis, coccidioidomy cosis, AIDS
- HEMORRHAGE anticoagulants, sepsis (Water house Friderichsen syndrome, associated with meningococcemia), trauma, anticardiolipin antibodies
- INFILTRATION cancer, sarcoidosis, amyloidosis SECONDARY (\perp ACTH secretion) exogenous glu cocorticoid therapy, pituitary or hypothalamus tumor, infarction, infection, infiltration, irradiation

## CLINICAL FEATURES

HISTORY fatigue, weight loss, nausea and vomiting, syncope, severe abdominal pains, muscle weakness, dehydration, salt cravings, hyperpig mentation (Addison's only), visual field changes (pituitary tumor), evidence of steroid use, past medical history (TB, cancer, sarcoidosis), medications (anticoagulation)

**PHYSICAL** orthostatic hypotension, hyperpigmen tation (Addison's only)

# DISTINGUISHING FEATURES BETWEEN PRIMARY AND SECONDARY ADRENAL INSUFFICIENCY Addison's disease Secondary adrenal insufficiency

Adrenal hormones affected Cortisol DHEAS Cor

Aldosterone

ACTH ↑

 $\begin{array}{ccc} \text{Electrolytes} & & \downarrow \text{Na,} \uparrow \text{K} \\ \text{Symptoms} & & \text{Hyper pigmentation} \end{array}$ 

Cortisol DHEAS

↓ ∴ Na only

No skin changes. GI symptoms and hypotension less prominent

350 Cushing's Syndrome

### 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 sus pect sepsis

### DIAGNOSTIC ISSUES

### **ACTH STIMULATION TEST**

- STANDARD HIGH DOSE baseline cortisol and ACTH, give cosyntropin 250 μg IV, measure cortisol 30 and 60 min after; cortisol level should double from its baseline and be >550 nmol/L to exclude adre nal insufficiency
- LONG VERSION same as above except give cosyn tropin 250  $\mu g$  IV over 8 h daily  $\times 3$  days. The response will be abnormal by the third day if primary adrenal insufficiency, but normal if secondary

# MANAGEMENT

**ACUTE ADRENAL CRISIS** ABC, O<sub>2</sub>, IV. Fluids (D5NS 2 3L IV bolus). **Corticosteroid** (hydrocortisone

### MANAGEMENT (CONT'D)

100 mg IV q6h or *dexamethasone* 4 mg IV q6h (dex amethasone does not interfere with ACTH stimula tion test). **Treat precipitant** (sepsis, viral qastroenteritis)

LONG TERM TREATMENT physiologic replace ment (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 gluco corticoids 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 anaes thetic) double the regular dose of glucocorti coids (e.g. prednisone 15 mg/day)
- MODERATE STRESS (e.g. orthopedic surgery, perivas cular surgery) hydrocortisone 100 mg IV on call to OR, followed by 100 mg IV q8h ×24 h postop, then regular daily dose
- HIGH STRESS (e.g. intraabdominal operations, car diac surgery) hydrocortisone 100 mg IV, followed by 50 mg IV q8h ×24 h, and taper by 50% per day until regular daily dose

# **Cushing's Syndrome**

## DIFFERENTIAL DIAGNOSIS

IATROGENIC (↓ ACTH)

**PITUITARY** (↑ ACTH) Cushing's disease

**ECTOPIC** (↑ ACTH) small cell lung cancer

**ADRENAL** (↓ ACTH) adenoma, carcinoma

# CLINICAL FEATURES

# SIGNS AND SYMPTOMS OF CUSHING'S SYNDROME

- NEUROLOGICAL euphoria, depression, psychosis, restlessness, irritability, insomnia
- **OPHTHALMIC** glaucoma, cataract
- CARDIOVASCULAR hypertension, fluid retention
- GASTROINTESTINAL gastritis, ulcers, GI bleed
- HEMATOLOGICAL leukocytosis, immunosuppression
- ENDOCRINE hyperglycemia, insulin resistance, hypogonadism, central obesity, hirsutism, weight gain
- MUSCULOSKELETAL osteoporosis, avascular necro sis, proximal myopathy
- DERMATOLOGICAL striae, moon face, buffalo hump, supraclavicular fat pad, skin thinning, easy bruising, acne, poor wound healing

## CLINICAL FEATURES (CONT'D)

Note that typical symptoms and signs of Cushing's may be absent or minimal with ectopic ACTH produc tion. 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 (leukocy tosis with relative lymphopenia), lytes, urea, Cr, glucose, HbA1C, fasting lipid profile
- DEXAMETHASONE SUPPRESSION TEST a functional test to determine the cause of Cushing's syn drome. 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

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### 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 sup press 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. Fail ure to suppress cortisol confirms Cushing's syndrome HIGH DOSE DEXAMETHASONE SUPPRESSION TEST give dexamethasone 2 mg PO q6h for 2 days and measure AM cortisol, ACTH, afternoon cortisol, and 24 h urine cortisol and creatinine for 2 days. Partial suppression of cortisol confirms pituitary Cushing's. Failure to suppress cortisol confirms ectopic or adrenal Cushing's

# DIAGNOSTIC ISSUES (CONT'D)

**CORTISOL BINDING GLOBULIN** plasma cortisol is bound to cortisol binding globulin. Oral contra ceptive pills increase cortisol binding globulin and thus the measured plasma cortisol. However, 24 h urinary cortisol will be normal as it measures unbound cortisol

### MANAGEMENT

### TREAT UNDERLYING CAUSE

- IATROGENIC avoid or reduce the dose of steroids if possible
- PITUITARY first line transsphenoidal surgery (90% cure rate) or pituitary irradiation. Second line bilat eral adrenalectomy. Third line ketoconazole or metyrapone.
- ADRENAL unilateral adrenalectomy
- ECTOPIC resection of ectopic source if appropri ate; otherwise, bilateral adrenalectomy and keto conazole 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 adrenocortico lytic medical therapy, lifelong replacement is needed. Do not forget stress dose!

EQUIVALENT DOSING TABLE					
	Half life (h)	Equivalent anti inflammatory potency <sup>a</sup>	Equivalent mineralocorticoid potency <sup>a</sup>		
Glucocorticoids					
Short acting					
Cortisone	8 12	0.2	2		
Hydrocortisone	8 12	0.25	2		
Intermediate acting					
Methylprednisolone	18 36	1.25	0		
Prednisolone	18 36	1	1		
Prednisone	18 36	1	1		
Triamcinolone	18 36	1.25	0		
Long acting					
Betamethasone	36 54	8.33	0		
Dexamethasone	36 54	6.66	0		
Mineralocorticoid					
Fludrocortisone	12 24	0.5	125		
<sup>a</sup> Higher number indic	ates greater po	tency as compared to predisone			

352 Hypocalcemia

### SPECIFIC ENTITIES

### PSEUDO CUSHING'S SYNDROME

- CAUSES hypercortisolism associated with severe stress, depression, obesity, and chronic alcoholism
- CLINICAL FEATURES may mimic Cushing's syn drome clinically, but rarely associated with derma tologic and muscular complications (e.g. bruising, thinning of skin, proximal muscle weakness)

### **NELSON'S SYNDROME**

 PATHOPHYSIOLOGY following bilateral adrenalect omy for Cushing's disease, residual pituitary tumor enlarges and marked skin pigmentation results

### SPECIFIC ENTITIES (CONT'D)

- DIAGNOSIS clinical history and ↑ ACTH (>44 pmol/L [>200 pg/mL]) associated with hyperpigmentation
- TREATMENTS most cases preventable with pituitary irradiation with bilateral adrenalectomy. Medical therapy relatively ineffective. Refer for transsphe noidal surgery or irradiation before development of macroadenoma. Consult endocrinology

# Hypocalcemia

### **DIFFERENTIAL DIAGNOSIS**

### PTH ABNORMALITIES (PO<sub>4</sub> ↑)

- HYPOPARATHYROIDISM surgery, irradiation, autoim mune, congenital, infiltrative, DiGeorge's syndrome
- FUNCTIONAL HYPOPARATHYROIDISM Mg deficiency
- **PTH RESISTANCE** pseudohypoparathyroidism

# VITAMIN D ABNORMALITIES (PO4 1)

- VITAMIN D DEFICIENCY nutritional, malabsorption
- ALTERED VITAMIN D METABOLISM cirrhosis, chronic renal failure, anticonvulsant
- VITAMIN D RESISTANCE

DRUGS phosphates (hyperphosphatemia), calci tonin, bisphosphonates, plicamycin, loop diuretics ACUTE CAUSES acute pancreatitis, rhabdomyo lysis, tumor lysis, large transfusions of citrate con taining blood products, toxic shock syndrome OTHERS calcium malabsorption, hypoalbu minemia

### PATHOPHYSIOLOGY

 $\begin{array}{ll} \textbf{DEFINITION OF HYPOCALCEMIA} & corrected serum Ca \\ < 2.1 \text{ mM } [< 8.4 \text{ mg/dL}]. \text{ For every 10 mg/L } [1 \text{ g/dL}] \downarrow \text{in albumin, correct serum Ca by adding } 0.2 \text{ mM } [0.8 \text{ mg/dL}] \\ \end{array}$ 

## PTH AND VITAMIN D

- VITAMIN D FORMATION 7 dihydrocholesterol  $\rightarrow$  skin with UV  $\rightarrow$  cholecalciferol (vitamin D<sub>3</sub> may be obtained via diet as well)  $\rightarrow$  liver  $\rightarrow$  250H D<sub>3</sub> (used to determine vitamin D status)  $\rightarrow$  kidney (stimulated by PTH or hypo PO<sub>4</sub>)  $\rightarrow$  1,25(OH)<sub>2</sub>D<sub>3</sub> (also known as calcitriol, the active form of vitamin D)
- 1,25(OH)<sub>2</sub>D<sub>3</sub> ↑ Ca reabsorption at gut, kidney, and bone, ↑ PO<sub>4</sub> reabsorption at gut and kidney
- PTH ACTION ↑ Ca reabsorption at distal tubule and bone, ↓ PO<sub>4</sub> reabsorption at proximal tubule, ↑ 1,25(OH)<sub>2</sub>D<sub>3</sub>

### CLINICAL FEATURES

**HISTORY** tetany, stridor (laryngospasm), seizures, confusion, weakness, past medical history (thyroid

### CLINICAL FEATURES (CONT'D)

surgery), medications (loop diuretics, bisphospho nates, calcitonin, anticonvulsants)

**PHYSICAL** hypotension, Trousseau's sign, Chvos tek's sign, carpal/pedal spasm, weakness

### INVESTIGATIONS

### **BASIC**

 LABS Ca, albumin, Mg, PO<sub>4</sub>, PTH, ALP, 25OH D<sub>3</sub>, 1,25(OH)<sub>2</sub>D<sub>3</sub>, lytes, urea, creatinine

### SPECIAL

• ECG may show prolonged QT interval

# MANAGEMENT

**SYMPTOM CONTROL** if severe symptoms, *Ca glu conate* 1 2 amps IV push then run a calcium drip 0.5 1.5 mg/kg/h, and  $MgSO_4$  2 g IV over 2 h. If mild symptoms,  $CaCO_3$  1 2 g PO TID, calcitriol (1,25(OH)<sub>2</sub>D<sub>3</sub>) 0.25 1  $\mu$ g daily

TREAT UNDERLYING CAUSE

### **Related Topic**

Hypophosphatemia (p. 83)

### SPECIFIC ENTITIES

### VITAMIN D DEFICIENCY

 CAUSES vitamin D deficient diet and/or lack of exposure to sunlight, fat malabsorption syn dromes, extensive burns (decreased skin conver sion), nephrotic syndrome (renal loss), medications (anticonvulsants, glucocorticoids, immunosup pressants and HAART may lead to increased inac tivation of 1,25(OH)<sub>2</sub>D<sub>3</sub>), chronic kidney disease (decreased activation), liver failure (decreased activation) Hypercalcemia 353

# SPECIFIC ENTITIES (CONT'D)

- CLINICAL FEATURES hypocalcemia, hypophospha temia, osteomalacia with associated bone pain, osteoporosis with fractures and hyperparathyroid ism. Vitamin D deficiency has also been postulated to be associated with chronic diseases such as cancer, cardiovascular diseases, diabetes, autoim mune disorders, and osteoarthritis
- **DIAGNOSIS** 25 hydroxyvitamin D is used to deter mine the level of vitamin D as it represents the

# SPECIFIC ENTITIES (CONT'D)

combined level from both dietary and skin sources. A level <80 nmol/L is considered to be abnormal

• **TREATMENTS** vitamin D2 50,000 IU per week ×8 weeks for most causes; repeat for another 8 weeks if 25 hydroxyvitamin D still low. Long term use of vitamin D3 800 1000 IU PO daily. For renal failure, calcitriol 0.25 1 μq PO BID should be given

NEJM 2007 357:3

# Hypercalcemia

# DIFFERENTIAL DIAGNOSIS

HYPERPARATHYROIDISM (most common cause among outpatients) parathyroid adenoma, para thyroid hyperplasia, parathyroid carcinoma (rare) MALIGNANCY (most common cause among inpatients) lung, breast, prostate, renal, thyroid, Gl, melanoma, sarcoma, multiple myeloma, lym phoma, 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)  $\downarrow$  in albumin, correct serum Ca by adding 0.2 mmol/L [0.8 mg/dL]

**PTH ACTION**  $\uparrow$  Ca reabsorption at distal tubule and bone,  $\downarrow$  PO<sub>4</sub> reabsorption at proximal tubule,  $\uparrow$  1,25(OH)<sub>2</sub>D<sub>3</sub>

MALIGNANCY RELATED MECHANISMS local osteo lytic bone lesions, humoral hypercalcemia of malig nancy (PTH related peptide), 1,25(OH)<sub>2</sub>D<sub>3</sub> secretion (lymphomas), ectopic hyperparathyroidism (very rare) SARCOIDOSIS MECHANISM unregulated synth esis of 1,25(OH)<sub>2</sub>D<sub>3</sub>, the active metabolite of vitamin D, in macrophages of granulomas

# CLINICAL FEATURES

#### SYMPTOMS

- GI abdominal pain from constipation, pancreati tis, or peptic ulcer disease (moans), N&V
- MSK bony pain (groans)
- RENAL calculi (stones), polyuria
- CNS delirium (psychiatric overtone)

### INVESTIGATIONS

#### BASIC

 LABS Ca, albumin, Mg, PO<sub>4</sub>, PTH, ALP, 1,25(OH)<sub>2</sub>D<sub>3</sub>, lytes, urea, creatinine

#### SPECIAL

- MALIGNANCY WORKUP consider PTHrP, serum protein electrophoresis, urine protein electro phoresis, 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 famil ial hypocalciuric hypercalcemia, ↓ in vitamin D excess or PTHrP

#### DISTINGUISHING FEATURES BETWEEN IMPORTANT CAUSES OF HYPERCALCEMIA **Primary** PTH Sarcoidosis PTHrP **FHH** Ca $\uparrow \uparrow$ PO<sub>4</sub> PTH ↑ ↑ / N ↑/N PTHrP Calcitriol I/N**↑/N** Urine Ca

### MANAGEMENT

**SYMPTOM CONTROL NS** 200 500 mL/h IV  $\pm$  *fur osemide* 20 40 mg IV TID PRN. If Ca is 3.0 mmol/L [12 mg/dL] or more give **bisphosphonates** (*pami dronate* 60 90 mg in 500 mL NS IV over 4 h or *zoledronate* 4 mg in 50 mL NS IV over 15 min). Malign 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

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### TREATMENT ISSUES

INDICATIONS FOR PARATHYROIDECTOMY IN PATIENTS WITH ASYMPTOMATIC HYPERPAR ATHYROIDISM age <50, Ca > 2.85 mmol/L [>11.4 mg/dL], GFR <60 mL/min, osteoporosis with a *T* score of 2.5 at any site and/or previous fragility fracture or difficult to provide follow up

### SPECIFIC ENTITIES

### FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FHH)

- PATHOPHYSIOLOGY autosomal dominant inactivating mutations in the calcium sensor receptor in parathyroid gland and kidneys, leading to a change in set point and increased serum calcium level to suppress PTH release and reabsorption of calcium in the kidneys
- CLINICAL FEATURES usually asymptomatic. Renal stones uncommon
- DIAGNOSIS ↑ serum calcium, ↓ urinary calcium, ↑/
  N PTH. Family history can be helpful. Important to
  differentiate from primary hyperparathyroidism as

# SPECIFIC ENTITIES (CONT'D)

- 15 20% of FHH will have elevated PTH, and FHH does not require treatment
- TREATMENTS not required

#### MILK ALKALI SYNDROME

- PATHOPHYSIOLOGY ingestion of significant amounts of calcium and absorbable alkali (e.g. CaCO<sub>3</sub>) used as antacids and treatment of osteo porosis. The combination of increased alkali intake, decreased renal function, and hypercalce mia contributes to metabolic alkalosis, which decreases calcium excretion and in turn contri butes to hypercalcemia
- CLINICAL FEATURES triad of hypercalcemia, meta bolic 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
- **TREATMENTS** low calcium diet. Hydration. Sup portive measures

# Osteoporosis

Canadian Osteoporosis Guidelines 2002 NEJM 1998 338:11 NEJM 2005 353:2

# CAUSES

**ENDOCRINE** estrogen deficiency (post menopau sal), 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 cir rhosis), 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 osteo porosis based on bone mineral density (BMD) mea surements, relative to a normal young adult popula tion of the same sex and ethnicity. *T* score is the number of standard deviations above/below the mean BMD for normal young adults, while *Z* score compares with peers (of the same age, sex, and ethnicity)

Status	T score	
Normal	+ 2.5 to	1.0 (inclusive)
Osteopenia	Between	1.0 and 2.5

# PATHOPHYSIOLOGY (CONT'D)

Status	T score
Osteoporosis	≤ 2.5
Severe	≤ 2.5 and fragility fracture
osteoporosis	

## CLINICAL FEATURES

**HISTORY** history of fragility fractures, height loss, Dowager's hump (thoracic kyphosis), milk/calcium consumption, sedentary lifestyle, other risk factors, past medical history, medications (steroids, heparin), family history, smoking, alcohol, and caffeine intake

# RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS WOMAN HAVE OSTEOPOROSIS?

	LR+	LR
History		
Self reported humped back	3.0	0.85
Physical		
Weight <51 kg	7.3	0.8
Kyphosis	3.1	0.8
Tooth count <20	3.4	0.8
Rib pelvis distance ≤2 finger	3.8	0.6
breadths (indicative of spinal		
fracture)		
Wall occiput distance >0 cm	4.6	0.5
(indicative of spinal fracture)		

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CLINICAL FEATURES (CONT'D)				
	LR+	LR		
Decision Rules				
Simple calculated osteoporosis risk	1.2	0.02		
estimation (score $\geq$ 6)				
Osteoporosis risk assessment	1.4	0.1		
instrument (score $\geq$ 9)				
National osteoporosis foundation	1.2	0.2		
(score $\geq$ 1)				
Age/body size/no estrogen (score	1.6	0.3		
≥2)				

**APPROACH** "no single physical examination find ing or combination of findings is sufficient to rule in osteoporosis or spinal fracture without further test ing. 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, PO<sub>4</sub>, 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)</li>
- 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 his tory of fragility fracture after age 40 or any clinical risk factors (1 major or 2 minor)

- MAJOR age >65, vertebral fracture, family his tory, systemic glucocorticoid treatment >3 months, malabsorption syndrome, primary hyper parathyroidism, propensity to fall, osteopenia apparent on X ray, hypogonadism, early meno pause age <45</li>
- MINOR rheumatoid arthritis, hyperthyroidism, chronic anticonvulsant treatment, low dietary cal cium, smoker, excessive alcohol, excessive caf feine, weight <57 kg [<126 lb], weight loss >10% of weight at 25 years, chronic heparin treatment

# DIAGNOSTIC AND PROGNOSTIC ISSUES (CONT'D)

**PROGNOSIS** an average 50 year old Caucasian woman has a remaining lifetime risk of 40% of devel oping hip, vertebra, or wrist fractures

### MANAGEMENT

**LIFESTYLE CHANGES** CaCO<sub>3</sub> 500 mg PO TID. Vita min D 800 IU PO daily. Physical activity >30 min 3×/week. Avoid excess caffeine (>4 cups/day) and avoid dietary Na (>2100 mg/day)

MEDICATIONS bisphosphonates (patients over the age of 50 should be stratified as to their 10 year fracture risk. Patients who are at high risk of having a fracture in the next 10 years should be started on bisphosphonates. Bisphosphonates should be taken with water >60 min before first meal, and remain upright ×30 min. Alendronate 70 mg PO weekly, risedronate 35 mg PO weekly, etidronate/Didrocal kit 1 tablet/day). Duration of therapy is controversial (e.g. 5 10 years, with possibly "drug holiday" for 1 5 years between treatment courses). **SERM** (ralox ifene 60 mg PO daily). hPTH(1 34) (first line for treatment if severe osteoporosis). Calcitonin (second line for prevention, first line for pain. Calcitonin nasal spray 200 IU NAS daily alternate nostrils). Hormone replacement (no longer used in osteoporosis, used only for control of hot flashes)

### TREATMENT ISSUES

# WHO SHOULD BE TREATED?

- IF-2.5 < BMD< 1.5 plus any one of following: personal history of fragility fracture after age 40, non traumatic vertebral deformities, or clinical risk factors (1 major or 2 minor) lifestyle  $\Delta$  + medications
- IF BMD < 2.5 lifestyle  $\Delta$  + 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 7 score 1 to 2 SD (+2), 2 to 2.5 SD (+3), < 2.5 SD (+4)
- 5-YEAR FRACTURE RISK for vertebral, non vertebral and hip fractures, score 1 2=1.2, 9.6, 0.4%, respectively. Score 3 4=2.5, 13.1, 0.9%. Score 5=5.3, 16.5, 1.9%. Score 6 7=7.1, 19.8, 3.9%. Score 8 13=11.2, 27.5, 8.7%. A score of 4 or greater war rants treatment

# SPECIFIC ENTITIES

# PAGET'S DISEASE OF BONE

 PATHOPHYSIOLOGY aggressive bone resorption by osteoclasts (skull, pelvis, vertebra, femur, tibia) that 356 Amenorrhea

# SPECIFIC ENTITIES (CONT'D)

extends by 1 cm/year. This is followed by imper fect 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 hear ing 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 thick ening (hyperostosis) disorganized coarse trabecu lae (osteosclerosis), and bone expansion may be

# SPECIFIC ENTITIES (CONT'D)

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 sur gery planned for pagetic site (e.g. hip replace ment) 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, adeno mas, craniopharyngioma
- OVARIAN FAILURE Turner's syndrome (XO)
- UTERUS/VAGINA MALFORMATION androgen insen sitivity syndrome (XY), agenesis of uterus/vagina (Mullerian agenesis), imperforated hymen
- OTHERS constitutional delay, causes of second ary amenorrhea

## SECONDARY AMENORRHEA

- PREGNANCY
- HYPOTHALAMIC SUPPRESSION physiologic or emo tional stress, strenuous exercise, weight loss, anor exia nervosa, infiltrative disease (lymphoma, sarcoidosis)
- PITUITARY DISEASE prolactinoma, Sheehan's syn drome, hypothyroidism

# DIFFERENTIAL DIAGNOSIS (CONT'D)

- OVARIAN PCOS, menopause (chemotherapy, radiation, birth control pills), premature ovarian failure
- UTERUS Asherman syndrome

## PATHOPHYSIOLOGY

#### **DEFINITION OF AMENORRHEA**

- PRIMARY AMENORRHEA absence of menstruation by age 14 with the absence of secondary sexual char acteristics 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, dura tion, previous menstruation), pregnancy and related symptoms, puberty milestones, headaches, visual

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# CLINICAL FEATURES (CONT'D)

field defects, fatigue, polyuria, polydipsia, weight change, physiologic or emotional stressors, galactor rhea, 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 hir sutism, acne, striae, acanthosis nigricans, vitiligo, and signs of hypothyroidism. Perform pelvic examination

### INVESTIGATIONS

### **BASIC**

- LABS glucose, TSH, prolactin, βhCG, LH, FSH, estradiol, testosterone, DHEA S
- IMAGING U/S pelvis (if suspect PCOS), CT abd/ pelvis (if suspect adrenal tumor)

# INVESTIGATIONS (CONT'D)

### SPECIAL

- LAPAROSCOPY
- HYSTEROSALPINGOGRAM Asherman syndrome
- PROGESTERONE CHALLENGE TEST administer pro gesterone for 7 days. Presence of withdrawal bleed within 7 days of completion of progester one suggests anovulation with progesterone deficiency (e.g. PCOS). Absence of withdrawal bleed suggests ovarian failure or outflow tract obstruction

### MANAGEMENT

**TREAT UNDERLYING CAUSE** hypothalamic sup pression (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, spiro nolactone, metformin)

# Hirsutism

### **DIFFERENTIAL DIAGNOSIS**

# **TESTOSTERONE EXCESS**

- POLYCYSTIC OVARY SYNDROME most common, insulin resistance with hyperinsulinemia
- IDIOPATHIC HIRSUTISM common
- OVARIAN TUMORS Sertoli Leydig cell tumor, granulosa theca cell tumor, hilus cell tumor
- ADRENAL TUMORS carcinoma, adenoma
- ANDROGEN THERAPY testosterone

# **DHEAS EXCESS**

- CONGENITAL ADRENAL HYPERPLASIA
- ADRENAL TUMORS carcinoma, adenoma
- ANDROGEN THERAPY DHEA, danazol

# PATHOPHYSIOLOGY

HIRSUTISM androgen excess leading to excessive male pattern hair growth (terminal body hairs on face, chest, abdomen, and back). There may be asso ciated 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.

### PATHOPHYSIOLOGY (CONT'D)

Most commonly familial or caused by systemic dis orders (hypothyroidism, anorexia nervosa, malnutri tion, 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 his tory, medications, family history

PHYSICAL BMI, skin and hair growth pattern, signs of virilization, abdominal and pelvic examination

### INVESTIGATIONS

### BASIC

- LABS testosterone, DHEA S, prolactin, LH and FSH (may be elevated in PCOS), 17 OH progesterone
- IMAGING U/S pelvis (if suspect PCOS), CT abd/ pelvis (if suspect adrenal tumor)

### **SPECIAL**

 LAPAROSCOPY/LAPAROTOMY if suspect ovarian tumor

DIAGNOSTIC ISSUES					
DISTINGUISHING FEATURES					
	PCOS	CAH	Idio pathic	Ovary tumor	
Age	Puberty	Puberty	Puberty	30 s	
Menstruation	Altered	May be altered	Normal	Normal	
Hirsutism	+	+	+	+++ virilization	
Course	Slow	Slow	Slow	Acute	
Testosterone/DHEAS	+	+	Normal	++	
17 OH prog.		+			

### MANAGEMENT

### TREAT UNDERLYING CAUSE

### SPECIFIC ENTITIES

## POLYCYSTIC OVARIAN SYNDROME (PCOS)

- PATHOPHYSIOLOGY increased androgen production in both puberty (increased ovarian steroid production) and adrenarche (increased adrenal androgen production). Increased insulin resistance leads to maturation arrest of the developing follicle. Increased testosterone is released from the ovaries instead. Cycles are anovulatory
- CLINICAL FEATURES menstrual irregularity, hyperan drogenism (hirsutism, acne, male pattern balding)
- DIAGNOSIS clinical (oligomenorrhea, evidence of hyperandrogenism, and exclusion of other causes of hyperandrogenism/menstrual irregularity), labora tory (elevated testosterone levels, LH/FSH > 2)
- TREATMENTS weight loss, birth control pills (hir sutism, and endometrium protection), spironolac tone (hirsutism), metformin (ovulatory induction), electrolysis, and laser therapy

# SPECIFIC ENTITIES (CONT'D)

### IDIOPATHIC HIRSUTISM

- CLINICAL FEATURES no menstrual irregularity, hirsutism
- DIAGNOSIS normal androgen levels, diagnosis of exclusion
- TREATMENTS hair removal (electrolysis, laser ther apy), 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 hydroxylase and an androgen precursor) and androstenedione
- CLINICAL FEATURES sometimes menstrual irregularity, hirsutism, no cortisol deficiency. May be indistinguishable from PCOS
- DIAGNOSIS elevated 17 OH progesterone level, elevated DHEAS
- TREATMENTS birth control pills, spironolactone, glucocorticoid at hs to turn off ACTH stimulation, hair removal (electrolysis, laser therapy)

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# Notes

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# Notes

# **12** Dermatology

# Section Editor: Dr. Susan Chon

# **Eczema**

### DIFFERENTIAL DIAGNOSIS OF PRURITUS

## INFLAMMATORY

- DERMATITIS atopic dermatitis, asteatotic eczema, nummular eczema, dyshidrotic eczema, seborrheic dermatitis, stasis dermatitis, irritant contact dermatitis, allergic contact dermatitis
- PSORIASIS
- URTICARIA
- DERMATITIS HERPETIFORMIS

**INFECTIONS** tinea, scabies

**NEOPLASTIC** lymphoma (mycosis fungoides), myeloma, solid tumors

#### **IATROGENIC**

- · DRUG ERUPTION antibiotics, anti seizure
- DRUG-INDUCED PRURITUS opiates, steroids, aspirin, antimalarials

#### SYSTEMIC

- ENDOCRINE diabetes, hypothyroidism, hyperthy roidism
- HEPATOBILIARY PBC, cholestasis
- RENAL uremia, hemodialysis
- INFECTIONS HCV, HIV
- OTHERS sarcoidosis, iron deficiency

# PATHOPHYSIOLOGY

**PATHOGENESIS** chronic inflammatory skin disor der 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 aller gic 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 pla ques 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, hypoal lergenic soaps, daily moisturizers). **Topical corticos teroids** BID ×3 weeks, off 1 week, repeat PRN (typi cally hydrocortisone 1 2.5% for the face, 0.1% triamcinolone for the body), and topical calcineurin inhibitors (tacrolimus, pimecrolimus). **Antihistamines** (diphenhydramine, loratadine, fexofenadine, hydroxy zine, and doxepin. Side effects depend on the indivi dual patient)

# SPECIFIC ENTITIES

### **DERMATITIS HERPETIFORMIS**

- ASSOCIATIONS celiac disease, IgA nephropathy, autoimmune thyroid disease, type 1 diabetes, SLE, Sjogren's syndrome, sarcoidosis, vitiligo, and alope cia areata. Strong linkage to HLA B8, DR3, and DQw2. Increased risk of non Hodgkin's lymphoma
- CLINICAL FEATURES pruritic papulovesicles on exten sor 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 dar ker, scalier, and may even form stasis ulcers **362** Psoriasis Vulgaris

### 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  $\times$ 1 dose, rinse off after 8 14 h. Second line treatments include ivermectin 200 mcg/kg PO  $\times$ 1 dose and repeat PO  $\times$ 1 dose 2 weeks later, lindane 1% lotion or cream  $\times$ 1 dose, rinse off after 8 h, and benzyl benzoate 10 or 25% lotions  $\times$ 1 dose, rinse off after 24 h

NEJM 2006 354:16

# **Psoriasis Vulgaris**

# DIFFERENTIAL DIAGNOSIS OF PAPULOSQUAMOUS LESIONS

**INFLAMMATORY** psoriasis vulgaris, lichen pla nus, nummular eczema, discoid lupus

**INFECTIONS** tinea, pityriasis rosea, secondary syphilis, seborrheic dermatitis

MALIGNANCY mycosis fungoides, basal cell car cinoma, squamous cell carcinoma

IATROGENIC drug eruption

### PATHOPHYSIOLOGY

**INFLAMMATION** a chronic inflammatory skin dis order 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 subun gual 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, coron ary 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 demar cated erythematous plaques with silvery scales that when scratched off reveals punctate blood droplets (Auspitz sign)
- GUTTATE PSORIASIS predilection for trunk. May follow a streptococcal infection. Multiple discrete erythematous papules with silvery scales
- PALMOPLANTAR PSORIASIS mild to severe forms.
   Well demarcated erythematous plaque with silver

# CLINICAL FEATURES (CONT'D)

scales. Cracking, fissures, or bleeding may be seen. Pustular variant also found

- INVERSE PSORIASIS perianal, genital, and axillary well demarcated erythematous plaques that are more likely to be macerated and fissured due to location in a moist and warm environment
- $\begin{array}{ll} \textbf{ERYTHRODERMIC PSORIASIS} & generalized erythema \pm \\ \text{characteristic erythematous plaques with white sil} \\ \text{ver scale and nail changes. Often spares the face} \\ \end{array}$
- PUSTULAR PSORIASIS initial stinging and burning in area may promote scratching, followed by erup tion 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, fluocino nide, 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 aci tretin, cyclosporine, and methotrexate should be con sidered in patients with moderate to severe psoriasis with >10% body surface involvement or severe functional impairment (hands, feet, arthritis, and genitals). If unresponsive or unable to tolerate these, **biologic therapy** such as the TNF $\alpha$  inhibitors should be con sidered. 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 Acne Vulgaris 363

# 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. Topi cal steroid to relieve pruritus

### **LICHEN PLANUS**

- PATHOPHYSIOLOGY autoimmune disease with lymphocytic infiltration in epidermis
- ASSOCIATIONS drugs (β blockers, methyldopa, penicillamine, NSAIDs, ACE inhibitors, carbamaze pine, 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 (lacy white reticular lesions). Lesions may last for a year
- TREATMENTS no treatment needed usually. Topi cal steroids, antihistamines, and antiinflamma tories to relieve pruritus

#### SEBORRHEIC DERMATITIS

- PATHOPHYSIOLOGY a common skin disorder affect ing areas rich in sebaceous glands such as the scalp, face, mid chest, and intertriginous areas. It is caused by the yeast Pityrosporum ovale, with increased host response leading to dermatitis. It is also known as "dandruff" in adults
- CLINICAL FEATURES pink to erythematous plaques with yellow scales or greasy crusts, which may occasionally be pruritic
- TREATMENTS gentle emollients, ketoconazole shampoo or cream, and 1 2.5% hydrocortisone cream. Severe scalp involvement in an adult may also be treated with shampoos containing selenium sulfide, zinc pyrithione, and stronger steroid liquids

### **Related Topic**

Psoriatic Arthritis (p. 282)

### **URTICARIA (HIVES)**

 PATHOPHYSIOLOGY an acute (<6 weeks) or chronic (>6 weeks) type I hypersensitivity reac tion. Most cases are idiopathic but triggers may include infections and medications

### SPECIFIC ENTITIES (CONT'D)

- CLINICAL FEATURES characterized by superficial transient edema with pink highly pruritic papules or plaques with individual lesions having rapid onset and resolution within 24 h. Dermatograph ism 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 erythe matous patches/plaques that slowly enlarge over scalp (tinea capitis), feet (tinea pedis), hand (tinea manuum), groin (tinea cruris), body (tinea cor poris), and nails (onychomycosis). May be asso ciated with pruritus and vesicles
- DIAGNOSIS skin and nail lesions may be difficult to distinguish from psoriasis, eczematous conditions, and lichen planus. KOH examination from skin scrapings shows segmented hyphae and spores
- TREATMENTS tinea capitis (griseofulvin 20 25 mg/kg/day for 6 8 weeks, terbinafine, itra conazole), tinea pedis or cruris (terbinafine 1% cream daily BID, clotrimazole/Lotrimin 1% cream BID), onychomycosis (terbinafine 250 mg PO daily ×6 12 weeks, itraconazole 200 mg PO daily ×8 12 weeks. Need to monitor LFTS)

#### TINEA VERSICOLOR

- PATHOPHYSIOLOGY Malassezia furfur
- CLINICAL FEATURES young adult with hypopig mented, light brown, or salmon colored scaly macules coalescing into patches
- DIAGNOSIS KOH examination from skin scrapings show classic "spaghetti and meatballs" pattern representing hyphae and spores
- TREATMENTS topical (terbinafine 1% cream daily BID, clotrimazole 1% cream BID), systemic (keto conazole, terbinafine, itraconazole)

**GROIN SKIN LESIONS** common causes include tinea cruris, candidiasis, erythrasma (*Corynebacterium minutissimum*), and inverse psoriasis

# **Acne Vulgaris**

NEJM 2005 352:14

### DIFFERENTIAL DIAGNOSIS OF ACNEIFORM LESIONS

ACNE VULGARIS ROSACEA

**PERIORAL DERMATITIS** 

**DRUGS EGFR inhibitors** (erlotinib, gefitinib, cetux imab, panitumumab) can cause pustular folliculitis

### PATHOPHYSIOLOGY

**PATHOGENESIS** condition affecting pilosebaceous units, commonly seen during puberty. Pathogenesis involves androgens, follicular kertinization, and the Gram positive bacteria *Proprionibacterium acnes*. Lesions may present as non inflammatory come dones or inflammatory papules. Inflammatory cysts

364 Exanthematous Lesions

### PATHOPHYSIOLOGY (CONT'D)

may leave behind hyperpigmentation and sometimes scaring

RISK FACTORS drugs (steroids, phenytoin, lithium), androgen excess (PCOS, Cushing's, congenital adrenal hyperplasia)

### CLINICAL FEATURES

### SEVERITY OF ACNE VULGARIS

- MILD mainly comedones with few papules/pustules
- MODERATE moderate papules and pustules (10 40) and comedones (10 40)
- MODERATELY SEVERE numerous papules and pus tules (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

### TREAT UNDERLYING CAUSE

- FIRST-LINE AGENTS topical agents include benzoyl peroxide 2.5 10% daily BID, sulfur based washes, topical retinoids (tretinoin 0.025 0.1% qhs, tazar otene 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

### MANAGEMENT (CONT'D)

BID, tetracycline 250 500 mg daily BID, erythromy cin 250 500 mg BID QID) or antiandrogen therapy such as birth control pills may be used in female patients

SEVERE CASES respond well to oral isotretinoin
 0.5 1 mg/kg/day, with a cumulative dose of
 120 mg/day. Close monitoring with laboratory and clinical follow up. High risk for teratogenicity

#### TREATMENT ISSUES

**RETINOIDS** inhibit sebum excretion and *P. acnes*. Reserved for severe nodulocystic acne. Topical retinoids may cause photosensitivity. Retinoids should never be used in pregnant women as highly teratogenic. Fertile women should take oral contraceptive pills 2 months before and 1 month after oral retinoids

### SPECIFIC ENTITIES

#### ROSACEA

- CLINICAL FEATURES middle age adults with central facial telangiectasias, flushing (especially after ingestion of hot liquids, spicy foods, and other triggers), and acneiform papulopustules in cheeks, nose, forehead, and chin. No comedones. Maybe also associated with rhinophyma (more in men), conjunctivitis, iritis, and keratitis
- TREATMENTS oral antibiotics (tetracycline, ery thromycin), topical antibiotics (metronidazole 0.75%), sulfur based products (sodium sulfaceta mid lotion 10%), pulsed dye laser

### PERIORAL DERMATITIS

- CLINICAL FEATURES young woman with papules and pustules over chin, upper lip, and nasal labial folds
- TREATMENTS oral antibiotics (tetracycline, erythromycin)

# **Exanthematous Lesions**

# DIFFERENTIAL DIAGNOSIS OF EXANTHEMATOUS LESIONS

### INFECTIONS

- VIRAL HCV, HIV, EBV, parvovirus B19, measles, rubella, roseola
- BACTERIAL toxic shock, Staphylococcal scalded skin syndrome, Streptococcal toxic shock syn drome, scarlet fever, meningococcus, rocky mountain spotted fever, typhus

**IATROGENIC** medications (see DRUG ERUPTIONS p. 372)

### CLINICAL FEATURES

**TYPICAL PRESENTATION** widespread erythema tous maculopapular lesions that may be accompanied by fever and malaise

## MANAGEMENT

**TREAT UNDERLYING CAUSE** discontinue any offending drugs. Usually resolve spontaneously

### Related Topic

Fever and Rash (p. 234)

### SPECIFIC ENTITIES

**PARVOVIRUS B19** slapped cheek rash on face and erythematous eruption on trunk, neck, and extremi ties. 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 disor der 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, fol lowed by an exfoliative phase with perioral exuda tion 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 blis ters (blood, conjunctivae, nasopharynx) demon strating staphylococci
- TREATMENTS antibiotics for treatment of staphylococci

### TOXIC SHOCK SYNDROME

 PATHOPHYSIOLOGY exotoxin by specific strains of S. aureus or group A Streptococcus leading to clea vage at the granular layer of the dermis

## SPECIFIC ENTITIES (CONT'D)

- CLINICAL FEATURES young person with fever, malaise, generalized macular, erythematous rash including mucous membranes, palms and soles, evolves into petechiae, vesicles, and bullae. Ulcera tions may be seen on mucous membranes. Hypo tension and organ failure may occur
- **TREATMENTS** fluid resuscitation as needed, *vanco mycin* (30 mg/kg/day IV divided BID) or β lactam plus *clindamycin* (600 mg IV q8h). If unresponsive to fluids or vasopressors, consider *IVIG* (400 mg/kg ×1 dose, limited evidence)

### SCARLET FEVER

- PATHOPHYSIOLOGY erythrogenic toxin by specific strains of group A Streptococcus leading to clea vage at the granular layer of the dermis
- CLINICAL FEATURES children with fever, sore throat, petechiae, and punctate red macules on hard and soft palate and uvula (Forchheimer spots), circumoral pallor, strawberry tongue, erythematous patches involving ears and chest, extend to trunk and extre mities 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\*, pemphi gus 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, Cox sackie 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

### PATHOPHYSIOLOGY (CONT'D)

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 pro drome involves a flu like syndrome with fever, malaise, arthralgias, myalgias, and mucous membrane lesions. This is followed by the development of irregular target like lesions often with necrotic centers that coalesce over time. Flaccid blisters form that spread with pressure (Nikolsky sign) resulting in sheet like loss of epidermis and exposure of the underlying dermis. 90% of patients have mucous membrane involvement and 60% have ocular involvement

### CLINICAL FEATURES (CONT'D)

**NIKOLSKY'S SIGN** pressing on the edges of an intact blister helps to discriminate between an intrae pidermal blistering process (pemphigoid vulgaris, blister extends and breaks easily) and a subepidermal process (TEN, bullous pemphigoid, blister would not advance)

### INVESTIGATIONS

### BASIC

- · LABS CBCD, lytes, Cr, urea
- MICROBIOLOGY fluid C&S, HSV serology, VZV serology
- SKIN BIOPSY

### PROGNOSTIC ISSUES

**PROGNOSIS** mortality rate for SJS and TEN is about 5 and 30 50%, respectively, typically from sepsis and multi organ failure

### MANAGEMENT

**TREAT UNDERLYING CAUSE** identifying and stop ping the offending drug. Corticosteroids may be help ful but can be deleterious in severe forms of SJS/TEN. High dose IVIG is controversial but may halt progres sion. Systemic antibiotics may be necessary

**SUPPORTIVE MEASURES** patients should be man aged in a burn unit or ICU, as electrolyte abnormal ities, renal failure, and pulmonary edema may occur

# SPECIFIC ENTITIES

### **ERYTHEMA MULTIFORME**

- PATHOPHYSIOLOGY immune mediated hypersen sitivity reaction involving the skin and VERY LIM ITED mucous membranes
- ASSOCIATIONS infections (HSV, HBV, HCV, mycopla sma, bacterial, fungal), drugs, pregnancy, malignancy
- CLINICAL FEATURES skin lesions usually preceded by a few weeks of viral prodrome. Macules or papules evolve to form targetoid lesions. Palms, soles, forearms, legs most commonly affected
- TREATMENTS discontinue offending drugs. Treat suspected HSV infection with appropriate antivirals

### **IMPETIGO**

- PATHOPHYSIOLOGY intra epidermal infection by Staphylococcus aureus or β hemolytic streptococci
- CLINICAL FEATURES in bullous form, flaccid, pus filled lesions often found in intertriginous areas.
   More commonly found in children

# SPECIFIC ENTITIES (CONT'D)

- TREATMENTS antibiotics (cefazolin, cephalexin)
  BULLOUS PEMPHIGOID
- PATHOPHYSIOLOGY autoimmune disease with IgG binding to subepidermal proteins, leading to separation of epidermis from dermis
- ASSOCIATIONS furosemide, captopril, thiazide, spironolactone, penicillamine, phenothiazines, tri cyclic antidepressants, benzodiazepines
- CLINICAL FEATURES multiple chronic, pruritic, tense blisters in the elderly. Commonly affecting flexural areas, axillae, and groin. Mucous mem branes affected in <1/3 of cases, but rarely pre senting feature. Nikolsky's sign negative
- **TREATMENTS** discontinue offending drugs. Treat with antiinflammatories and immunosuppres sants, including tetracycline and niacinamide. *Pre dnisone* 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 (para neoplastic)
- 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. Con sider burn unit admission. Prednisone 1 2 mg/kg PO daily. Azathioprine, cyclosporine, mycopheno late 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 bal looned and multi nucleated cells
- TREATMENTS acyclovir, valacyclovir, famciclovir VARICELLA ZOSTER VIRUS (VZV)
- CLINICAL FEATURES crops of vesicles over entire body (varicella) or specific dermatone with reacti vation (zoster, also known as shingles)
- TREATMENTS acyclovir, valacyclovir, famciclovir.
   Amitriptyline, gabapentin, and opioids may be useful for post herpetic neuralgia

Ulcers 367

# **Ulcers**

### DIFFERENTIAL DIAGNOSIS OF ULCERS

### **VENOUS HYPERTENSION**

stasis immobility, CHF, incompetent valves, pregnancy

# • DVT

### ATHEROSCLEROTIC

**NEUROPATHIC** diabetes, leprosy, syphilis, syrin gomyelia, peripheral neuropathy

**VASCULITIC** temporal arteritis, polyarteritis nod osa, systemic sclerosis

### INFECTIONS

- BACTERIAL gumma, mycobacteria
- VIRAL chronic ulcerative herpes simplex
- FUNGAL deep fungal infections
- PARASITIC cutaneous leishmaniasis, cutaneous amehiasis

**TUMOR** squamous cell carcinoma, basal cell carcinoma, melanoma, Kaposi's sarcoma

### **TRAUMA**

### INVESTIGATIONS

### BASIC

- LABS CBCD, lytes, glucose, urea, Cr, HbA1C
- MICROBIOLOGY wound Gram stain, AFB, C&S, TB culture
- ANKLE BRACHIAL INDEX <0.8 indicates arterial origin</li>
- IMAGING doppler ultrasound, venous plethysmography

# **SPECIAL**

- PYODERMA GANGRENOSUM
  - COLONOSCOPY if suspect IBD
  - MALIGNANCY WORKUP serum protein electro phoresis, CXR
  - INFLAMMATORY WORKUP ESR, antiphospholi pid 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 histolo gic evaluation and ulcer edge for bacterial, fungal, and mycobacterial culture

### MANAGEMENT

See SPECIFIC ENTITIES for details

### SPECIFIC ENTITIES

### **VENOUS ULCERS**

 PATHOPHYSIOLOGY result from chronic increases in venous pressure due to either incompetent valves, failure of pump activity from immobility or obesity, or venous outflow obstruction. Increased pressure

### 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 stand ing, and multiple pregnancies
- CLINICAL FEATURES shallow, relatively painless, and typically located from the mid calf to the ankle, classically on the medial malleolus. Other common lower extremity findings include edema, lipodermatosclerosis (firm and indurated skin), hyperpigmentation, and dermatitis
- TREATMENTS compression stockings (need to rule out arterial insufficiency), leg elevation, walking/ physiotherapy. Occlusive dressing (DuoDerm. Weekly if not infected. Twice daily if infected). Diuretics (decrease leg edema). Antbiotics if super infected. Superficial vein surgery may pre vent 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, rheu matic 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 pain ful. Associated features include intermittent clau dication, diminished peripheral pulses, and pro longed capillary refill
- TREATMENTS treat underlying cause, such as sur gical bypass for peripheral arterial disease. Avoid ance of trauma. Apply moist occlusive dressings. Surgical debridement and systemic antibiotics may be necessary if infected. See PERIPHERAL VASCU LAR DISEASE (p. 54)

### **NEUROPATHIC ULCERS**

- PATHOPHYSIOLOGY most common in diabetic patients. A combination of sensory and motor neu ropathy due to enzymatic glycosylation impairs protective sensation and alters the distribution of forces on the lower extremity during normal move ment. Many diabetic patients have a combination of neuropathic and arterial ulcers
- RISK FACTORS diabetes mellitus, syphilis, leprosy, and peripheral neuropathies

### SPECIFIC ENTITIES (CONT'D)

- CLINICAL FEATURES a pure neuropathic ulcer is painless. There is diminished sensation in the lower extremity. Patients have warm extremities with palpable pulses, as opposed to arterial ulcers
- TREATMENTS diabetic patients require tight glu cose control. Treat infection with systemic antibio tics. Debridement of the ulcer, hyperbaric oxygen therapy, and occlusive dressings are applied to promote wound healing. Immobilization and ortho tic devices are used to alleviate pressure on the wound. Amputation may be required in severe

### **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

### SPECIFIC ENTITIES (CONT'D)

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 methylpredni solone* 1 g IV daily  $\times$ 3 day), cyclosporine, and TNF  $\alpha$  blockade and *IVIG* 400 mg/kg IV daily  $\times$ 5 day or 1 g/kg IV daily  $\times$ 2 day have been effective. Other options include sulfasalazine, sulfones, minocycline, and dapsone. Topical and intralesional steroids and tacrolimus have also been used

NEJM 2002 347:18

# **Melanoma and Skin Tumors**

NEJM 2005 353:21; NEJM 2004 351:10; NEJM 2001 344:13

### DIFFERENTIAL DIAGNOSIS OF PIGMENTED LESIONS

**BENIGN nevus** (congenital, acquired), freckle, seborrheic keratosis, cafe au Lait

PRE MALIGNANT dysplastic nevi syndrome
MALIGNANT melanoma (superficial spreading,
nodular, lentigo maligna, acral lentiginous), pig
mented 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 syn drome, 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 (respira tory, GI, GU), palate, gingival, vulva and anus

### SYMPTOMS

- LOCOREGIONAL skin lesion (see JAMA series below)
- METASTATIC depending on location (lung, Gl 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 irregu larity, Color variegation, Diameter >6 mm (sens 92 100%, spc 98% depending on how many criteria

Melanoma and Skin Tumors 369

# CLINICAL FEATURES (CONT'D)

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, dia meter ≥7 mm, crusting or bleeding, sensory change (sens 79 100%, spc 30 37%, depending on how many criteria used)

**APPROACH** "using either checklist, misdiagnos ing 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 sensi tive than those performed by dermatologists"

JAMA 1998 279:9

### INVESTIGATIONS

### **BASIC**

• EXCISIONAL BIOPSY all lesions suspicious for mel anoma 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 pathol ogy confirmation
- IMAGING CXR as part of staging workup after pathology confirmation

### DIAGNOSTIC AND PROGNOSTIC ISSUES

# CLARK'S LEVELS (LIMITED UTILITY FOR SMALL LESIONS)

Level	TNM	5 year survival
1	Intraepidermal (in situ)	100%
II	Invasion into papillary dermis	85%
III	Extensive invasion of papillary dermis	65%
IV	Invasion into reticular dermis	50%
V	Invasion into subcutaneous	15%

# **TNM STAGING 2009**

T STAGE (Breslow depth/thickness)

- T1  $\leq$ 1 mm
  - T1a=without ulceration and mitosis <1/mm<sup>2</sup>
  - **T1b**=with ulceration or mitosis >1/mm<sup>2</sup>
- 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 ≥4 nodes, or matted nodes, or in transit metastasis/satellites with metastatic nodes

**M STAGE** (lungs, bone, liver, skin, and essentially any organ. Biologically heterogeneous with variable course)

- M1a=distant skin, subcutaneous, or nodal metastasis with normal LDH
- M1b=lung with normal LDH
- M1c=visceral organs or elevated LDH

# STAGE GROUPINGS

Stage	TNM @=any	10 year survival
IA	T1aN0M0	95%
IB	T1b T2aN0M0	85%
IIA	T2b 3aN0M0	70%
IIB	T3b 4aN0M0	60%
IIC	T4bN0M0	40%
III	T@N1 3M0	
IIIA	T1a 4aN1aM0,	70%
	T1a 4aN2aM0	
IIIB	T1b 4bN1aM0,	45%
	T1b 4bN2aM0,	
	T1a 4aN1bM0,	
	T1a 4aN2bM0,	
	T1 4aN2cM0	
IIIC	T1b 4bN1bM0,	25%
	T1b 4bN2bM0,	
	T1 4bN2cM0, T@N3M0	
IV	T@N@M1	10%

SENTINEL LYMPH NODE BIOPSY usually done if primary melanomas 1 4 mm thick or ulcerated PROGNOSIS BY SITE OF METASTASIS M1a=62% 1 year survival, M1b=53% 1 year survival, M1c=33% 1 year survival

### MANAGEMENT

**PREVENTION sun avoidance** (sun protective clothing, wide brimmed hat, sunscreens)

**SURVEILLANCE** particularly for high risk individuals **STAGE I III** standard of care is **wide local exci sion**. Mohs micrographic surgery may be used. Exci sion margin 1 cm for lesions <1 mm thick, 2 cm for

### MANAGEMENT (CONT'D)

lesions 1 4 mm thick, >3 cm for lesions >4 mm thick). Sentinel lymph node biopsy for lesions >1 mm thick. If palpable node or sentinel LN positive. consider lymph node dissection and adjuvant high dose interferon  $\alpha 2b$  (5 days/week IV  $\times 4$ weeks, then 3 days/week SC  $\times$ 48 weeks). If extrano dal extension or LN > 3 cm, consider adjuvant radia tion. For locoregional recurrence, consider re exci sion. Follow up of these patients should include a complete review of systems including headache, visual changes, cough, lymph node examination, and for patients with deep melanomas an LDH and imaging to rule out metastasis. Patients should continue skin examinations at least semi annually for new lesions as patients have a 3 5% chance of developing another melanoma

STAGE IV palliative chemotherapy (dacarbazine with response rate 15 20% and median duration of response 4 6 months. Consider temozolomide if CNS metastases). Palliative radiation (if localized pain). Excision of solitary brain or lung metastasis is occa sionally done

### SPECIFIC ENTITIES

**DYSPLASTIC NEVI** acquired moles characterized by cytologic atypia and architectural disorder. They remain dynamic throughout life, constantly appearing, changing, or disappearing

 $\begin{array}{ll} \textbf{DYSPLASTIC NEVUS SYNDROME} & \text{melanoma in } \geq 2 \\ \text{blood relatives and dysplastic nevi in other family} \\ \text{members} \end{array}$ 

# **BASAL CELL CARCINOMA**

- PATHOPHYSIOLOGY the most common form of skin cancer. Although they rarely metastasize, basal cell carcinomas are locally destructive and must be removed
- CLINICAL FEATURES
  - NODULAR SUBTYPE (50 80%) pearly semi trans lucent papules with telangiectasias and central depression; may ulcerate crust or bleed
  - **SUPERFICIAL SUBTYPE** (>15%) psoriasiform scaly plaque; most common on trunk and extremities
  - PIGMENTED SUBTYPE (6%) more common in Latin Americans and Asians
  - MORPHEAFORM SUBTYPE (2 6%) white sclerotic plaque, can mimic a scar; predilection to recur
- RISK FACTORS history of prior sunburns (especially in childhood), radiation therapy, family history, immunosuppression, fair complexion, and red hair
- TREATMENTS usually treated by either excision or electrodessication and curettage. However, if super ficial they may be treated with topical imiquimod

### **ACTINIC KERATOSIS**

 PATHOPHYSIOLOGY form after chronic sun exposure in susceptible individuals usually on the face, scalp,

### SPECIFIC ENTITIES (CONT'D)

forearms, and dorsal hands. Actinic keratoses are foci of superficial keratinocyte dysplasia capable of evolving into squamous cell skin cancer

- CLINICAL FEATURES thin pink to red papules and plaques with overlying scale, may sometimes con tain focal pigment. They are most common on people with fair skin (type I or II) and occur with increased frequency in patients who are immuno suppressed or have received phototherapy
- TREATMENTS cryotherapy for focal lesions. If diffuse damage is present, one may use topical imiquimod, 5 fluorouracil, diclofenac, trichloroacetic acid peels, and photodynamic therapy. If there is a thick component below the skin surface, one should consider a skin biopsy to rule out under lying squamous cell carcinoma

### SQUAMOUS CELL CARCINOMA

- PATHOPHYSIOLOGY second most common form of skin cancer. On average 0.5 5.2% of squamous cell carcinomas metastasize, but they are much more aggressive on mucosal surfaces such as the lip and in areas of previous irradiation and scarring
- RISK FACTORS same as risk factors for actinic ker atoses, plus HPV infection for genital lesions
- CLINICAL FEATURES typically firm red scaly plaques that frequently become ulcerated and occur in areas of heavy sun exposure in fair skinned individuals. Subtypes include
  - Bowen's disease squamous cell carcinoma in situ
  - ERYTHROPLASIA OF QUEYRAT squamous cell car cinoma in situ of the penis
  - **KERATOACANTHOMA** rapidly developing volcano like nodule that may spontaneously involute
  - VERRUCOUS CARCINOMA clinically and histologically resembles a wart
- TREATMENTS surgical excision is the treatment of choice

### SEBORRHEIC KERATOSIS

- PATHOPHYSIOLOGY benign tumor of keratinocytes.
  Generally familial in nature
- CLINICAL FEATURES benign skin colored to black papules and plaques with well defined borders. They often have a warty surface and a stuck on appearance. Seborrheic keratoses are most com monly located on the back but can occur on the head, neck, and extremities. It is important to try to differentiate seborrheic keratoses clinically from melanoma. The Leser Trelat sign denotes the sud den onset of numerous pruritic seborrheic kerato sis along with skin tags and acanthosis nigricans and may indicate underlying malignancy (adeno carcinoma of the stomach and lung, leukemia, lymphoma, Sezary syndrome)
- TREATMENTS liquid nitrogen cryotherapy, curet tage, or shave removal

## SPECIFIC ENTITIES (CONT'D)

### VERRUCA VULGARIS (COMMON WARTS)

- PATHOPHYSIOLOGY a human papillomavirus (HPV) infection of keratinocytes. Lesions are benign but may cause cosmetic concern and are increased in immunocompromised individuals
- CLINICAL FEATURES lesions are well defined, firm papules or plaques with a hyperkeratotic cauli flower like or flat surface. Lesions may have brown black dots which represent thrombosed capillaries.
   Typically occur over extremities and genital area.
   Spontaneous resolution within 6 months for 30% of patients and 2 years for 65% of patients

### SPECIFIC ENTITIES (CONT'D)

 TREATMENTS manual paring of the lesions, cryotherapy, topical salicylic acid (e.g. salicylate cream 40% daily with glutaraldehyde 10 25% daily), imiquimod, 5 fluorouracil, cantharidin, podophylin, laser therapy, and intralesional bleomycin

#### VITILIGO

- PATHOPHYSIOLOGY autoimmune process against melanocytes. Differential diagnoses include tinea, leprosy, morphea, lichen sclerosus, post inflamma tory hypopiqmentation, and chemicals
- CLINICAL FEATURES hypopigmented patch(es)
- TREATMENTS topical steroids, UV light

# **Cutaneous Lupus Erythematosus**

## DIFFERENTIAL DIAGNOSIS OF PHOTOSENSITIVITY

### IATROGENIC (DRUGS)

- AMIODARONE
- DIURETICS hydrochlorothiazide, loop
- ANTIBIOTICS tetracycline
- NSAIDs
- ANTINEOPLASTIC methotrexate, vincristine, 5 fluorouracil

**INFLAMMATORY** SLE, dermatomyositis

**IDIOPATHIC** polymorphic light eruption, prur igo, actinic dermatitis, solar urticaria, chronic photosensitivity dermatitis

**OTHERS** photocontact dermatitis, phytocontact dermatitis (celery, parsley, lime, lemon, yarrow), porphyria, xeroderma pigmentosum

# CLINICAL FEATURES (CONT'D)

- BULLOUS LESIONS photosensitivity
- LIVEDO RETICULARIS SEE SPECIFIC DISORDERS
- NAIL LESIONS up to 25% of lupus patients. Changes include pitting, ridging, onycholysis and lunula (red ness of half moon), periungual erythema
- MUCOUS MEMBRANE ULCERS
- LUPUS ALOPECIA
   INVESTIGATIONS

# BASIC

- BLOOD TESTS CBCD, ANA, ENA, dsDNA SPECIAL
- SKIN BIOPSY
- PORPHYRIA WORKUP porphyrin, urine porphyrin

### CLINICAL FEATURES

### **CUTANEOUS MANIFESTATION OF SLE**

- MALAR RASH "butterfly rash" in up to 50% of lupus patients. Erythema in a malar distribution over the cheeks and bridge of the nose that spares nasola bial folds, especially after UV exposure
- DISCORD LUPUS up to 50% of lupus patients. Dis crete, erythematous, scaly plaques with follicular plugging over face, neck, and scalp, especially after UV exposure. May lead to central scars, atrophy, telangiectasias, and hyper /hypopigmentation
- SUBACUTE CUTANEOUS LUPUS up to 10% of lupus patients. Erythematous, slightly scaly papules that evolve into a papulosquamous or annular lesion over shoulders, forearms, neck, and upper torso. Usually no follicular plugging, hyperkeratosis, atro phy, pigment changes, and scarring
- LUPUS PROFUNDUS firm, painful nodules over scalp, face, arms, chest, back, thighs, and buttocks
- **LUPUS TUMIDUS** chronic violaceous papules and pla ques or nodule lesions over areas exposed to the sun

# MANAGEMENT

**TREATMENT UNDERLYING CAUSE** sun protec tion. Topical steroid ointments. Topical immunosup pressants (tacrolimus). Antimalaria (hydroxychloro quine). Systemic immunosuppressants

### **Related Topics**

Systemic Lupus Erythematosus (p. 279) Porphyria (p. 421)

# SPECIFIC ENTITIES

CENTRAL FACIAL TELANGIECTASIA OR ERYTHEMA common causes include rosacea, der matomyositis, SLE, dermatitis (seborrheic, atopic, con tact), glucocorticoid induced dermal atrophy, flushing TELANGIECTASIA common causes include sun damage, aging, hypertension, alcoholism, diabetes, rosacea, amyloidosis, lupus, other rheumatic diseases, and ataxia telangiectasia

### SPECIFIC ENTITIES (CONT'D)

### LIVEDO RETICULARIS

- CAUSES vascular (polyarteritis, SLE, livedo vascu litis, cryoglobulinemia, antiphospholipid antibody syndrome, atherosclerosis, syphilis, TB), hypervisc osity (polycythemia, thrombocytosis, macroglobu linemia), congenital, cerebrovascular disease (Sneddon's syndrome), idiopathic
- CLINICAL FEATURES reddish cyanotic, reticular patches over the arms, legs, and torso, particularly in cold environments. May progress to vascular occlusion with ischemia and tissue infarction (livedo vasculitis with triad of purpuric macules, cutaneous nodules, and painful ulcerations)

# SPECIFIC ENTITIES (CONT'D)

### **PORPHYRIA CUTANEA TARDA**

- PATHOPHYSIOLOGY heterozygous deficiency of uroporphyrinogen decarboxylase, important for heme synthesis
- ASSOCIATIONS hemochromatosis, alcohol, HCV, HIV, estrogens, smoking, hemodialysis
- CLINICAL FEATURES photodistributed blistering or superficial skin erosion
- TREATMENTS avoid exacerbating factors (alcohol, estrogens, iron supplements, drugs). Phlebotomy. Chloroquine, hydroxychloroquine

# **Drug Eruptions**

### DIFFERENTIAL DIAGNOSIS

### **EXANTHEMS**

- **ANTIBIOTICS** penicillins, sulfonamides, erythro mycin, gentamicin
- ANTICONVULSANTS
- ALLOPURINOL
- GOLD

# URTICARIA, ANGIOEDEMA

- IMMUNE IGE-MEDIATED penicillins, cephalospor ins, sulfonamides, local anesthetic agents, radio contrast, transfusion, latex
- NON-IMMUNE BRADYKININ-MEDIATED radiocon trast. ACE inhibitors
- MAST CELL DEGRANULATION narcotics, muscle relaxants (atracurium, vecuronium, succinylcho line, curare), vancomycin

### FIXED DRUG ERUPTION

- LAXATIVES phenolphthalein
- ANTIBIOTICS tetracyclines, sulfonamides, barbi turates
- ANTIINFLAMMATORIES NSAIDs, ASA photo sensitivity
- **DIURETICS** hydrochlorothiazide, loop
- ANTIBIOTICS tetracycline
- ANTINEOPLASTICS methotrexate, vincristine, 5 fluorouracil)

# ERYTHEMA MULTIFORME, STEVENS JOHNSON SYNDROME ★4A'S★

- ALLOPURINOL
- Antibiotics sulfonamides, penicillins, cepha losporins
- Anticonvulsants phenytoin, carbamazepine, phenobarbital
- Antiinflammatories NSAIDs

**CONTACT DERMATITIS** neomycin, benzocaine, paraben, ethylenediamine, formaldehyde, para aminobenzoic acid

### DIFFERENTIAL DIAGNOSIS (CONT'D)

#### HYPERSENSITIVITY VASCULITIS

- ALLOPURINOL
- **DIURETICS** furosemide, thiazide
- ANTIBIOTICS penicillins, sulfonamides
- OTHERS cimetidine, hydantoin

### **PIGMENTARY CHANGES**

- AMIODARONE
- ANTIBIOTICS tetracycline, minocycline, antimalarials
- METALS silver, mercury, gold
- OTHERS TCA, quinine, oral contraceptives

### INVESTIGATIONS

### SPECIAL

- BLOOD TESTS CBCD (eosinophils), quantitative lg (lgE increased), tryptase (marker of mast cell degranulation)
- ALLERGY TESTING radioallergosorbent test, patch testing
- SKIN BIOPSY

# MANAGEMENT

**DISCONTINUE OFFENDING DRUG** see SPECIFIC ENTITIES for further details

### SPECIFIC ENTITIES

# **EXANTHEMATOUS DRUG REACTION**

- PATHOPHYSIOLOGY the most common type of cutaneous drug reaction. Common offenders include penicillins, sulfonamides, carbamazepine, allopurinol and gold
- CLINICAL FEATURES exanthematous rash usually appears within 14 days of drug initiation or 3 days of re offending drug. The reaction is charac terized by the development of symmetric, red, maculopapular rash almost always found on the

Erythema Nodosum 373

# SPECIFIC ENTITIES (CONT'D)

trunk and extremities, which may be very pruritic.
Usually lasts 1 2 weeks

 TREATMENTS identification and cessation of the offending drug. Oral antihistamines for relief of itching.
 Topical glucocorticoids may speed up recovery. Oral and IV steroids may be used for severe symptoms

### **URTICARIA AND ANGIOEDEMA**

- PATHOPHYSIOLOGY urticaria involves the develop ment 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 sensi tized patients and are classically associated with penicillin as well as cephalosporins and sulfona mides. 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, cal cium channel blockers, and radiocontrast
- TREATMENTS cessation of the offending drug. Antihistamines and oral steroids may be used. For acute, life threatening reactions, ABC, O<sub>2</sub>, epinephr ine 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 I IV bolus, salbutamol 2.5 mg NEB q5min PRN, dimen hydrinate 25 50 mg IV, steroids (methylpredniso lone 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

# SPECIFIC ENTITIES (CONT'D)

appear ill with fever and leukocytosis. Most cases begin within 2 3 days of drug administration

 TREATMENTS typically resolve within 2 weeks after the drug is stopped

### FIXED DRUG ERUPTION

- PATHOPHYSIOLOGY the appearance of a solitary erythematous patch or plaque within 30 min to 8 h after ingestion of a drug. Offending agents include antibiotics (tetracyclines, sulfonamides), analgesics (NSAIDs, salicylates), and yellow dyes
- CLINICAL FEATURES erythematous, edematous pla ques with a grayish center or bullae over genitalia (most common), lips, tongue, face, and acral areas. Characterized by presence of post inflammatory hyperpigmentation and the recurrence at exactly the same site with reexposure. Lesions may be accompanied by itching or burning
- **TREATMENTS** cessation of the offending drug and application of topical steroid ointment

#### CONTACT DERMATITIS

- PATHOPHYSIOLOGY due to topical agents or con tact. Type IV hypersensitivity reaction (delayed cell mediated, T cell activated)
- CLINICAL FEATURES erythematous, papular, urti carial, 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 pur pura, bullae, and/or necrosis. May also have fever, myalqia, and arthralqia
- ACR CRITERIA age at disease onset >16 years, medication at disease onset, palpable purpura, maculopapular rash, biopsy including arteriole and venule. Need three of five criteria (sens 71%, spc 84%)
- TREATMENTS discontinue offending drug

### **Related Topics**

Antibiotics (p. 254) Penicillin Allergy (p. 257)

# **Erythema Nodosum**

### DIFFERENTIAL DIAGNOSIS OF PAINFUL NODULES

**PANNICULITIS** erythema nodosum, erythema induratum, Weber Christian disease (relapsing feb rile nodular panniculitis)

**INFECTIONS** bacteria, fungi

# DIFFERENTIAL DIAGNOSIS OF PAINFUL NODULES (CONT'D)

CUTANEOUS VASCULITIS
SUPERFICIAL THROMBOPHLEBITIS

374 Clubbing

### PATHOPHYSIOLOGY

### **CAUSES OF ERYTHEMA NODOSUM**

- INFECTIOUS bacterial (Streptococcal, Yersiniosis), atypical (Chlamydia pneumoniae), TB, fungal (Coc cidioidomycosis, 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. Pre sence of GI symptoms and/or hilar adenopathy may help in narrowing differential

# INVESTIGATIONS

### BASIC

- · LABS CBCD, antistreptolysin O titer, ANA
- MICROBIOLOGY wound C&S, throat C&S (for Streptococcus), TB skin test
- IMAGING CXR

### **SPECIAL**

DEEP INCISIONAL BIOPSY

### MANAGEMENT

SYMPTOM CONTROL NSAIDs, potassium iodide, glucocorticoids (beware of TB)

TREAT UNDERLYING CAUSE

### Related Topics

Tuberculosis (p. 250) Fungal Infections (p. 265) Sarcoidosis (p. 420)

# Clubbing

# DIFFERENTIAL DIAGNOSIS

RESPIRATORY lung cancer, lung abscess, bronchiectasis, cystic fibrosis, empyema, mesothe lioma, idiopathic pulmonary fibrosis, asbestosis

CARDIAC cyanotic heart disease, congenital,

subacute endocarditis

GI colon cancer, esophageal cancer, inflamma

tory bowel disease, celiac disease, cirrhosis

**OTHERS** hyperthyroidism, hemoglobinopathies, local vascular disease, familial

### PATHOPHYSIOLOGY

MECHANISM proliferation of the connective tissue between the nail matrix and the distal phalanx STAGES periungual erythema → spongy nail bed

→ loss of Lovibond's angle → increased phalangeal depth ratio → hypertrophic osteoarthropathy

# CLINICAL FEATURES

# RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE CLUBBING?

INSPECTION nail fold profile angle (angle that nail projects from nail fold, normal ≤176°, simplified to straight line of <180° for clinical use), hypony chial nail fold angle (angle that nail directs toward the nail tip, normal ≤192°, simplified to <190° for clinical use), phalangeal depth ratio (distal phalan geal finger depth/interphalangeal finger depth ratio normal ≤1), Schamroth sign (normal=diamond)

# CLINICAL FEATURES (CONT'D)

**PALPATION** floating nail bed elicited by rocking the distal and proximal nail back and forth

**APPROACH** "the profile angle and phalangeal depth ratio can be used as quantitative indices to assist in identifying clubbing. In individuals without clubbing, values for these indices do not exceed  $192^{\circ}$ , and 1.0, respectively. Inter observer agreement by clinicians is highly variable ( $\kappa$  values 0.39 0.90). Because of the lack of an objective diagnostic stan dard, 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 dis ease (LR+ 2.8 and 3.7 for active Crohn's disease and ulcerative colitis, respectively)"

JAMA 2001 286:3

# INVESTIGATIONS

#### BASIC

IMAGING CXR

### SPECIAL

- CARDIAC WORKUP ECG, echocardiogram
- OTHER ETIOLOGY WORKUP CBCD, TSH, AST, ALT, ALP, bili

### MANAGEMENT

### TREAT UNDERLYING CAUSE

Dupuytren's Contracture 375

# SPECIFIC ENTITIES

**HYPERTROPHIC OSTEOARTHROPATHY** clubbing and periarticular pain and swelling, most often affect ing the wrists, ankles, and knees. Associated with bronchogenic cancer, chronic pulmonary infections, cystic fibrosis, and cyanotic congenital heart disease

# **Related Topics**

Celiac Disease (p. 124) Inflammatory Bowel Disease (p. 120) Lung Cancer (p. 185)

# **Dupuytren's Contracture**

# DIFFERENTIAL DIAGNOSIS

**DIABETIC CHEIROARTHROPATHY** (usually all four fingers)

INTRINSIC JOINT DISEASE
DUPUYTREN'S CONTRACTURE
VOLKMANN'S ISCHEMIC CONTRACTURE
TRAUMATIC SCARS

**PALMAR FASCIITIS** malignancy (usually bilateral)

### PATHOPHYSIOLOGY

**RISK FACTORS** alcoholism, smoking, diabetes, repetitive hand motions/vibrations, reflex sympa thetic dystrophy

**4 STAGES** progressive fibrosis of the palmar fascia  $\rightarrow$  nodules form on the palmar fascia  $\rightarrow$  flexion deformity  $\rightarrow$  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

376 Notes

# Notes

# **13**GERIATRICS

Section Editor: Dr. Fiona Lawson

# **Geriatric-Specific Issues**

#### THE FRAIL ELDERLY

THE CONCEPT OF FRAILTY frailty is a "weakened" or "precarious" state resulting in heightened suscept ibility 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 pharma cokinetics, frailty is a more important treatment mod ifying factor. In general, less aggressive (and some times more palliative) treatments are offered to frail patients. Clinical outcomes for frail seniors can be improved with various interventions, such as compre hensive geriatric assessment and exercise programs

**POTENTIAL PRECIPITANTS** acute illness, infections, infarction, medications, social stress, environ mental changes, and surgical intervention. Patients with frailty are at higher risk of complications, such as increased mortality, morbidity, and rates of institutio nalization 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, transporta tion, shopping, phoning, laundry, cooking, accounting, housekeeping, medications), falls (number, causes, frac tures), 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 geria tric syndromes, inquire about the number and

#### COMPREHENSIVE GERIATRICS ASSESSMENT (CONT'D)

severity of co existing diseases that are either life threatening or function limiting

**POLYPHARMACY** number of medications, poten tial 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

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 inter disciplinary teams consisting of geriatricians, nurses, social workers, physiotherapists, occupational therapists, pharmacists, registered dieticians, speech language therapists, recreational therapists, psychologists, and family

Discipline	Task
Dieticians	Nutrition and diet
Nurses	Education and assistance with
	ADLs, IADLs
Occupational	Cognitive and functional
therapists	assessments, ADL training
Pharmacists	Medication use
Physiotherapists	Training to ↑ ROM, strength,
	endurance, coordination,
	mobility

#### COMPREHENSIVE GERIATRIC MANAGEMENT (CONT'D)

Discipline
Recreational therapists
Social workers
Counseling, evaluation, and disposition within community

Speech Training in communication and language therapists disorders

### HEALTH CARE AND FINANCIAL PROXY

**ADVANCE DIRECTIVE** (living will) a document that is created when patient is competent. Allows direction of their care in future (e.g. regarding tube feeding, resuscitation status) when they are no longer capable of expressing their own wishes

**PERSONAL DIRECTIVE** agent assigned when patient competent so that if they become incompetent, agent can act on patient's behalf regarding decisions for personal care and accommodation

**POWER OF ATTORNEY** agent assigned when patient competent so that if they become incom

#### HEALTH CARE AND FINANCIAL PROXY (CONT'D)

petent, agent can act on patient's behalf regarding finances

**GUARDIANSHIP** created when patient is incompe tent and personal directive not available. Guardian assists with decisions regarding personal care and accommodation

**TRUSTEESHIP** created when patient is incompetent and power of attorney not available. Trustee assists with finances

#### COMPETENCY ASSESSMENT

**ENSURE IT IS NECESSARY** suspect incapacity, risk, undue influence

**DIAGNOSED PHYSICAL/MENTAL ILLNESS** chronic vs. acute

OBTAIN RELEVANT COLLATERAL INFORMATION reliable? Ask what concerns them (ADLs, financial) PERFORM FORMAL TESTING ask patient details about ADLs, finances, medical condition, living will. Are they consistent in their choices? Do they understand and appreciate the consequences of their actions?

INFORM AND ACT

# **Dementia and Cognitive Impairment**

### DIFFERENTIAL DIAGNOSIS

#### PRIMARY PROGRESSIVE DEMENTIA

- ALZHEIMER'S slow insidious cognitive decline but otherwise no physical findings, mini mental status examination globally low, CT may show white matter change, mostly a diagnosis of exclusion, but accounting for 60% of dementias
- VASCULAR acute stepwise or slow progressive decline, focal neurological deficits, mini mental status examination patchy, CT may show white matter change, pure vascular dementia uncom mon, more frequently occurs with Alzheimer's like dementia (mixed vascular)
- PARKINSON'S Parkinsonian symptoms for a long time, slow decline, Parkinson's patients have 6× increased risk for dementia
- LEWY BODY Parkinsonism, persistent visual hal lucinations, progressive decline, fluctuating cog nition especially attention/alertness, marked adverse hypersensitivity to typical antipsychotic medications, supportive features include syn cope, delusions, and sleep disturbance
- FRONTOTEMPORAL prominent impairment in exe cutive function, disinhibited or passive presenta tion, impaired judgment, significant social indif ference, declining hygiene, prominent language

#### DIFFERENTIAL DIAGNOSIS (CONT'D)

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, hypo thyroidism
- STRUCTURAL NPH, subdural hemorrhage, neo plastic, vascular
- **INFECTIONS** chronic meningitis, HIV, neurosy philis, Whipple's
- INFLAMMATORY vasculitis, Hashimoto encepha litis, multiple sclerosis

**DEMENTIA MIMICS** depression, delirium, develop mental disorder, age associated memory impairment

#### PATHOPHYSIOLOGY

**DEMENTIA** acquired, progressive, global decline in cognition resulting in impairment in function. Learn ing and memory impairment are present, plus ≥1 of the following: aphasia, agnosia, apraxia, impairment of executive function. Deficits result in impaired function. Disorientation and impairment in regulation of emotion and aggression may also be present

# PATHOPHYSIOLOGY (CONT'D)

MILD COGNITIVE IMPAIRMENT predominant memory complaints with other cognitive domains largely intact and preservation of functional

#### PATHOPHYSIOLOGY (CONT'D)

independence; 10 15% of patients progress to Alz heimer's annually

#### CLINICAL FEATURES

DISTINGUISHING FEATURES BETWEEN VARIOUS TYPES OF DEMENTIA					
	Alzheimer's	Vascular	Fronto temporal		
Physical findings	Relatively normal	Focal neurological deficits	Disinhibited or passive Primitive reflexes		
MMSE	Globally low	Patchy changes Early executive loss	Early executive loss		
CT	White matter changes	White matter changes	Frontal temporal atrophy		

#### **Related Topics**

Delirium (p. 380) Parkinson's disease (p. 320) Stroke (p. 299) Vitamin B12 deficiency (p. 405)

#### CLINICAL FEATURES (CONT'D)

Cambridge Cognitive Examination, Modified Mini Mental State Examination, Community Screening Interview for Dementia, or the Montreal Cognitive Assessment"

JAMA 2007 297:21

#### CLINICAL FEATURES (CONT'D)

#### RATIONAL CLINICAL EXAMINATION SERIES: DOES THIS PATIENT HAVE DEMENTIA? MINI MENTAL STATE EXAMINATION (MMSE)

orientation to place (5), time (5), immediate and delayed recall (6), spell 'WORLD" backward (5), 3 step commend (3), name 2 objects (2), close your eyes (1), repeat sentence 'No, if's, and's, or but's" (1), write a sentence (1), intersecting pentagons (1). Maximum score is 30, generally <24 is impaired but varies with education and age

**MEMORY IMPAIRMENT SCREEN** recall four objects (an animal, a city, a vegetable, and a musi cal instrument). Two points for free recall of each object and one point if prompting needed ("Tell me the name of the city."). Maximum score is 8. Takes 4 min

#### SELECTED TOOLS

	LR+	LR
MMSE	6.3	0.19
Reports from an informant	6.5	
that the patient has		
memory loss		
Memory impairment	33	0.08
screen		
Clock drawings	1.2 7.7	0.13 0.710

**APPROACH** "to detect cognitive impairment of at least moderate severity, consider the mini mental state examination. The Hopkins Verbal Learning Test or the Word List Acquisition Test may be used to screen for mild impairment in highly educated patient. If very little time is available, consider the Memory Impairment Screen or the Clock Drawing Test. If plenty of time is available, consider the

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, creatinine, glucose, Ca, TSH, vitamin B12
- IMAGING head CT

#### **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  $\leq$ 23 suggests dementia (LR+ 6 8) in the absence of delir ium. Newer thresholds:  $\leq$ 20 rules in dementia (LR+ 14.5, sens 39 69%, spc 93 99%),  $\geq$ 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)

380 Delirium

#### 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 disor der (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 DYSLI PIDEMIA 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.

#### MANAGEMENT (CONT'D)

survival, quality of life, prevention of aspiration pneu monia, reduction of pressure sores or infections, func tional improvement)

#### SPECIFIC ENTITIES

SEQUENCE OF SYMPTOMS IN ALZHEIMER'S DIS EASE mood changes, cognitive decline, loss of functional autonomy, neuropsychiatric manifesta tions, 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 spasti city, hyperreflexia, and extensor plantar responses
  - DIAGNOSIS clinical diagnosis and MRI. Improve ment 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 (ventricu loperitoneal, ventriculoatrial, lumboperitoneal)
- PARKINSON'S-PLUS SYNDROMES include progres sive 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

### **Delirium** NEJM 2006 354:11

### DIFFERENTIAL DIAGNOSIS

#### **★DIMS**★

#### DRUGS ★ABCD★

- ALCOHOL intoxication, withdrawal, Wernicke Korsakoff
- ANTICHOLINERGICS atropine, benztropine, scopolamine
- ANTIDEPRESSANTS SSRIs, TCA

#### DIFFERENTIAL DIAGNOSIS (CONT'D)

- **ANTICONVULSANTS** carbamazepine, phenytoin, valproate, phenobarbital
- ANALGESICS opioids, NSAIDs, steroids
- ANTIBIOTICS penicillins, quinolones, sulfona mides, isoniazid, rifampin, streptomycin, chloroquine, acyclovir
- ANTI-HISTAMINES cimetidine, famotidine, ranitidine

Delirium 381

#### DIFFERENTIAL DIAGNOSIS (CONT'D)

- BENZODIAZEPINES AND BARBITURATES
- CARDIAC amiodarone, β blockers, digoxin, diuretics
- DOPAMINE AGENTS amantadine, bromocriptine, levodopa

**INFECTIOUS** pneumonia, UTI, meningitis, ence phalitis, abscess, sepsis

#### METABOLIC

- ORGAN FAILURE hepatic, azotemia, hypothy roidism, hypoxia, hypercapnia, hypothermia, hypertensive
- ELECTROLYTE IMBALANCE ketoacidosis, glucose (hypo, hyper), hyponatremia, hypernatremia, hypomagnesemia, hypercalcemia

#### STRUCTURAL

HEMORRHAGE subarachnoid, epidural, subdural, intracerebral

#### DIFFERENTIAL DIAGNOSIS (CONT'D)

- STROKE basilar
- TUMOR
- ABSCESS
- SEIZURES

#### PATHOPHYSIOLOGY

**HOSPITALIZATION** hospitalized patients, particularly the elderly, are at high risk of developing delirium. The prevalence of delirium in geriatric patients on admis sion to hospital is 14 24%. The estimated incidence is up to 40% on the medical ward, 7 26% for general surgery, 29 42% for vascular surgery, 8 42% for cardiac surgery, and 16 62% for orthopedic surgery

**FRAILTY IN ELDERLY** limited reserve so easily tipped over by any event, leading to delirium

### DISTINGUISHING FEATURES BETWEEN DELIRIUM AND DEMENTIA

	Delirium	Dementia
Onset	Abrupt	Insidious
Course	Fluctuating, usually reversible	Slowly progressive and usually irreversible
Duration	Days to weeks	Years
Level of consciousness	Hyperactive or hypoactive	Affected in late stages
Attention span	Usually affected	Affected in late stages
Orientation	Usually affected	Usually affected
Memory	May be affected	Usually affected
CT head	May be normal; structural changes	White matter changes, atrophy

#### PATHOPHYSIOLOGY (CONT'D)

#### **DELIRIUM SUBTYPES**

- HYPERACTIVE DELIRIUM characterized by agitation and/or hallucinatory symptoms
- MIXED DELIRIUM variable course with alternating hyperactive and hypoactive features. A majority of patients with delirium fall under this category
- HYPOACTIVE DELIRIUM characterized by excessive drowsiness and decreased level of consciousness. May mimic depression

**COMPLICATIONS** delirium can have a negative impact on patients' quality of life, symptom expres sion, emotions, and decision making ability. Delirium also prolongs hospitalization and is associated with a poor prognosis and caregiver distress

#### CLINICAL FEATURES

**CONFUSION ASSESSMENT METHOD (CAM)** posi tive test argues strongly for delirium (LR 10.3) and negative test argues against delirium (LR 0.2). Posi tive test requires both major criteria 1+2 *and* either of the minor criteria 3 or 4 ★AIDS★

 Acute onset and fluctuating confusion abnor mal behaviors come and go, ↑/↓ severity

#### CLINICAL FEATURES (CONT'D)

- 2. **INATTENTION** difficulty focusing/difficulty following conversation (serial subtraction with distraction)
- 3. **DISORGANIZED THINKING** rambling, irrelevant, illo gical conversation
- Sensorium Change (ALTERED LOC) agitated, hyperalert, lethargic, stuporous, or comatose

**EXAMINATION OF THE DELIRIOUS PATIENT** in addition to general physical and neurological exam inations, obtain a baseline mini mental status exam ination (useful for monitoring)

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, Ca, urinalysis
- IMAGING CXR, head CT
- MICROBIOLOGY urine C&S, blood C&S (if any fever) SPECIAL
- METABOLIC WORKUP TSH if suspect thyroid dis ease, AST, ALT, ALP, bilirubin, INR, PTT, NH<sub>4</sub> if suspect liver disease, Mq, PO<sub>4</sub>
- CARDIAC WORKUP ECG, CK, troponin if suspect ACS
- SEIZURES WORKUP EEG

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#### INVESTIGATIONS (CONT'D)

- DRUG OVERDOSE WORKUP medication serum levels (e.g. digoxin, phenytoin salicylate, aceta minophen), alcohol level, osmolality
- MENINGITIS WORKUP lumbar puncture

#### DIAGNOSTIC ISSUES

**PERSISTENT DELIRIUM** if delirium persists despite basic workup, think through differential diagnosis again (VERY CAREFULLY). Also consider dehydration, depression, urinary/fecal retention, abscess

#### MANAGEMENT

**PREVENTION** ensure adequate O<sub>2</sub>, fluid and elec trolyte 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 offend ing 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

#### MANAGEMENT (CONT'D)

of day night cycle (optimal lighting during day, pro mote sleep hygiene at night), avoidance of unneces sary 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, olan zapine 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 withdra wal (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 avail able, consider calling closest family to discuss treat ment options

#### Related Topics

Overdose (p. 102)

Alcohol Withdrawal (p. 105) Hypercalcemia (p. 353) Meningitis (p. 241) Metabolic Acidosis (p. 77)

#### **Falls**

# JAGS 2000 48:8; NEJM 2003 348:1

#### DIFFERENTIAL DIAGNOSIS

**SYNCOPE** neurogenic, cardiogenic, neurocardiogenic **DROP ATTACKS** transient vertebrobasilar insufficiency

POSTURAL HYPOTENSION
CONFUSION delirium

DIZZINESS vertigo, dysequilibrium

FALLS accidental, imbalance

#### PATHOPHYSIOLOGY

**PREDISPOSITION TO FALLS IN ELDERLY** multi factorial in nature; 50% of patients who fall do so repeatedly. Multiple falls are a marker for other underlying factors, including chronic diseases and functional disability

- HIGHER CORTICAL/CNS decreased reaction time
- VESTIBULAR SYSTEM decreased balance
- VISUAL SYSTEM presbyopia, decreased peripheral vision, and accommodation
- AUTONOMIC SYSTEM postural hypotension

#### 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, benzodiaze pines, class IA antiarrhythmics
- ENVIRONMENT
- PRECIPITANTS infection, infarction, medications, social stress

**COMMUNITY DWELLING** 41% of falls secondary to environment (trips, slips), 13% weakness or gait/bal ance disorder

**NURSING HOME DWELLING** 26% of falls second ary to weakness, gait/balance disorder, 16% environ ment related

**COMPLICATIONS** institutionalization, fear of recurrent falls, long lies (risk for dehydration, pressure sores, pneumonia, rhabdomyolysis), and death

Urinary Incontinence 383

#### **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, tempera ture), cardiovascular (murmurs, rhythm, volume sta tus), respiratory (adventitious sounds), musculoskele tal (strength in knee/hip extensors, joint stability and range of motion, pain, feet, footwear, walking aids), neurologic (focal signs, vision/hearing, cerebellar, sensory), cognitive exam (MMSE, CAM)

# PERFORMANCE ORIENTED EVALUATION OF GAIT AND BALANCE

- TIMED UP AND GO TEST rise from chair, walk 10 ft, turn, and return to chair. Should finish in less than 10 s. If takes >20 s, further evaluation required
- TINETTI'S PERFORMANCE-ORIENTED ASSESSMENT easy to administer, incorporates gait, and balance scales to identify high risk of falls, score ≤20/28 predictive of recurrent falls

# RATIONAL CLINICAL EXAMINATION SERIES: WILL MY PATIENT FALL? RISK FACTORS FOR FALLS

		LN+
Fallen in the past year		2.3 2.8

Clinically detected abnormalities of gait 1.7 2.4 or balance

Age, visual impairment, medication variables, decreased activities of daily living, and impaired cognition did not consistently predict falls across studies. Orthostatic hypotension did not predict falls after controlling for other factors

#### CLINICAL FEATURES (CONT'D)

**APPROACH** "screening for risk of falling during the clinical examination begins with determining if the patient has fallen in the past year. For patients who have not previously fallen, screening consists of an assessment of gait and balance. Patients who have fallen or who have a gait or balance problems are at higher risk of future falls"

JAMA 2007 297:1

#### INVESTIGATIONS

#### BASIC

- LABS CBCD, lytes, urea, Cr, glucose, TSH, CK, ESR, urinalysis
- IMAGING head CT

#### SPECIAL

- CARDIAC WORKUP ECG, Holter monitor if suspect arrhythmia
- SEIZURES WORKUP EEG if suspect seizures
- NEUROLOGIC WORKUP EMG/NCS if significant weakness thought to be related to peripheral lesion

#### MANAGEMENT

PREVENTION education (proper shoes, avoid hot tubs, drink 1.5 2 L/day, getting up slowly). Exercise (balance and gait training, muscle strengthening, day programs). Environmental assessment (remove loose rugs, non slip bath mats, lighting, stair rails). Tapering and discontinuation of medications, if appropriate. Referral (physiotherapy, occupational therapy, ophthalmology, geriatrics, cardiology if appropriate). Treatment and prevention of osteo porosis (see OSTEOPOROSIS)

### 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

### CMAJ 1997 157:8; NEJM 2008 358:10

# DIFFERENTIAL DIAGNOSIS OF CHRONIC URINARY

**STRESS** (small volumes with † abdominal pressure)

- URETHRAL HYPERMOBILITY childbirth, menopausal • SPHINCTER WEAKNESS TURP
- **OVERFLOW** (over distended bladder, small volumes

INCONTINENCE (CONT'D)

but continuous leakage, incomplete emptying)

• BLADDER OUTLET OBSTRUCTION BPH, prostate

BLADDER OUTLET OBSTRUCTION BPH, prostate cancer

# DIFFERENTIAL DIAGNOSIS OF CHRONIC URINARY INCONTINENCE (CONT'D)

- URETHRAL/BLADDER NECK STRICTURE
- DETRUSOR HYPOCONTRACTILITY peripheral neu ropathy, alcohol, herniated disc, spinal stenosis, fibrotic detrusor

MIXED/DETRUSOR HYPERACTIVITY WITH IMPAIRED CONTRACTILITY (DHIC) combines symptoms of urge and overflow incontinence with frequency and large volume, usually late stages of above (e.g. BPH or diabetes mellitus)

REDUCED MOBILITY (inability to ambulate to toilet)

# DIFFERENTIAL DIAGNOSIS OF TRANSIENT URINARY INCONTINENCE

**★DIAPERS**★

DELIRIUM

**INFECTION** symptomatic UTI

ATROPHIC VAGINITIS/URETHRITIS
PROSTATE

**PHARMACY** diuretics, benzodiazepines, alcohol **PSYCHOLOGICAL** 

**ENDOCRINE** hypercalcemia, diabetes, diabetes insipidus

RESTRICTED MOBILITY STOOL IMPACTION

#### PATHOPHYSIOLOGY

#### PHYSIOLOGY OF URINATION

- **DETRUSOR MUSCLES** parasympathetic S234 (con tract), β2 sympathetic T10 L2 (relax)
- INTERNAL SPHINCTER  $\alpha$ 1 sympathetic T10 L2 (contract)
- EXTERNAL SPHINCTER somatic S234 (contract)

# RATIONAL CLINICAL EXAMINATION SERIES: WHAT TYPE OF URINARY INCONTINENCE DOES THIS WOMAN HAVE?

	LR+	LR
Stress incontinence		
Simple question: "Do you lose urine	2.2	0.39
during sudden physical exertion,		
lifting, coughing or sneezing?'		
Filled bladder stress test (fill bladder	9.4	0.07
with 200 cc of saline, supine, and		
observe while cough)		
Systematic assessment	3.7	0.20
Urge incontinence		
"Do you experience such a strong	4.2	0.48
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

#### PATHOPHYSIOLOGY (CONT'D)

type of incontinence. The most helpful component of the assessment for determining the presence of urge incontinence is a history of urine loss asso ciated with urinary urgency. A filled bladder stress test may be helpful for diagnosing stress incontinence. For primary care physicians unable to perform stress tests in their office, it would be reasonable to refer patients for further evaluation when a diagnosis is needed with more certainty. Measurement of the post void residual urine volume detects incomplete bladder emptying, but no data support using this in women for separating out incontinence type"

JAMA 2008 299:12

### INVESTIGATIONS

#### BASIC

- LABS lytes, urea, Cr, glucose, Ca, urinalysis
- MICROBIOLOGY urine C&S

#### SPECIAL

URODYNAMIC STUDIES

# MANAGEMENT OF CHRONIC URINARY INCONTINENCE

#### **GENERAL MEASURES**

- ABSORPTIVE PADS incontinence pad or adult dia pers (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 pes saries/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 acet ylcholine agonist** († bladder contractility; *bethane chol* 10 30 mg PO BID QID for short term only, may require clean intermittent catheterization)

**RESTRICTED MOBILITY** bedside urinal/commode, call bell, prompted voiding

# **Hearing Impairment**

See HEARING IMPAIRMENT (p. 317)

# Pharmacological Issues in the Elderly

Lancet 2007 370:9582; BMJ 2008 336:7644

#### PRINCIPLES OF DRUG USE IN THE ELDERLY

PRINCIPLES OF PHARMACOLOGY elderly are at increased risk of adverse drug reactions because of altered physiology of aging, multiple co existing illnesses, reduced homeostatic reserve, polypharmacy, and medical error. Of the 4 key components of phar macokinetics (absorption, distribution, metabolism, excretion), only the last 3 are meaningfully affected by age. Pharmacokinetic changes are related to decreased renal (most important) and hepatic function (phase I reactions |, phase II reactions unaffected), decreased lean body mass († fat), decreased total body water, and increased total body fat

**COMPLICATIONS** falls, delirium, incontinence, renal impairment, heart failure, gastrointestinal hemorrhage, hypoglycemia, drug drug interactions PRESCRIBING PRINCIPLES initiate most medica tions at half usual starting dose, increase dose slowly. Carry out regular medication reviews and stop any unnecessary medications. Avoid medica tions with known significant side effects in the elderly. Avoid treating adverse drug reactions with further drugs

#### UNDER PRESCRIBING IN THE ELDERLY

FOR UNDER PRESCRIBING under REASONS 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 dos ing 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, barbitu rates, 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 diet ary supplements and are at increased risk of herb drug interaction (e.g. ginkgo biloba and warfarin resulting in increased bleeding risk)

AVOID TREATING ADVERSE DRUG REACTIONS WITH FURTHER DRUGS medications are often inappropriately prescribed to symptomatically treat side effect of another medication. For example, metoclopramide -> extrapyramidal effects -> levodopa. Metoclopramide users are >3 times more likely to be prescribed levodopa compared to non users, a treatment generally reserved for management of idiopathic Parkin son's disease

#### COMMON ADVERSE DRUG REACTIONS AND DRUG DRUG INTERACTIONS

# CHARACTERISTIC SIDE EFFECTS OF DRUGS FREQUENTLY USED IN THE ELDERLY Adverse effects

α1 blockers (doxazosin) Anticholinergics (diphenhydramine)

Benzodiazepines (lorazepam)

NSAIDs (indomethacin)

(amitriptyline)

Sulfonylureas (chlorpropamide) Tricyclic antidepressants

Falls, orthostatic hypotension, dry mouth

Delirium, urinary retention, constipation, dry mouth, blurred vision, postural hypotension

Falls, confusion

Gastrointestinal irritation and hemorrhage, renal impairment, hypertension, heart failure

Hypoglycemia

Falls, orthostatic hypotension, sedation, delirium, arrhythmias

# COMMON ADVERSE DRUG REACTIONS AND DRUG DRUG INTERACTIONS (CONT'D)

WARFARIN INTERACTIONS many medications implicated in increasing bleeding risk († INR) with warfarin. Most severe interactions described with trimethoprim sulfamethoxazole, erythromycin, amiodarone, propafenone, ketoconazole, fluconazole, itraconazole, metronidazole. Antibiotics, aceta minophen, steroids, and ginkgo biloba may also increase bleeding risk

# COMMON ADVERSE DRUG REACTIONS AND DRUG DRUG INTERACTIONS (CONT'D)

**GRAPEFRUIT JUICE INTERACTIONS** grapefruit interferes with drugs that are metabolized by CYP3A4, including statins (simvastatin/lovastatin > atorvastatin), calcium channel blockers, and benzodiazepines

**HEART FAILURE PRECIPITANTS AND EXACER BANTS** NSAIDs (>2 times risk for admission for HF, correlating with dose of drug), thiazolidinediones, sodium polystyrene sulfonate

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# PALLIATIVE CARE

### Section Editors:

Dr. Sriram Yennurajalingam and Dr. Eduardo Bruera

### **Palliative Care-Specific Issues**

#### INTRODUCTION

**DEFINITION** according to the World Health Orga nization, 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 assess ment and treatment of pain and other problems, physical, psychosocial and spiritual... Palliative care is applicable early in the course of illness, in conjunc tion with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better under stand 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, psy chosocial, and existential suffering

**REFERRAL TO PALLIATIVE CARE** while palliative care is commonly associated with end of life care, it is

#### INTRODUCTION (CONT'D)

most effective when incorporated early in the disease trajectory of life limiting illnesses. Timely incorpora tion of palliative care principles can help to optimize symptom management, improve psychosocial inter ventions, 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 dis ease 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 PRE	SYMPTOM PREVALENCE IN TERMINALLY ILL PATIENTS				
Symptom	Cancer	AIDS	Heart Failure	COPD	CKD
Pain	35 96%	63 80%	41 77%	34 77%	47 50%
Depression	3 77%	10 82%	9 36%	37 71%	5 61%
Delirium	6 93%	30 65%	30 65%	18 32%	18 33%
Fatigue	32 90%	54 85%	69 82%	68 80%	73 87%
Dyspnea	10 70%	11 62%	60 88%	90 95%	11 62%
Anorexia	30 92%	57%	21 41%	35 67%	25 64%
				JPS	M 2006 31:1

### SYMPTOM COMPLEX AND ASSESSMENT (CONT'D)

**COMPREHENSIVE PALLIATIVE CARE ASSESS MENT** 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, anxi ety, drowsiness, appetite, well being, shortness of breath, and sleep), global assessment scale

- PAIN Edmonton Pain Classification System
- DELIRIUM Mini Mental State Examination, Mem orial Delirium Assessment Scale

#### 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 perfor mance scale (PPS). Performance status has prog nostic utility and is one of the key factors in deci sion making at the end of life (e.g. discharge location, initiation, or termination of treatment)

#### DEPRESSION IN THE PALLIATIVE SETTING

DIAGNOSIS somatic symptoms (anorexia, fati gue, insomnia, weight loss) are less useful for diag nosis 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, hypercalce mia, 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

#### CARE FOR CAREGIVERS

daily, dextroamphetamine, pemoline)

**EMPHASIS ON CAREGIVERS** palliative care is unique among medical disciplines in placing a particular emphasis on the well being of patients' care givers. This is because caregivers play a crucial role caring for their loved ones both physically and emotionally, and their well being is often one of the key concerns for patients. Caregivers are at risk of developing psychosocial distress themselves, given the physical burden of providing care and the emotional burden of seeing their loved ones suffer. Moreover, many patients develop delirium close to the end of life, necessitating substitute decision making

**INTERVENTIONS FOR CAREGIVERS** specific inter ventions may include (1) educating caregivers regard ing 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 under standing of their disease, treatment options, and prog nosis to make decisions. The section on "Communica tion Issues" (p. 399) covers a number of basic techniques in breaking bad news. For further information, readers

# COMMUNICATION IN THE PALLIATIVE SETTING (CONT'D)

are referred to a recent review that covers various communication topics related to the end of life, including discussion of diagnosis, prognosis, treat ment 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 initia tion or discontinuation of treatments (e.g. che motherapy, 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

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#### SPIRITUALITY IN THE PALLIATIVE SETTING (CONT'D)

expertise and role, or imposing own religious beliefs, provide premature reassurance

**RESOURCES** caregivers, spiritual counselors, cha plains, faith community

JAMA 2006 296:11

#### DIAGNOSIS OF DYING

**CHALLENGE** clinicians usually reluctant to make the diagnosis if any hope of improvement exists, particularly if no definitive diagnosis has been established. When recovery is uncertain, it is better to discuss this with patient and family. It is important to understand that the diagnosis of dying can be made, knowing that there may still be a small chance of recovery in some patients

#### **FEATURES OF DYING PATIENTS**

- CANCER bed bound, semicomatose, only able to take sips of fluid, unable to take oral drugs
- HEART FAILURE previous admissions with worsen ing heart failures, no identifiable reversible precipitant, medications optimized, deteriorating renal function, failure to respond within 2 3 days to

#### DIAGNOSIS OF DYING (CONT'D)

appropriate changes in diuretic or vasodilator drugs. The diagnosis of dying is particularly difficult to make because worsening heart failure may be associated with secondary causes and could potentially be reversible once treated

**OVERALL** no specific criteria for diagnosis of dying, but based on overall clinical impression. Helpful if other members of the inter professional team agree that the patient is going to die soon

# MEDICATION ADMINISTRATION IN THE PALLIATIVE SETTING

**SUBCUTANEOUS ROUTE** preferred over intrave nous route because it is associated with greater com fort, fewer complications, less maintenance, and medications can be given at home. Disadvantages include less rapid onset of medication effects. This route may not be suitable for certain medications

**HYDRATION** hypodermoclysis rate is typically 1 2 ml./ min per needle site. Contraindicated if severe edema, severe bleeding disorder, or severe thrombocytopenia

### **Principles of Pain Control**

#### TYPES OF PAIN

**NOCICEPTIVE PAIN somatic** (musculoskeletal pain, fractures, arthritis, bone metastases), **visceral** (obstruction, liver metastases)

**NEUROPATHIC PAIN dysesthetic** (constant burning), **neuralgic/lancinating** (paroxysms of shooting pain)

**SOMATIZATION** 

#### PATHOPHYSIOLOGY

**DEFINITION OF PAIN** an unpleasant sensory and emotional experience associated with actual or potential tissue injury or described in terms of such damage. The concept of total pain is the sum of all physical, emotional, psychosocial, and spiritual pain **PREVALENCE OF CANCER PAIN** about 80% experience some form of pain during their course of illness; 80% due to tumor; 20% due to cancer therapy, and >5% due to other unrelated diseases

**TOLERANCE** normal pharmacophysiological effect in which increasing doses of opioids are required to provide the same analgesic effect over time

#### PATHOPHYSIOLOGY (CONT'D)

**DEPENDENCE** normal pharmacophysiological effect with the development of withdrawal symp toms (e.g. agitation, pain, fever, sweats, tremor, tachycardia) if opioid is stopped abruptly after a prolonged period of use. In general, a minimum of one third of total daily opioid dose is required to prevent withdrawal symptoms

**ADDICTION** abnormal psychopathological com pulsion to use a substance affecting daily function. Although the great majority of patients using analge sics as prescribed will not get addicted and should be reassured, approximately 10 20% of patients (with a history of substance use, CAGE positive) are at risk for developing opioid dependence/addiction. These individuals may be prescribed an ever escalating dose of opioid, without adequate pain control. It is important to minimize use of opioids and to empha size the use of analgesics to maintain function rather than to treat pain

#### DISTINGUISHING FEATURES OF PAIN

Somatic Visceral Neuropathic

Location Localized Poorly localized, referred Radiation, dermatome

Nature Aches Squeezing, cramping Shooting, burning

Analgesics Opioids, NSAIDs Opioids Opioids, TCAs, antiepileptics, venlafaxine

#### PATHOPHYSIOLOGY (CONT'D)

**CAUSES OF INTRACTABLE CANCER PAIN** disease progression, neuropathic pain, bone pain, break through pain, delirium, substance use, delirium, depression/anxiety, and somatization (i.e. psychoso cial/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 poten tially 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/ splanchnic block, subarachnoid block, cordotomy, epidural/intrathecal infusion, vertebroplasty) may be added to any line as needed

#### **ADJUVANT THERAPIES**

- MEDICATIONS MITIGATING ADVERSE EFFECTS OF OPIOIDS start bowel protocol (senna 2 tab PO qhs) and anti nausea (metoclopramide 10 mg PO q4h) at the same time of opioids. Methylphenidate 5 10 mg PO qAM and 5 10 mg qnoon may be used for opioid sedation
- TRICYCLIC ANTIDEPRESSANTS (neuropathic pain) 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, Strontium<sup>89</sup>, or Samarium<sup>153</sup> for multifocal osteoblastic bone metastases), hor monal agents
- BISPHOSPHONATES (bone metastases, hypercalce 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 compres sion, visceral distension, increased intracranial pres sure, and soft tissue infiltration) dexametha sone 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 con stipation. 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 respira tory 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 fail ure, hypercalcemia), and symptom management (e.g. treat nausea and constipation)

#### TREATMENT ISSUES (CONT'D)

**OPIOID ROTATION** if severe side effects (sedation, nightmares, hallucinations, myoclonus), switch to

#### TREATMENT ISSUES (CONT'D)

another opioid with a 25 50% dose reduction. If poor analgesic response, switch without dose reduction

<b>EQUIANALGESIC TAE</b>	BLE			
	Ratio <sup>a</sup>	Starting	q1h PRN	Route
Codeine <sup>b</sup>	0.1	30 60 mg q4h PRN		PO/PR
Hydrocodone <sup>c</sup>	0.5 1	5 10 mg q4h PRN		PO
Morphine	1	5 mg q4h	2.5 5 mg	PO/PR/SC/IV
Hydromorphone	5	1 2 mg q4h	0.5 1 mg	PO/PR/SC/IV
Oxycodone <sup>d</sup>	1.5	5 mg q4h	2.5 mg	PO/PR/SC
Fentanyl drip	100	10 50 μg/hr	25 μg	IV
Methadone	2 20 <sup>e</sup>	5 mg q8 12h		PO/PR/IV
alle i le le				

<sup>&</sup>lt;sup>a</sup> Higher number indicates greater potency

<sup>&</sup>lt;sup>e</sup> See methadone conversion table below

TREATMENT ISSUES (CONT'D)			
FENTANYL DURAGESIC CONVERSION			
Fentanyl TD (μg/h)	Morphine PO (mg)		
25	45 134		
50	135 224		
75	225 314		
100	315 404		
125	405 494		
150	495 584		

- CONVERSION BETWEEN FENTANYL PATCH (IN μG/H) AND ORAL MORPHINE (IN MG/DAY) consider using a ratio of 3.6, e.g. fentanyl patch of 25 μg/h is equivalent to 25×3.6=90 mg of oral morphine/day
- CONVERSION BETWEEN INTRAVENOUS FENTANYL AND INTRAVENOUS MORPHINE consider using a ratio of 10 µg:1 mg
- BIOAVAILABILITY OF FENTANYL IS HIGHLY VARIABLE transdermal 90%, sublingual 65%, and transmuco sal (lozenge) 50%

#### METHADONE CONVERSION

1. DETERMINE THE DOSE EQUIVALENT

Oral morphine			
equivalent daily dose	Initial dose ratio		
(mg/day)	(morphine:methadone)		
<30 mg/day	2:1		
30 99 mg/day	4:1		
100 299 mg/day	8:1		
300 499 mg/day	12:1		
500 999 mg/day	15:1		
>1000 mg/day	20:1 or greater		

### TREATMENT ISSUES (CONT'D)

#### 2. DETERMINE THE SCHEDULE

	Day 1	Day 2	Day 3	Day 4
Morphine (MS)	66%	33%	0%	0%
	TDD	TDD	TDD	TDD
Methadone (ME)	33%	66%	100%	100%
	TDD	TDD	TDD	TDD
Break through	10%	10%	10%	10%

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 con version 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 CON

**TROL** 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 fail ure 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 activ ity. Also consider use of non opioids such as gaba pentin, pregabalin, carbamazepine, venlafaxine, and TCAs

b Tylenol #1 3 = acetaminophen plus codeine with or without caffeine

<sup>&</sup>lt;sup>c</sup> Vicodin, Lortab, Norco = acetaminophen plus hydrocodone

<sup>&</sup>lt;sup>d</sup> Percocet = acetaminophen plus oxycodone

#### **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, hepa tic/renal failure, neurologic/endocrine failure such as hypothyroidism, hypogonadism, adrenal insuffi ciency, infections

#### PATHOPHYSIOLOGY

**DEFINITION** a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that interferes with usual functioning. Cancer related fatigue is distinct from everyday tired ness as it does not correspond to the patient's level of exertion and is not typically relieved by rest or sleep. Note that fatigue has not been well studied in other palliative care settings, although the underlying patho physiology and treatments are similar to cancer related fatigue

#### PATHOPHYSIOLOGY (CONT'D)

**PREVALENCE** cancer related fatigue is essentially present throughout the cancer journey, including 40% at diagnosis, 80 90% during cancer treatment, 30% 1 year post treatment, 75% with metastatic dis ease, 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?"

0		Absence of fatigue
1	3	Mild fatigue
4	6	Moderate fatigue
7	10	Severe fatigue

#### INVESTIGATIONS

#### BASIC

 LABS CBCD, lytes, urea, Cr, glucose, TSH, Mg, Ca, albumin

#### MANAGEMENT

**NON PHARMACOLOGIC** exercise for at least 30 min/day (strongest evidence), psychosocial inter ventions, 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 (dexa methasone 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 regurgi tation, endocarditis
- PERICARDIAL pericardial effusion, tamponade
   SYSTEMIC sepsis, metabolic acidosis, anemia
   OTHERS neuromuscular (cachexia), anxiety,
   tense ascites

#### PATHOPHYSIOLOGY

**DEFINITION** a subjective experience of breathless ness 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<sub>2</sub> if hypoxe mic, 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, con sider thoracentesis, pleurodesis, or PleurX catheters

#### TREATMENT ISSUES

#### PALLIATIVE SEDATION

 DEFINITION the use of medications to relieve intolerable suffering from refractory symptoms through sedation. Refractory symptoms are defined as those for which all possible treatment has failed or it is estimated that no methods are available for palliation within the time frame and the risk benefit ratio that the patient can tolerate

#### TREATMENT ISSUES (CONT'D)

- INDICATIONS when suffering (delirium/agitation, dyspnea, pain) persists despite all other means; not to be confused with euthanasia. Must ensure detail discussion with patient (if possible), family, and pal liative 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, chlorproma zine, 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 respira tory 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 Gl/bladder spasms and is dosed very differently)

**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 infarc tion/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<sub>4</sub>, 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 *metoclo* pramide to SC infusion 60 120 mg/day. Also con sider adding haloperidol 1 2 mg SC g8 12h and a1h PRN
- FURTHER OPTIONS
  - H1 BLOCKADE dimenhydrinate 50 mg PO/SC/IV q4h or diphenhydramine 50 mg PO/SC/IV q4h
  - STEROIDS dexamethasone 4 10 mg PO/SC/IV BID
  - **NEUROLEPTICS** methotrimeprazine 5 25 mg PO TID, chlorpromazine 10 25 mg PO q4h
  - CANNABINOID AGONISTS nabilone 1 mg PO daily may also be considered
  - 5HT3 ANTAGONISTS ondansetron 8 mg PO daily TID for chemotherapy induced nausea and vomiting
  - PROMOTILITY AGENTS domperidone 10 mg PO TID QID, cisapride 10 mg PO TID QID (special release)

#### SPECIFIC ENTITIES

#### **BOWEL OBSTRUCTION IN THE PALLIATIVE SETTING**

- PATHOPHYSIOLOGY 3% of all advanced cancers, particularly ovarian (11 42%), colorectal (5 24%), gastric, endometrial, prostate, and bladder. If inop erable, median survival is only 2 months
- CAUSES intraluminal (mass, constipation, intussus ception), luminal (carcinomatosis causing dysmoti lity, bowel infarction), and extraluminal (compres sion, adhesions)
- CLINICAL FEATURES nausea and vomiting, abdom inal distension and pain, obstipation, absent bowel sounds
- DIAGNOSIS AXR
- MANAGEMENT
  - SUPPORTIVE MEASURES intravenous fluids, bowel rest, pain control (opioids, hyoscine butyl bromide/buscopan), antiemetics, NG suction (clump when output <100 cc/day and ensure no further N&V before removal). Consider vent ing PEG tube insertion sooner than later
  - ANTI-SPASMODIC/ANTISECRETORY AGENTS antimus carinic agents (hyoscine butylbromide 10 20 mg PO/IV/IM TID, atropine), somatostatin analogues (octreotide 10 µg/h IV or 50 µg SC q8h)
  - BYPASS OBSTRUCTION surgery, stent placement, venting gastrostomy, corticosteroids to decrease local inflammation

## **Constipation in the Palliative Setting**

#### **DIFFERENTIAL DIAGNOSIS**

#### **★DUODENUM**★

**DIET** low fiber, dehydration

**ΨSYCHIATRY** depression, somatization, obses sive compulsive disorder **OBSTRUCTION** cancer, strictures, adhesions

**DRUGS** opioids, TCAs, neuroleptics, antihista mines, 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 CONSTIPATION IN THE PALLIATIVE CARE SET

TING the most common causes are opioids, other medications, dehydration, and immobility. Even if there is no food intake, a small amount of stool is

#### PATHOPHYSIOLOGY (CONT'D)

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 rhea, hemorrhoids, anal fissures, confusion/delirium, fear of opioid use

#### INVESTIGATIONS

#### BASIC

IMAGING AXR

#### SPECIAL

lytes, urea, Cr, glucose, Mg, Ca, albu WORKUP min, TSH

#### DIAGNOSTIC ISSUES

CONSTIPATION SCORE based on flat abdominal X ray. Divide into 4 quadrants (ascending, transverse, descending, and rectosigmoid colon). Rate amount Anorexia–Cachexia 397

#### 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 cer eals, 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

#### MANAGEMENT (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 4 L PO/NG ×1 for severe constipation

- µ-OPIOID RECEPTOR ANTAGONISTS indicated for patients with opioid induced constipation despite at least 3 days of laxatives. Methylnaltrexone 12 mg SC ×1 d, repeat every other day as needed. These antagonists are peripheral acting, and thus do not affect pain control which happens centrally
- MANUAL DISIMPACTION as last resort. For patients with spinal cord compression, it is important to use rectal measures (enemas, suppositories) as significant diarrhea/leakage could occur with oral medications alone

**TREAT UNDERLYING CAUSE** stop potentially con stipation causing medications if possible. Methadone and fentanyl *may be* less constipating than other opioids (controversial)

### Anorexia-Cachexia

#### DIFFERENTIAL DIAGNOSIS

**MALIGNANCY solid tumors** (primary, meta static), **hematologic** 

CHRONIC INFECTION atypical (TB), viral (HIV, HCV), fungal, parasitic

**CONNECTIVE TISSUE DISEASE seropositive** (RA, SLE, dermatomyositis, polymyositis), **serone gative**, **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

#### PATHOPHYSIOLOGY (CONT'D)

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 exces sive 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 CBCD, lytes, urea, Cr, Ca, PO<sub>4</sub>, ESR, CRP, fasting glucose, TSH, AST, ALT, ALP, bilirubin, INR, albumin, fasting lipid profile, AM total tes tosterone level
- BODY WEIGHT regular and frequent assessments
- CALORIE COUNT determine daily intake

  SPECIAL
- BODY COMPOSITION AND METABOLISM STUDIES bone density scan, bioelectrical impedance, indirect calorimetry
- MALIGNANCY WORKUP (if no obvious cause for cachexia) serum protein electrophoresis, PSA (if male), fecal occult blood, CXR
- INFECTION WORKUP (if no obvious cause for cachexia) serologies (HBV, HCV, HIV, Treponema pallidum)
- INFLAMMATORY WORKUP (if no obvious cause for cachexia) ANA, RF, C3, C4, p ANCA, c ANCA, cryoglobulins

#### MANAGEMENT

**NUTRITIONAL COUNSELING** patients with advanced disease should be encouraged to eat things they enjoy in small and frequent portions, without have having to worry too much about their nutritional content. Dietician referral may be useful. Aggressive measures such as parenteral or enteral feeding have limited impact on survival but may significantly decrease the quality of life. Their use should be limited to patients for whom starvation is a major component of weight loss (e.g. dysphagia from esophageal or head and neck cancer, bowel obstruction from peritoneal carcinomatosis)

**OREXIGENIC AGENTS** (appetite stimulants) **corti costeroids** (*dexamethasone* 4 mg PO daily, patients may experience an increase in appetite and sense of

#### MANAGEMENT (CONT'D)

well being. Weight gain may not occur and duration of appetite stimulation is often short. Risk of myo pathy 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 thromboem bolic risk, swelling, impotence, and GI upset). **Sero tonin antagonists** 

**ANTICATABOLIC AGENTS** (antimetabolic and antic ytokine) 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, mirtaza pine, thalidomide, lenalidomide are considered investigational at this time

**TREATMENT OF CONTRIBUTORS** consider treat ment of nausea with antiemetics, mucositis with lido caine vicous 2% or lidocaine spray, taste changes with zinc sulfate 220 mg PO BID, early satiety with meto clopramide, pain with analgesics, constipation with laxatives, and depressive mood with antidepressants

### TREATMENT ISSUES FOR ANOREXIA CACHEXIA

#### MEGESTROL ACETATE VS. CORTICOSTEROIDS

megestrol has been shown to increase appetite and weight (but not lean body mass) and may be con sidered 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 399

#### **Communication Issues**

#### COMMUNICATION TECHNIQUES

- ASSESS PATIENT'S UNDERSTANDING of their dis ease and their expectations before sharing information
- "ASK TELL ASK" APPROACH if information is sensitive, ask for patient's permission before starting, then share information tailored to her intellectual comprehension and emotional resilence and assess her need for further information before proceeding
- EMPATHIC RESPONSES acknowledge patient's emotion and facilitate its expression, using phrases such as "I can see this is a difficult time for you."
- ACTIVE LISTENING facilitate discussion by sum marizing, use of appropriate pauses or phrases such as "Tell me more."
- NON VERBAL COMMUNICATION pay atten tion to speech, posture, facial expression, appear ance, and setting

#### DISCUSSING RESUSCITATION STATUS

The following overview is based on JCO 2001 19:5, with a number of citations from the article

**CONTEXT** establish an appropriate setting for the discussion. Sit down and talk slowly with good eye contact. Get healthcare team and family members involved (if appropriate)

#### WHAT DOES THE PATIENT UNDERSTAND?

- 'What do you understand about your current health situation?"
- 'Tell me about how you see your health?"
- 'What do you understand from what the doctors have told you?"

#### WHAT DOES THE PATIENT EXPECT?

- 'What do you expect in the future?"
- 'Have you ever thought about how you want things to be if you were much more ill?'
- · 'What are you hoping for?'

#### **DISCUSS DNR ORDER, INCLUDING CONTEXT**

- 'If you should die despite all of our efforts, do you want us to use 'heroic measures' to bring you back?"
- 'How do you want things to be when you die?"
- 'So, what you are saying is you want to be as comfortable as possible when the time comes."
- 'What I hear you saying is you do not want us to 'call a code' if it would not do any good."
- 'What you have said is you want us to do 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/ intu bation/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 ratio 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?"

# BREAKING BAD NEWS THE GENTLE ART OF TRUTH TELLING (CONT'D)

- 'Would you like me to tell you everything? Or would you prefer a more general overview?"
- 'Some people like a whole lot of details, others do not. What do you like?"

KNOWLEDGE: DELIVER INFORMATION discuss diagnosis, treatments, prognosis, and provide under standing of the natural history of disease. Pause fre quently to check understanding. If delivering prognosis, discuss it in terms of "days," "weeks," "months", or "years' instead of quoting median survival num bers. Check patient's understanding frequently "Any questions? Would you like me to continue?"

#### **EMOTIONS: EMPATHIC RESPONSE, NORMALIZE**

"This is a very difficult time for you and your family."

# BREAKING BAD NEWS THE GENTLE ART OF TRUTH TELLING (CONT'D)

- "Many people feel frustrated and sad... Is this your experience?"
- · "I'd like to check so I know where you're at."

# STRATEGY: EMPOWER PATIENT AND PROVIDE FOLLOW UP, SUPPORT RESOURCES, AND APPROPRIATE COUNSELING

- "There is a lot we can do even though there is no cure for your disease. We will keep our eyes open for new treatments and discuss them together."
- "I know this is very difficult news and a lot of information. It may be very difficult for you to think right now. I am available anytime with any questions."

Oncologist 2000 5:4

# **Prognostication in Far Advanced Cancer Patients**

#### REASONS FOR DISCUSSING PROGNOSIS

**PATIENT AUTONOMY** patients have the right to know, cultural appropriateness

**END OF LIFE PLANNING** important personal decisions influenced by time, time to express wishes (verbal, written), control of the situation/autonomy **CARE PLANNING** helps to avoid harm and discom fort by inappropriate therapies, initiation of medica tions (e.g. antidepressants), hospice admission

**NOTE** advanced cancer patients are defined as pre dicted survival 3 12 months; far advanced cancer patients are defined as predicted survival <3 months

#### PROGNOSTIC FACTORS

**CLINICIAN PREDICTION OF SURVIVAL** clinician esti mation of survival (generally 2 5× overestimation) **SYMPTOMS** poor performance status (median survival palliativa performance, scale, 60, 70% – 105

vival palliative performance scatus (median survival palliative performance scale 60 70% = 108 days, 30 50% = 41 days, 10 20% = 6 days), anorexia, cachexia, dysphagia, dyspnea, delirium

**LABORATORY TESTS** elevated CRP, leukocytosis, lymphopenia, hypoalbuminemia, elevated LDH

**OTHERS** cancer type and stage (less important in patients with far advanced cancer), comorbidities (less important if prognosis is poor. More useful in patients with longer expected survival such as those with prostate cancer)

#### Related Topics

Death and Dying (p. 391) Discussing Prognosis (p. 400)

#### PROGNOSTIC TOOLS

#### PALLIATIVE PROGNOSTIC SCORE (PaP)

- CLINICIAN PREDICTION OF SURVIVAL >12 weeks=0,
   11 12 weeks=2, 7 10 weeks=2.5, 5 6 weeks=4.5,
   3 4 weeks=6, 1 2 weeks=8.5
- Karnofsky performance status  $\geq$ 50%=0, 10 40%=2.5
- ANOREXIA absent=0, present=1.5
- DYSPNEA absent=0, present=1
- TOTAL WBC 4.8 8.5=0, 8.5 11=0.5, >11=1.5
- LYMPHOCYTE PERCENTAGE 20 40%=0, 12 19.9% = 1, 0 11.9%=2.5
- **UTILITY** 30 day survival for total score 0 5.5 = 97%, 5.6 11 = 59%, 11.1 17.5 = 25%

#### PALLIATIVE PROGNOSTIC INDEX (PPI)

- PALLIATIVE PERFORMANCE SCALE  $\geq$ 60%=0, 30 50%= 2.5, 10 20=4
- ORAL INTAKE normal=0, moderately reduced=1, severely reduced=2.5
- EDEMA absent=0, present=1
- DYSPNEA AT REST absent=0, present=3.5
- **DELIRIUM** absent=0, present=4
- UTILITY with total score of 4 as cutoff, PPV for 6 week survival is 83%, NPV is 71%

PROGN	PROGNOSTIC TOOLS (CONT'D)							
PALLIATIVE PERFORMANCE SCALE (PPS)								
PPS	Mobility	Activity and evidence of disease	Self care	Intake	LOC			
100%	Full	Normal activity and work No evidence of disease	Full	Normal	Full			
90%	Full	Normal activity and work Some evidence of disease	Full	Normal	Full			
80%	Full	Normal activity with effort Some evidence of disease	Full	Normal or reduced	Full			
70%	Reduced	Unable to do normal job Significant disease	Full	Normal or reduced	Full			
60%	Reduced	Unable to do hobby/house work Significant disease	Occasional assist	Normal or reduced	Full or confusion			
50%	Mainly sit or lie	Unable to do any work Extensive disease	Considerable assist	Normal or reduced	Full or confusion			
40%	Mainly in bed	Unable to do most activity Extensive disease	Mainly assist	Normal or reduced	Full or drowsy $\pm$ confusion			
30%	Totally bed bound	Unable to do any activity Extensive disease	Total care	Minimal to sips	Full or drowsy $\pm$ confusion			
20%	Totally bed bound	Unable to do any activity Extensive disease	Total care	Mouth care only	Full or drowsy $\pm$ confusion			
10%	Totally bed bound	Unable to do any activity Extensive disease	Total care		Drowsy or coma $\pm$ confusion			
0%	Dead							
J Pall Care 2007					Pall Care 2007 23:4			

402 Notes

# Notes

# **15** Nutrition

# Section Editor: Dr. Raj Padwal

### Obesity

# NEJM 2007 356:21; NEJM 2008 358:18

#### COMPLICATIONS AND ASSOCIATED DISORDERS

#### **ENDOCRINE**

- INSULIN RESISTANCE hyperinsulinemia, predia betes, type 2 diabetes
- REPRODUCTION irregular menses, anovulatory cycles, infertility

**CARDIOVASCULAR** hypertension, dyslipidemia ( $\uparrow$  chol,  $\uparrow$  LDL or normal with small, dense particles,  $\uparrow$  VLDL,  $\uparrow$  TGL,  $\downarrow$  HDL), coronary artery disease, heart failure, stroke

#### RESPIRATORY

- SLEEP APNEA
- OBESITY-ASSOCIATED HYPOVENTILATION SYNDROME (PaCO<sub>2</sub> ≥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, hir sutism, pressure sores

#### CANCER

- BREAST
- GENITOURINARY prostate
- GYNECOLOGICAL endometrial, ovarian
- GASTROINTESTINAL esophagus, colorectal, liver, gallbladder, pancreas, stomach
- KIDNEY
- NON-HODGKIN'S LYMPHOMA
- MULTIPLE MYELOMA

**PSYCHOSOCIAL** ↓ education, ↓ employment, depression

#### PATHOPHYSIOLOGY

**BODY MASS INDEX** (BMI, weight/height²) under weight <18.5 kg/m², normal 18.5 24.9 kg/m², over weight 25 29.9 kg/m², obesity  $\ge$ 30 39.9 kg/m², severe or morbid obesity >40 kg/m²

PATHOPHYSIOLOGY (CONT'D)					
WAIST CIRCUMFERENCE					
Ethnic group	Men	Women			
Europid	≥94 cm	≥80 cm			
	[≥37 in.]	[≥31.5 in.]			
South Asian, Chinese,	≥90 cm	≥80 cm			
Japanese	[≥35.4 in.]	[≥31.5 in.]			

Use Europid cutoff points for South and Central American, sub Saharan African, Eastern Mediterra nean, and Middle Eastern populations until more specific data are available

**BASAL ENERGY EXPENDITURE** approximately 22 kcal/kg/day [10 kcal/lb/day] is required for weight maintenance (e.g. 1540 kcal is the basal energy need for a 70 kg [154 lb] adult)

#### INVESTIGATIONS

#### RASIC

 LABS CBCD, lytes, urea, Cr, AST, ALT, ALP, bilirubin, Ca, albumin, fasting glucose, fasting lipid profile, HbA1C

#### SPECIAL

- cardiac workup after history and physical, consider ECG. Stress test if indicated
- SLEEP APNEA WORKUP sleep study if symptoms of obstructive sleep apnea
- OBESITY HYPOVENTILATION WORKUP ABG and PFT to demonstrate hypercarbia

#### MANAGEMENT

LIFESTYLE CHANGES reduced calorie diet (estimated energy requirement with 500 kcal/day deficit would lead to weight loss of 0.5 kg/week for first 3 months. A reduction of 5 10% of initial body weight is the minimal initial goal, as this correlates with improvement in comorbidities. Failing that, weight maintenance (no change from baseline weight) is the goal. Consult dieti tian for dietary/behavior modification. Exercise (at least 150 min of physical activity/week). Consult psychologist if psychological issues

404 Anorexia-Cachexia

#### 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 mor tality (NEJM 2008 375:8). Gastric restriction proce dures (gastric banding (adjustable band squeezes and restricts upper gastric area), gastroplasty (sta pling 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 HYPERLIPIDE MIA p. 61). Blood pressure control (see HYPERTEN SION p. 57). Glycemic control (see DIABETES p. 337)

#### TREATMENT ISSUES

#### **OVERALL APPROACH**

- 1. Identify overweight or obese adults
- 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 mod erate 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 fac tors. 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 life long monitoring

Canadian Clinical Practice Guidelines 2006 CMAJ 2006 176:8

PREDICTIVE FACTORS FOR LONG TERM WEIGHT CONTROL FROM THE NATIONAL WEIGHT CON

**TROL 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**

Sleep Apnea (p. 17)

Cardiovascular Disorders (p. 25) Diabetes Mellitus (p. 337) Hyperlipidemia (p. 61) Hypertension (p. 57) Fatty Liver (p. 128)

# **Malabsorption Syndromes**

See MALABSORPTION SYNDROMES (p. 125)

#### Anorexia-Cachexia

See ANOREXIA CACHEXIA (p. 397)

Vitamin B12 Deficiency 405

# **Vitamin B12 Deficiency**

#### DIFFERENTIAL DIAGNOSIS

**DIET** strict vegans

**GASTRIC** pernicious anemia, gastrectomy, gastri tis, achlorhydria

PANCREATIC insufficiency

**SMALL BOWEL** malabsorption syndromes, ileal resection, Crohn's blind loops, bacterial overgrowth **DRUGS** neomycin, metformin, proton pump inhi bitors, N<sub>2</sub>O

#### 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  $\mu g.$  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 sto mach). 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 fac tor complex

#### **Related Topics**

Macrocytic Anemia (p. 146) Malabsorption (p. 125) Vitamin Deficiencies (p. 126)

#### CLINICAL FEATURES

HISTORY anemia, dyspnea, chest pain, fatigue, weight loss, dementia, paresthesia, weakness, falls, diet history, past medical history (gastritis, IBD, pancrea tic disorders, bowel resection, alcoholism), medications PHYSICAL weight loss, lemon colored skin tone (anemia and jaundice), dementia, decreased visual acuity, optic atrophy, Lhermitte's sign, anemia, atrophic glossitis, spasticity, weakness, hyperreflexia, clonus, decreased vibration, and proprioception but preserved pain and temperature sensation, abnormal heel shin test, Romberg (unsteady with eyes closed), pronator drift, gait (altered proprioception, spastic), peripheral neuropathy, vaginal atrophy

#### CLINICAL FEATURES (CONT'D)

SUBACUTE COMBINED DEGENERATION lateral (corticospinal tract) and dorsal (vibration and proprio ception) columns affected. Spinothalamic tract (pain and temperature) spared. Legs affected more than arms

#### INVESTIGATIONS

#### BASIC

- LABS CBCD (megaloblastic anemia), peripheral smear (hypersegmented neutrophils), pancytope nia, bilirubin (†), LDH (†), vitamin B12, RBC folate SPECIAL
- SERUM ANTI-INTRINSIC FACTOR ANTIBODY sens
   50 70%
- SERUM HOMOCYSTEINE LEVEL ↑ if vitamin B12 deficiency. Perform if vitamin B12 level borderline
- 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 pancreati tis, 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 malab sorption (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 over growth syndrome. Another variation is to cook Cbl together with scrambled eggs. Patients with achlorydria will be unable to split Cbl from food proteins and urinary excre tion of Cbl will be <10%</li>

#### MANAGEMENT

TREAT UNDERLYING CAUSE diet adjustment. Vitamin B12 1000  $\mu g$  SC/IM daily  $\times 7$  days, then 1000  $\mu g$  SC/IM weekly for 1 month, and same dose monthly if pernicious anemia. Hematologic para meters improve within days to weeks; neurological

#### MANAGEMENT (CONT'D)

often fail to remit fully on treatment, but improve ment may be seen within months. Watch for

#### MANAGEMENT (CONT'D)

hypokalemia, salt retention, and thrombocytosis early in the course of therapy

# **Diet and Supplemental Nutrition**

#### INTRODUCTION

This chapter provides an overview of nutritional assessment, hospital diet types, enteral feeds, and supplemental parenteral nutrition

**GENERAL ADVICE** for patients with significant under nourishment or at risk of developing malnour ishment (e.g. ICU patients, head and neck or esopha geal cancer patients), consult dieticians for nutritional assessment and guidance regarding supplemental nutrition

#### NUTRITIONAL ASSESSMENT

**FACTORS INFLUENCING ENERGY REQUIRE MENTS** age, previous nutritional status, comorbid ities (sepsis, obesity), activity

#### **IDEAL BODY WEIGHT CALCULATIONS**

- **IBW** (kg)=(height in cm 152 cm) $\times$ 1.1+ 48.2 kg or in lbs=(height in inches 60 in.) $\times$ 6+106 lbs
- $\$  IBW (kg)=(height in cm 152 cm) $\times$ 0.9+45.5 kg or in lbs=(height in inches 60 in.) $\times$ 5+100 lbs

#### **DAILY ENERGY REQUIREMENTS**

- 14 KCAL/KG [6.4 KCAL/LB] BODY WEIGHT BM >40 kg/m<sup>2</sup>
- 21 KCAL/KG [9.5 KCAL/LB] BODY WEIGHT BMI 30 39 kg/m<sup>2</sup>
- 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/кg [0.36-0.45 g/lв] воду weight (pro

- tein restriction) renal failure (no dialysis)
   1–1.2 g/kg [0.45–0.55 g/LB] BODY WEIGHT not septic, minor trauma/surgery, non malnourished, single system failure, hepatic encephalopathy
- 1.2–1.4 G/KG [0.55–0.64 G/LB] BODY WEIGHT multi organ failure, hemodialysis, sepsis, major trauma/surgery, closed head injury, malnutrition
- 1.4–2.0 g/kg [0.64–0.91 g/lb] (IDEAL) BODY WEIGHT multiple surgeries, trauma, severe burns, long bone fractures. If BMI >30 kg/m², 1.5 g/kg [0.68 g/lb] IBW

#### **DAILY LIPID REQUIREMENTS**

 0.8-1 G/KG [0.36-0.45 G/LB] (IDEAL) BODY WEIGHT

#### NUTRITIONAL ASSESSMENT (CONT'D)

#### DAILY CARBOHYDRATE REQUIREMENTS

 2–4 MG/KG/MIN (start low and go slow if concern regarding refeeding syndrome)

#### HOSPITAL DIET TYPES

STANDARD regular, full fluid, clear fluid

**THERAPEUTIC** heart healthy, diabetic, renal (predia lysis, hemodialysis, peritoneal dialysis), sodium restricted (2 g Na, 4 g Na), fiber restricted, high protein/calorie

**SPECIAL** diets for cultural/religious modifications, dis ease specific requirements (e.g. gluten free), various nutrient specific therapeutic modifications (e.g. high K<sup>+</sup>, 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 swallow ing assessment to determine most appropriate consistency

#### ENTERAL NUTRITION OVERVIEW

**ADVANTAGES** maintains gut integrity and immu nologically favorable compared to total parenteral nutrition

**CONTRAINDICATIONS** hemodynamically unstable, severe ileus, bowel obstruction, UGI bleed, distal anastomosis, NG output >1 L/24 h, uncontrollable nausea, vomiting and/or diarrhea, short gut, radiation enteritis

#### **ROUTES FOR ENTERAL FEEDS**

# NASOGASTRIC/KAOFEED/OROGASTRIC TUBE

< 6 weeks. Risk of aspiration

**NASOJEJUNAL TUBE** <6 weeks. Less chance of aspiration/pneumonia

**GASTROSTOMY TUBE** >6 weeks. Risk of aspiration **JEJUNOSTOMY TUBE** >6 weeks. Decreased aspiration risk

#### ADMINISTRATION OF ENTERAL FEEDS

**CONTINUOUS** usually given over 24 h. Compared to bolus feed, decreased aspiration risk, and better

#### ADMINISTRATION OF ENTERAL FEEDS (CONT'D)

glycemic control. Start full strength formula at 25 mL/h, increase by 25 mL q4h to goal rate. Check gastric residuals q4h and continue to increase if <250 mL. If >250 mL, hold feeds, initiate pro motility therapies, and re check after 4 h

**NOCTURNAL** for patients eating 50% of require ments during daytime; wean off tube feed

**BOLUS/INTERMITTENT** for patients more mobile. More physiologic. Start with 1 can (250 mL) over 30 60 min 4×/day

#### ENTERAL NUTRITION FORMULAS

**ISOSOURCE HN** 1.2 kcal/mL, goal usually 60 85 mL/h; 0.053 g protein/mL. Fiber containing. Standard formula

**ISOSOURCE 1.5** 1.5 kcal/mL, 0.068 g protein/mL, fiber containing

**RESOURCE 2.0** 2.025 kcal/mL, 0.084 g protein/mL. For fluid restricted patients

**PERATIVE** 1.3 kcal/mL, 0.067 g protein/mL arginine containing

**NOVASOURCE RENAL** 2 kcal/mL, 0.074 g protein/mL For renal patients on dialysis or pre renal with high electrolytes

**ISOSOURCE VHN** 1 kcal/mL, 0.063 g protein/mL. For catabolic patients, high protein

**RESOURCE DIABETIC** 1.06 kcal/mL, 0.064 g pro tein/mL. Higher fat, low carbs, fiber containing. For difficult to control blood sugars.

**PEPTAMEN 1.5** 1.5 kcal/mL, 0.068 g protein/mL. Used for patients with malabsorption problems, severe diarrhea

**PULMOCARE** 1.5 kcal/mL, 0.063 g protein/mL. Low carbohydrate to lower CO<sub>2</sub> production. For patients with COPD or CO<sub>2</sub> retention

#### ADDITIONS TO ENTERAL FEEDS

PECTIN 20 mL BID. Soluble fiber to aid in diarrhea
BENEPROTEIN one scoop = 6 g protein and 25 kcal
GLUTAMINE main fuel for gut enterocytes. For
burns and trauma. Consult dietician for
recommendations

#### COMPLICATIONS OF ENTERAL FEEDS

**DIARRHEA** due to osmotic load, medications, gas troenteritis, *Clostridium difficile* 

**VOMITING** associated with aspiration

**ASPIRATION** prevent by using small bore feeding tube (<10 Fr), monitor tube migration, post pyloric position of tube, continuous schedule, elevation of head of bed by  $>30^\circ$  during feeding, positioning of patient on right side, ambulation, use of promotility

#### COMPLICATIONS OF ENTERAL FEEDS (CONT'D)

agents 30 min before feeding (*metoclopramide* 10 mg PO OID), ensure bowel routine

#### PARENTERAL NUTRITION OVERVIEW

#### **TOTAL PARENTERAL NUTRITION (TPN)**

- INDICATIONS unusable Gl tract for at least 5 7 days. Severe pancreatitis, bowel resection/obstruc tion/fistula without distal feeding access, intract able diarrhea/malabsorption/vomiting, acute Gl bleed, failure of enteral nutrition to meet nutri tional 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/ill ness, aggressive support not desired, risks of TPN outweigh benefits
- COMPLICATIONS no Gl tract mucosal growth, no maintenance of gut barrier, metabolic disturbances if overfeeding (hyperglycemia, cholestasis/hepatic steatosis, electrolyte imbalances), line sepsis

**PERIPHERAL PARENTERAL NUTRITION (PPN)** short term use only as nutritionally inadequate; addition of low dose heparin and hydrocortisone to prevent line thrombosis; must be <1000 mOsm

#### COMPONENTS OF TOTAL PARENTERAL NUTRITION

#### TRAVASOL

**PROTEIN** 4 kcal/g, 10% amino acid

**CARBOHYDRATE** 3.4 kcal/g; 70% dextrose solution **LIPID** 2 kcal/mL: 20% lipid emulsion

**ELECTROLYTES** Na (60 150 mmol/day), K (30 80 mmol/day), Ca (5 15 mmol/day), Mg (4 8 mmol/day), PO<sub>4</sub> (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 ner vosa, cancer, alcoholism, severe unintentional weight loss

**MECHANISM** carbohydrate administration leading to a sudden shift from fat to carbohydrate metabo lism  $\rightarrow \uparrow$  insulin secretion  $\rightarrow$  stimulates cellular uptake of phosphate  $\rightarrow \downarrow \mathrm{Mg}, \downarrow \mathrm{PO}_4, \downarrow \mathrm{K}$ 

**TIME FRAME** usually occurs within 3 days of initiation of feed (parenteral, enteral feed, oral intake, IV glucose) **MANAGEMENT** start carbohydrate/feeds low and increase slowly. Monitor electrolytes (lytes, Mg, PO<sub>4</sub> daily ×3 days sand replete PRN), monitor glycemic control

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# Notes

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# OBSTETRIC MEDICINE

Section Editor: Dr. Winnie Sia

# Preeclampsia/Eclampsia/HELLP Syndrome

JOGC 2008 30:3 S1

# DIFFERENTIAL DIAGNOSIS OF HYPERTENSION IN PREGNANCY

**PREECLAMPSIA** new onset or worsening hyper tension,  $\pm$  proteinuria ( $\geq$ 300 mg/day or  $\geq$ 30 mg/mmol spot urine protein to creatinine ratio),  $\pm$  adverse clinical signs or symptoms or abnormal labs. A disease >20 weeks gestation

**ECLAMPSIA** preeclampsia with generalized tonic clonic seizures

**HELLP SYNDROME** a variant of preeclampsia with **H**emolysis (i.e. microangiopathic hemolytic anemia), **E**levated **L**iver enzymes (i.e. RUQ or epi gastric pain), and **L**ow **P**latelets

**PREEXISTING HYPERTENSION** BP > 140/90 mmHg prior to 20<sup>th</sup> week of gestation, complicates 3 5% of pregnancies, 20% risk of developing preeclampsia

PREECLAMPSIA SUPERIMPOSED UPON PREEXIST ING HYPERTENSION new onset proteinuria in women with preexisting hypertension or worsening of blood pressure despite 3 antihypertensive medications GESTATIONAL HYPERTENSION hypertension ≥ 20 weeks without proteinuria without adverse effects

#### **Related Topics**

Hypertension (p. 57) Proteinuria (p. 74) Seizures (p. 309)

# PATHOPHYSIOLOGY

# **DEFINITION OF HYPERTENSION IN PREGNANCY** diastolic BP ≥90 mmHg

**RISK FACTORS** age ≥40, nulliparity, multiple gesta tions, prior preeclampsia, obesity, chronic hypertension, diabetes mellitus, chronic kidney disease, antiphospholi pid antibodies, and inter pregnancy interval >10 years

### CLINICAL FEATURES

**HISTORY** inquire about headaches, visual distur bances, epigastric or RUQ pain, and swelling. Adverse events include seizures,  $\Delta$  level of consciousness, pulmonary edema, heart failure, renal failure, liver

#### CLINICAL FEATURES (CONT'D)

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 CBCD, Cr, spot urine for protein to creati nine ratio, AST, ALT, albumin, uric acid

#### SPECIAL

- **BLOOD TESTS** peripheral smear, lytes, urea, bilirubin, INR, LDH if indicated
- FETAL EFFECTS biophysical profile and fetal U/S

#### MANAGEMENT

**ACUTE** ABC,  $O_2$  to keep sat >95%, IV with judicious fluid volume

ACUTE LOWERING OF SEVERE HYPERTENSION (SBP ≥160 mmHg or DBP ≥110 mmHg) labetalol (start with 20 mg IV, repeat 20 80 mg IV q10 30min, or infusion 1 2 mg/min, max 300 mg), nifedipine short acting capsule 5 10 mg PO q30min, or nifedipine PA tablet 10 mg PO q45min, max 80 mg/day, avoid SL tab) or hydralazine (start with 5 mg IV, repeat 5 10 mg IV q20 30min, max 20 mg). Severe cases may require continuous infusion. Consider urgent delivery if not controlled

CHRONIC MANAGEMENT OF NON SEVERE HYPER TENSION (SBP 140 159 mmHg DBP 90 109 mmHg) target BP at 130 140/80 90 mmHg if renal disease, diabetes, cardiovascular disease, or cere brovascular 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, nifiedipine PA tablet 10 20 mg PO TID, max 180 mg/day, or nifiedipine XL 20 60 mg PO daily, max 120 mg/day are good choices. Avoid ACE inhibitors, ARBs, and atenolol. Other β blockers, clonidine, hydrala zine are alternatives

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#### MANAGEMENT (CONT'D)

**SEIZURE PREVENTION AND TREATMENT**  $MgSO_4$  4 g IV bolus, then 2 g/h (contraindicated in myasthe nia gravis)

**DELIVERY** the cure for preeclampsia, eclampsia, and HELLP. Administer steroids to promote fetal lung maturation prior to 34 weeks if early delivery

#### MANAGEMENT (CONT'D)

**RECURRENCE** recurrence rate of preeclampsia is 18 66% in subsequent pregnancies. Rule out anti phospholipid syndrome if preeclampsia or placental insufficiency <34 weeks. ASA 81 mg/day before and during next pregnancy is recommended

## **Pulmonary Diseases in Pregnancy**

#### ASTHMA

**ASTHMA** treatments similar to non pregnant patients.  $\beta$  Agonists, anticholinergics, and glucocorticoids (inhaled, systemic) are all safe. Leukotriene antagonists only if refractory to above. Keep  $O_2$  sat >95% at all times. Stress dose steroids during delivery if patient required moderate systemic steroids for >3 weeks in the preceding year

#### VENOUS THROMBOEMBOLISM

PATHOPHYSIOLOGY increased risk of DVT/PE due to ↑ factors II, VII, X, and fibrin, as well as ↓ protein S and fibrinolytic activity, especially during T3. Also stasis due to ↓ venous tone and flow. Similar risk of DVT/PE in each trimester but highest post partum; 90% of DVT in pregnancies are left sided

**DIAGNOSIS** if suspect venous thromboembolism,

consider initiation of LMWH while waiting for investiga tions. 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 compres sion 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 leuke mia). Consider proximity of fetus to radiations site (i.e. radiation from CT chest > V/Q scan in T3)

# FETAL RADIATION EXPOSURE FOR COMMON IMAGING MODALITIES

VENOUS THROMBOEMBOLISM (CONT'D)				
Imaging	Estimated fetal radiation exposure (rad)			
CT chest (PE	0.0003 0.002 (T1)			
protocol)	0.0008 0.0077 (T2)			
	0.005 0.013 (T3)			
Pulmonary	< 0.05 via brachial route			
angiogram	0.2 0.3 via femoral route			
Cardiac angiogram	<1			
AXR	0.2 0.3			
IVP	0.8 (complete series)			
	0.2 (limited series)			
MRI/MRV/MRA	None			

#### Related Topics

Asthma (p. 1)

Pulmonary Embolism (p. 8)

TREATMENTS LMWH (monitor anti Xa level). LMWH is contraindicated for 12 24 h prior to neuraxial analge sia, 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 (deformi ties, fetal hemorrhage). Thrombolysis is generally con traindicated as risk of fetal demise

NEJM 2008 359:19

#### AMNIOTIC FLUID EMBOLISM

**PATHOPHYSIOLOGY** can occur during labor and delivery or with uterine manipulation. Risk factors include older age and multiparity

**DIAGNOSIS** clinical diagnosis. Differential diagnosis includes septic shock, pulmonary embolism, aspiration pneumonia, uterine rupture, abruptio pla centae, 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

#### AMNIOTIC FLUID EMBOLISM (CONT'D)

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 \(\perp \) 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** gen erally advise against pregnancy in following conditions: tetralogy of Fallot with severe cyanosis, Eisenmenger's syndrome, severe pulmonary hypertension, functional limitation NYHA 3 or 4, recent cardiac transplantation with high dose immunosuppression, Marfan's syndrome with aortic root >40 mm [1.6 in.], interstitial pulmonary fibrosis, lymphangioleiomyomatosis, and active lung cancer

#### Related Topics

Endocarditis (p. 52) Heart Failure (p. 33) Valvular Disorders (p. 51)

#### VALVULAR DISORDERS

**REGURGITANT VALVULAR HEART DISEASE** may improve during pregnancy due to ↓ systemic vascular resistance. Avoid Valsalva maneuver. Assist second stage with forceps

**STENOTIC VALVULAR HEART DISEASE** may worsen during pregnancy. Consider  $\beta$  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 6<sup>th</sup> week and continue throughout first trimester and possibly throughout pregnancy (aim for higher anti Xa level). Warfarin, which crosses the

#### VALVULAR DISORDERS (CONT'D)

ered during 2<sup>nd</sup> and 3<sup>rd</sup> trimesters for more thrombo genic valves until 36<sup>th</sup> 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;

placenta and may cause fetal bleeds, may be consid

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

#### DIFFERENTIAL DIAGNOSIS (CONT'D)

bile formation with severe **pruritus**. Jaundice in 20 60% 1 4 weeks after pruritus starts.  $\uparrow$  ALT,  $\uparrow$  AST,  $\uparrow$  bilirubin (less common),  $\uparrow\uparrow$  **bile acids**. Resolves following delivery without hepatic sequelae. Fetus at risk for sudden death especially with bile acids >40  $\mu$ mol/L [16  $\mu$ g/mL]

### DIFFERENTIAL DIAGNOSIS (CONT'D)

ACUTE FATTY LIVER OF PREGNANCY (T3, incidence 0.008%) may be associated with preeclamp sia. Characterized by severe liver dysfunction (encephalopathy, hypoglycemia, coagulopathy) and commonly jaundice. ↑↑ ALT, ↑↑ AST, ↑ bilirubin, ↑ WBC, ↑ PT, ↑ uric acid. U/S is often normal (micro vesicular fat on biopsy) and CT shows a lowdensity liver. May progress to acute hepatic failure and DIC in >75%. Increased maternal and fetal mortality

PREECLAMPSIA/ECLAMPSIA (T2 3, incidence 5 10%) see section under preeclampsia. May progress to HELLP (4 12%), DIC (7%), jaundice (5 14%) later HELLP SYNDROME (T3, incidence 0.1%) pre eclampsia symptoms. ↑ ALT, ↑ AST, ↑ bilirubin, ↓ platelets, ↑ LDH. May progress to DIC (30%) OTHER CONDITIONS drug induced hepatitis,

**OTHER CONDITIONS** drug induced hepatitis ascending cholangitis, acute cholecystitis, malig nancy, HBV, and HCV

### CLINICAL FEATURES

**HISTORY** jaundice, pruritus, abdominal pain, ascites, swelling, encephalopathy, nausea and vomit ing, headache, visual disturbances, fever, obstetrical history (current pregnancy course, previous births, previous preeclampsia), past medical history (hyper tension, hepatitis, alcohol, IDU), and medications

**PHYSICAL** check vitals (hypertension), edema (facial, limbs), heart (elevated JVP, S3, S4), hepatic tenderness, ascites, jaundice, and hyperreflexia

### INVESTIGATIONS

### BASIC

 LABS CBCD, peripheral smear, lytes, urea, Cr, spot urine for protein to creatinine ratio, AST, ALT, ALP (mild elevation could be from placenta), GGT, bilir ubin, INR, bile acids (intrahepatic cholestasis), uric acid (acute fatty liver), LDH, fibrinogen (DIC), TSH

### INVESTIGATIONS (CONT'D)

- MICROBIOLOGY HBV and HCV serology
- IMAGING U/S abd

### SPECIAL

. LIVER BIOPSY if not coagulopathic

### MANAGEMENT

**HYPEREMESIS GRAVIDARUM** rule out molar pregnancy and hyperthyroidism. Supportive fluids. Metoclopramide, dimenhydrinate, and diclectin acceptable. Consider ondansetron if refractory. Con tinuous metoclopramide infusion if severe

INTRAHEPATIC CHOLESTASIS OF PREGNANCY ursodeoxycholic acid or cholestyramine, increase fetal monitoring, consider early delivery as risk of

fetal monitoring, consider early delivery as risk of fetal demise if high bile acids

ACUTE FATTY LIVER OF PREGNANCY vitamin K if

coagulopathic, early delivery **HELLP** anti hypertensive, MgSO<sub>4</sub>, 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. Treat ments include lifestyle changes, antacids, raniti dine, PPIs, and metoclopramide
- CHOLECYSTITIS pregnant women are at increased risk due to hormonal changes. Medical manage ment with IV fluids, NG, and opioids. Broad spec trum antibiotics may be added for severe disease. Cholecystectomy safest during 2<sup>nd</sup> trimester

### **Related Topics**

Acute Liver Failure (p. 128) Dyspepsia (p. 113)

### **Infectious Diseases in Pregnancy**

### URINARY TRACT INFECTIONS

**ASYMPTOMATIC BACTERIURIA** occurring in 2 7% of pregnancies, associated with pre term birth, low birth weight, and perinatal mortality. 30 40% will develop symptomatic UTI if untreated, and therefore should be treated (depending on cul ture and local antibiotic resistance pattern, consider amoxicillin clavulanate 500 mg PO BID ×7 days, nitrofurantoin 100 mg PO BID ×7 days [risk of hemo lytic anemia]). Avoid trimethoprim if alternatives available. Follow up culture 1 week following treat ment completion and then monthly until pregnancy complete

### URINARY TRACT INFECTIONS (CONT'D)

ACUTE CYSTITIS occurring in 1% of pregnancies, with treatment and follow up as asymptomatic bacteriuria PYELONEPHRITIS occurring in <1% of pregnancies, complicated by septic shock and ARDS in 20%. In patient treatment with IV antibiotics (cefazolin, cef triaxone, or ampicillin plus gentamicin) until sympto matic improvement and afebrile for 24 48 h then PO based on drug sensitivities. Low dose suppressive antibiotics (nitrofurantoin 50 100 mg PO qhs [risk of hemolytic anemia] or cephalexin 250 500 mg PO qhs) for remainder of pregnancy as recurrent pyelone phritis occurs in 6 8% of women without prophylaxis

### HUMAN IMMUNODEFICIENCY VIRUS (HIV)

ANTEPARTUM CARE determine HIV symptoms, infections, immunization status, and perform ophthal mologic examination if CD4 <50/mm<sup>3</sup>. Baseline test ing include CBCD, lytes, urea, Cr, AST, ALT, ALP, bilir ubin, 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 treat ment, <1% with optimal and effective combination therapy), contraceptive use during pregnancy (con doms), and mode of delivery. If on HAART already, continue as combination therapy which should con tain AZT. For pregnant women not already on HAART, consider zidovudine from 2<sup>nd</sup> trimester onwards. Pro phylaxis for opportunistic infections same as in non pregnancy patients. Amniocentesis or other invasive procedures may increase vertical transmission risk

INTRAPARTUM CARE upon onset of labour or rup ture of membranes, give zidovudine 2 mg/kg | V 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 inter val between rupture of membranes and delivery

**POSTPARTUM CARE** treat newborn with zidovu dine for 6 weeks, to be followed by PJP prophylaxis. Determine HIV status at 1 2 days, 2 weeks, 1 2 months, and 3 6 months. Avoid breast feeding. Ensure good support system for mother. Counsel regarding contraceptive use

NEJM 2002 346:24

### TORCHES INFECTIONS

INFECTIONS ASSOCIATED WITH BIRTH DEFECTS
★TORCHES★ TOxoplasma, 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, azi thromycin, vancomycin, metronidazole, clindamy cin, 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, Hispa nic, Asian, African), maternal age  $\geq$ 35, obesity, PCOS, polyhydramnios, multiple gestation, fetal macrosomia (>4000 g or >90<sup>th</sup> 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 is <7.8 mmol/L [<140 mg/dL], then no GDM but re test if continued at high risk or high suspicion (e.g. macrosomia, poly hydramnios)

### DIABETES IN PREGNANCY (CONT'D)

- Step 2: 2 h Oral Glucose Tolerance Test (OGTT) 75 g glucose after overnight fast
  - Abnormal if fasting blood glucose ≥5.3 mmol/L [≥95 mg/dL]
  - Or 1 h blood glucose ≥ 10.6 mmol/L [≥190 mg/dL]
  - Or 2 hour blood glucose ≥8.6 mmol/L [>155 mg/dL]
- Step 3: Diagnosis based on OGTT
  - If 1 value abnormal, then impaired glucose tolerance of pregnancy (IGTP)
  - If >2 values abnormal, then GDM

**MONITORING** monitor blood glucose ac all meals for type 1 diabetics (goal <5.3 mmol/L [<95 mg/dL]), 1 h post all meals (goal <7.8 mmol/L [<140 mg/dL]), and qhs (goal <6 mmol/L [<108 mg/dL]). Hypergly cemia during the 1st trimester is a teratogen. Check urine ketones every morning

### Related Topics

Diabetes Mellitus (p. 337) Hyperthyroidism (p. 344) Hypothyroidism (p. 343)

### DIABETES IN PREGNANCY (CONT'D)

**TREATMENTS** diabetic diet and exercise. Ensure excellent glycemic control with normal HbA1C prior to and throughout pregnancy. Increase bedtime snack portion if ketonuria in morning

- TYPE 1 DIABETICS insulin injections and insulin pump equally effective
- TYPE 2 DIABETICS switch oral hypoglycemics to insulin, preferably preconception
- GESTATIONAL DIABETES insulin (Insulin Lispro or Aspart TID ac meals and Humulin N or NPH qhs) required if hyperglycemia persists. Glyburide acceptable if mild
- INTRAPARTUM during labor (and induction), monitor blood glucose q1 2h and check urine ketones q2h. IV fluids and insulin sliding scale may be required
- POSTPARTUM insulin rarely required for GDM postpartum. Test for diabetes several weeks post partum with 2 h OGTT

**COMPLICATIONS** maternal complications include preeclampsia, polyhydramnios, preterm labor, pro gression of existing diabetic retinopathy and nephro pathy. Fetal complications include macrosomia, shoulder dystocia, malformations, intrauterine death, cardiomyopathy, polycythemia, hypoglycemia, hypo calcemia and hyperbilirubinemia

http://www.diabetes.ca/files/cpg2008/cpg 2008

### HYPOTHYROIDISM IN PREGNANCY

PATHOPHYSIOLOGY may be due to ↑ thyroid binding globulin, ↑ volume of distribution of T4, and ↑ destruction of T4 by placental deiodinases. There is also increased metabolic demand during pregnancy TREATMENTS levothyroxine can be safely given during pregnancy. Dose may need to be increased in pregnancy. Take levothyroxine separate from vita mins, which decrease its absorption

**COMPLICATIONS** untreated hypothyroidism can lead to neurodevelopmental abnormalities in the child

### HYPERTHYROIDISM IN PREGNANCY

**PATHOPHYSIOLOGY** during T1, total T4  $\uparrow$  (sec ondary to  $\beta$ hCG  $\uparrow$ ) and thyroid binding globulin  $\uparrow$ , fT4 remains same and TSH  $\downarrow$ /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 T5H), the cause may be difficult to establish. Postpartum follow up may help. Thyroid radionuclide scan is contraindi cated in pregnant women. Consider anti T5H recep tor antibody if suspect Graves disease

### TREATMENTS

- GRAVES' DISEASE  $\beta$  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 possi ble. Graves' generally improves in pregnancy.  $\beta$  Blockers may lead to bradycardia, hypoglycemia, and IUGR
- **POSTPARTUM THYROIDITIS** may not require treat ment if mild symptoms. For significant hyperthyr oidism symptom, give  $\beta$  blocker. For hypothyroid ism, give *L thyroxine* 50 100  $\mu$ g PO daily  $\times$ 8 12 weeks and then reassess

### **Other Disorders in Pregnancy**

### SEIZURES IN PREGNANCY

PATHOPHYSIOLOGY for women with known epi lepsy, 25% will have ↑ frequency, 25% will have ↓ frequency, and 50% will not change in pregnancy. It is important to be seizure free, ideally off medications, for at least 6 months prior to conception to ensure good outcome. Risk of seizures in offspring is

### SEIZURES IN PREGNANCY (CONT'D)

elevated at 5%. Eclampsia, intracerebral bleed, and cerebral vein thrombosis may lead to seizures in pregnancy

**TREATMENTS** valproic acid has a relatively high risk of neural tube defects and should be switched to alter nate antiepileptic pre pregnancy if possible. Phenytoin,

### SEIZURES IN PREGNANCY (CONT'D)

carbamazepine, and phenobarbital are all teratogenic but may be used if indicated and after appropriate counseling. Lamotrigine seems to have reasonable data in pregnancy. *Folic acid* 0.4 mg PO daily should be prescribed to all women on antiepileptics in the childbearing age. Those planning a pregnancy should take *folic acid* 5 mg PO daily in the preconception period and in first trimester, then 1 mg PO daily throughout remainder of pregnancy. *Vitamin K* may be recom mended 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, pree clampsia, and maternal death. Children of patients with anti SSA and anti SSB are at increased risk for congenital heart block and neonatal lupus. Patients with antiphospholipid antibodies are at increased risk of preeclampsia, miscarriage, and possibly thrombosis

### BREAST CANCER IN PREGNANCY

**DIAGNOSIS** staging workup similar to non preg nant women. Use MRI (without gadolinium) or U/S instead of CT if imaging of abdomen required

**TREATMENTS** mastectomy preferred over lumpect omy to avoid radiation. If adjuvant radiation indicated, it should be deferred until after delivery. Anthracycline containing adjuvant chemotherapy can usually be safely given during 2<sup>nd</sup> and 3<sup>rd</sup> trimesters, but not in 1<sup>st</sup> trimester or within 2 weeks of delivery. Methotrex ate 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 can cer has similar prognosis to non pregnant counterpart

### PAIN CONTROL IN PREGNANCY

ACCEPTABLE acetaminophen, opioids CONTRAINDICATED NSAIDs in T3 (may use in T1 or T2)

### THROMBOCYTOPENIA IN PREGNANCY

**GESTATIONAL THROMBOCYTOPENIA** (T3) asymptomatic and resolves after pregnancy. May be difficult to distinguish from ITP except platelet count usually higher ( $>70\times10^9/L$ ) in gestational thrombo cytopenia. Follow platelet counts regularly

### THROMBOCYTOPENIA IN PREGNANCY (CONT'D)

**ITP** (T1 3) may use prednisone and IVIG in preg nancy. Platelet transfusion if acute. Monitor closely. Splenectomy is last resort (safest in T2). Epidural is generally performed if platelet  $>80 \times 10^9/L$ . Cesarean delivery safe if platelet  $>50 \times 10^9/L$ ; 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 defi
ciency, drugs, autoimmune diseases, and hypersplenism

## ANTIPHOSPHOLIPID ANTIBODY SYNDROME IN PREGNANCY

**PATHOPHYSIOLOGY** antibody against phospholi pids or cell surface proteins bound to anionic phos pholipids. These include lupus anticoagulants, anti cardiolipin antibody (false positive VDRL), and anti  $\beta$ 2GP1 antibody  $\rightarrow$  most lead to hypercoagulable state, some may inhibit coagulation

CLINICAL FEATURES venous and arterial thrombo sis and rarely hemorrhage affecting the lungs, heart, CNS, GI, kidneys, skin, and eyes. Also thrombocytope nia (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 rheu matic diseases such as SLE, infections such as HIV and

**DIAGNOSIS** clinical criteria of VTE or arterial throm bosis, 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 anticardioli 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 treat ment plus anticoagulation prophylaxis postpartum for 6 weeks (see p. 157 for more details on ANTIPHO SPHOLIPID ANTIBODY SYNDROME)

### **Related Topics**

Antiphospholipid Antibody Syndrome (p. 157) Breast Cancer (p. 189) Lupus (p. 279) Thrombocytopenia (p. 151) Seizures (p. 309) 416 Notes

### Notes

## **17**

### GENERAL INTERNAL MEDICINE

Section Editor: Dr. Peter Hamilton

### **Approach to Diagnostic Tests and Clinical Trials**

Total

### DIAGNOSTIC TESTS

# 2×2 TABLE Disease present Disease present Disease

Test positive a (true b (false a+b positive) positive)

Test c (false d (true c+d negative negative) negative)

Total a+c b+d a+b+c+d

### SENSITIVITY ★SNOUT★

$$= a/(a+c)$$

 out of 100 patients with disease, how many have a positive test result? Independent of prevalence and helps to rule out disease

### SPECIFICITY ★SPIN★

$$= d/(b+d)$$

= out of 100 people without disease, how many have a negative test result? Independent of prevalence and helps to rule in disease

### POSITIVE PREDICTIVE VALUE (PPV)

$$= a/(a+b)$$

= out of 100 patients with a positive test result, how many actually have disease? Dependent on prevalence of disease

### **NEGATIVE PREDICTIVE VALUE (NPV)**

$$= d/(c+d)$$

= out of 100 patients with a negative test result, how many do not have disease? Dependent on prevalence of disease

**LIKELIHOOD RATIOS (LR)** indicate how much a given diagnostic test result will change the pretest probability of the disorder under investigation:

 LR+ 1.0 means pre test probability = post test probability

### DIAGNOSTIC TESTS (CONT'D)

- LR+ >1.0 increases the probability the disorder is present. A test with LR+ >10 is particularly useful
- LR+ <1.0 decreases the probability the disorder is present. A test with LR+ <0.1 is particularly useful</li>

### POSITIVE LIKELIHOOD RATIO (LR+)

- = (positive test in disease)/(positive test in no disease)
- = sensitivity/(1 specificity)

### NEGATIVE LIKELIHOOD RATIO (LR )

- = (negative test in disease)/(negative test in no disease)
- = (1 sensitivity)/specificity

### **ACCURACY**

$$=(a+d)/(a+b+c+d)$$

= how often is test correct in predicting true positive and false negative

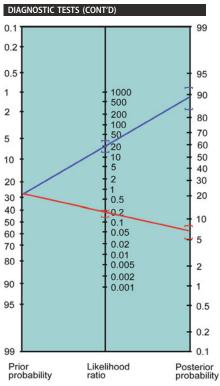
## TO CALCULATE THE POST TEST PROBABILITY OF A DIAGNOSIS AFTER A TEST

### PRE-TEST PROBABILITY

- probability of disease just prior to performing test of interest
- disease prevalence (if no other diagnostic test previously performed) or post test probability (after other initial investigations)
- PRE-TEST ODDS = pre test probability/(1 pre test probability)
- **POST-TEST ODDS** = pre test odds × likelihood ratio
- POST TEST PROBABILITY = (post test odds)/(1 + post test odds)

**FAGAN NOMOGRAM** easily converts from pre test probability to post test probability using LR (alleviating tedious calculations above)

418 Smoking Cessation



THERAPEUTIC	THERAPEUTIC INTERVENTIONS					
2×2 TABLE						
	Outcome positive	Outcome negative	Total			
Exposure positive	а	b	a+b			
Exposure negative	С	d	c+d			
Total	a+c	b+d	a+b+c+d			

ODDS RATIO (OR) case control study

= ad/bc. Odds ratio approximates RR if the disease is relatively rare

RELATIVE RISK (RR) cohort study

= [a/(a+b)]/[c/(c+d)]

RELATIVE RISK REDUCTION (RRR)

 $= [a/(a+b) \quad c/(c+d)]/[c/(c+d)]$ 

ABSOLUTE RISK REDUCTION (ARR)

= a/(a+b) c/(c+d)

### NUMBER NEEDED TO TREAT (NNT)

= 1/ARR = number of patients you would need to treat for one patient to benefit from the treat ment of interest

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### **Smoking Cessation**

### NEJM 2002 346:7; NEJM 2008 359:19

## COMPLICATIONS AND SMOKING ASSOCIATED DISORDERS

**CANCER** lung, head and neck (larynx, pharynx, oral cavity), esophagus, pancreas, bladder, kidney, sto mach, cervix, AML

**CARDIOVASCULAR DISEASES** CAD, CVD, PVD, Buerger's disease

**RESPIRATORY DISEASES** COPD, pneumonia **METABOLIC** diabetes mellitus, infertility, prema ture menopause, osteoporosis

COAGULOPATHY

### PATHOPHYSIOLOGY OF SMOKING

**NICOTINE ADDICTION** related to the combination of the following: (1) the pleasurable effects of nico tine such as relief of anxiety and arousal; (2) the pleasurable effects of associated environmental

### PATHOPHYSIOLOGY OF SMOKING (CONT'D)

triggers such as coffee and meals; and (3) the unplea sureable effects of nicotine withdrawal such as dys phoria, anxiety, irritability, insomnia, decreased con centration, increased appetite and over the long term increased weight

**LUNG CANCER** cigarette smoke contains numer ous carcinogenic substances. In particular, *N* nitro samines and polycyclic aromatic hydrocarbons are metabolized to nitrosamine ketone and *N'* nitroso nornicotine by the cytochrome P450 system, which form DNA adducts, leading to mutations and even tually 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 419

### 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  $2\times$  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 cog nitive 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 work ers 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 par tial agonist** (*Varenicline* 0.5 mg PO daily for d1 3, then 0.5 mg PO BID d4 7, then 1 mg PO BID for weeks 2 12)

### TREATMENT ISSUES

#### APPROACH TO COUNSELING

- SCREENING identification of smokers at every visit and explore willingness to quit
- EXPLORE PATIENT'S OWN REASONS TO QUIT
   health, social (e.g. children), or economic issues.
   Explain comorbidities associated with smoking.
   "As your doctor, I need you to know that quitting smoking is the most important thing you can do to protect your health"
- IF PATIENT READY TO QUIT WITHIN 30 DAYS offer counseling (quit date, what worked, what did not, express confidence, strategies) and aid (nicotine replacement, bupropion)
- IF PATIENT WANTS TO QUIT BUT NOT NOW smoker barriers to smoking cessation (nicotine dependence, fear of failure, lack of social support,

### TREATMENT ISSUES (CONT'D)

lack of self confidence, concern about weight gain, depression, substance abuse). Explore rea sons 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 CESSATION 2.3 4.5 kg [5 10 lb]
- PHYSIOLOGICAL withdrawal symptoms (see patho physiology) 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, dyspep sia, hiccups, and damage to dental work
- NICOTINE PATCH skin irritation and insomnia. Con traindications include unstable angina or MI <2 weeks and pregnancy
- BUPROPION SR insomnia, dry mouth, agitation, increased risk of seizure <0.1%</li>
- VARENICLINE nausea, vomiting, insomnia, abnormal dreams, headaches, constipation, diarrhea, flatu lence, 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 replace ment 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) **420** Multisystem Disorders

### **Multisystem Disorders**

### SELECTED MULTISYSTEM DISORDERS

### INFECTIONS

- BACTERIAL endocarditis, TB, Whipple's
- VIRAL HIV, HBV, HCV, EBV, CMV
- FUNGAL histoplasmosis, aspergillosis
- PARASITIC schistosomiasis

### MALIGNANCY

- **SOLID** metastatic, paraneoplastic
- LYMPHOPROLIFERATIVE leukemia, lymphoma
   INFLAMMATORY vasculitis, rheumatoid arthritis, scleroderma, SLE, IBD

IATROGENIC drugs

**INFILTRATIVE** cryoglobulinemia, hemochroma tosis, amyloidosis, sarcoidosis, porphyria

**ENDOCRINE** diabetes, hyperthyroidism

### HEMOCHROMATOSIS

**INHERITANCE** autosomal recessive. Among the North American population of European descent, approximately 10% are heterozygous and 0.3% are homozygous for hemochromatosis

**PATHOPHYSIOLOGY** mutation of HFE C282Y (nor mally forms a complex with transferrin receptor to decrease its affinity for transferrin)  $\rightarrow \uparrow$  absorption of Fe  $\rightarrow$  iron deposition in organs

CLINICAL FEATURES skin (bronze), joints (destructive arthritis, classically 2<sup>nd</sup> and 3<sup>rd</sup> 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  $\times$ 100%,  $\uparrow$ , most useful for screening), Fe ( $\uparrow$ ), TIBC, ferritin ( $\uparrow$ ), liver biopsy (hepatic iron index), HFE genotype testing

**TREATMENTS** alcohol cessation, phlebotomy (remove 1 2 U weekly until ferritin < 50 ng/mL)

NEJM 2004 350:23

### SARCOIDOSIS

**PATHOPHYSIOLOGY** cause unknown but may involve antigen exposure → activation of T cell immunity → non caseating granuloma formation

CLINICAL FEATURES constitutional (fatigue, weight loss, fever), pulmonary (staged according to CXR. Stage 0=no CXR changes, stage l=hilar adeno pathy, stage ll=hilar adenopathy with parenchymal opacities, stage lll=parenchymal opacities without hilar adenopathy, stage lV=advanced fibrosis with evidence of honey combing, hilar retraction, bullae, cysts, and emphysema. Stages are not necessarily

### SARCOIDOSIS (CONT'D)

chronological), cardiac (arrhythmia especially con duction blocks, HF), Gl tract (rarely ulcers, obstruction), renal (interstitial nephritis), neurologic (cranial nerve palsies especially CN VII, pituitary dysfunction, peripheral neuropathy, neuromuscular, transverse myelitis), ocular (uveitis), endocrine (hypercalce mia), 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 qood proqnosis with >80% remission in 2 years

INVESTIGATIONS blood tests (CBCD, lytes, urea, Cr, Ca, PO<sub>4</sub>, 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 sarcoi dosis, neurological or cardiac involvement, chronic uveitis, lupus pernio, chronic hypercalcemia, and nephrocalcinosis

### **TREATMENTS**

- LUNG INVOLVEMENT observation only if asympto matic, 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, cyclophospha mide and infliximab

NEJM 2007 357:21

### AMYLOIDOSIS

**PATHOPHYSIOLOGY** soluble amyloid precursor protein (AL=lg light chain variable region in mye loma, AA=serum amyloid A in chronic inflammatory conditions, ATTR=derived from mutant transthyretin protein, A $\beta$ =A $\beta$  protein precursor in Alzheimer's)  $\rightarrow$  insoluble fibrils in anti parallel  $\beta$  pleated sheet con figuration  $\rightarrow$  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),

Multisystem Disorders 421

### AMYLOIDOSIS (CONT'D)

neurologic (peripheral neuropathy, autonomic neu ropathy), **GI tract** (GI bleed, malabsorption, pseudo obstruction), **hepatic** (hepatomegaly), **hematologic** (bruising, factor X deficiency, binding of Ca depen dent 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 electrophor esis, biopsy of involved organ, subcutaneous fat, rec tal 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" bire fringence 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  $\lambda$  light chain, whereas light chain deposition disease involves  $\kappa$  light chain

NEJM 1997 337:13

### CRYOGLOBULINEMIA

PATHOPHYSIOLOGY chronic immune stimula tion 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=mono clonal IgM/IgA against polyclonal Ig, may be essential or due to persistent viral infections [HCV/HIV]; type III=polyclonal Ig against polyclo nal lg, may be essential or due to connective tissue diseases) cryoglobulin precipitates with complexes at temperature  $<37^{\circ}C$ [<98.6°F] → deposition in different organs/ves sels → systemic inflammation/vasculitis

**CLINICAL FEATURES OF TYPE I skin** (livedo reti cularis, purpura), **hyperviscosity/thrombosis** (Ray naud's phenomenon, digital ischemia)

CLINICAL FEATURES OF TYPE II/III constitutional (fatigue, weight loss, arthralgia, myalgia), neu rologic (peripheral neuropathy), renal (proteinuria, hematuria, MPGN, RPGN), pulmonary (small airway disease), rheumatologic (Sjogren's, Raynaud's), sple nomegaly, 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 electro phoresis, 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 cyto toxic agents

### PORPHYRIA

**INHERITANCE** mainly autosomal dominant with incomplete penetrance

**PATHOPHYSIOLOGY** enzymatic defect in the heme synthesis pathway  $\rightarrow$  continued production of toxic heme precursors by liver and RBC  $\rightarrow$  accu mulation 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 copropor phyria, and variegate porphyria. Preceded by anxiety, restlessness, and insomnia — autonomic neuropa thy (tachycardia, hypertension, arrhythmia, abdom inal 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 dysfunc tion, hyponatremia), and sometimes CNS symptoms (confusion, hallucinations, seizures) — usually decline within a week. Occasionally may progress to diffuse muscle weakness with respiratory muscle paralysis

### **CLINICAL FEATURES OF CUTANEOUS PORPHYR**

**IAS** variegate porphyria, hereditary copropor phyria, and porphyria cutanea tarda. Chronic photosensitive skin symptoms include excessive fragility, blistering and scarring, particularly on the back of hands, hypertrichosis, and hyperpig mentation of face

**DIAGNOSIS** 24 h urinary porphobilinogen, urinary ALAD, urinary porphyrins, fecal porphyrins. Ideally collect samples during acute attack. Other tests include erythrocyte porphyrins, plasma fluorescence spectrum, enzyme activity, DNA analysis, and skin biopsy

**TREATMENTS** for acute porphyria, **avoid precipi tating** medications, alcohol and infections if possible, with mostly supportive treatments during an epi sode. High dose carbohydrate (400 g/day) diet is recommended acutely and exogenous heme infu sions (*hematin* 4 mg/kg IV q12h) should be consid ered. 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 (polyar thritis, 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 myorhyth mia are pathognomonic), skin (hyperpigmentation, subcutaneous nodules, purpura), cardiac (myocar ditis, pericarditis, culture negative endocarditis),

### WHIPPLE'S DISEASE (CONT'D)

pulmonary (interstitial fibrosis, pleural effusion, hilar lymphadenopathy), **hematologic** (anemia, lympha denopathy), **constitutional** (fever, weight loss)

**DIAGNOSIS** small bowel or tissue biopsy (PAS positive macrophages). RT PCR

**TREATMENTS** antibiotics (*ceftriaxone* 2 g IV daily  $\times$ 2 4 weeks, then *trimethoprim sulfamethoxazole* DS 1 tab PO BID  $\times$ 1 2 years), nutritional supplement (protein, iron, folate)

NEJM 2007 356:1

### **Related Topics**

Chronic Liver Disease (p. 132) Glomerulonephritis (p. 70) Hepatitis C (p. 131) Monoclonal gammopathy (p. 179)

## Perioperative Assessment for Non-cardiopulmonary Surgery and Postoperative Complications

ACC guidelines 2007

### PERIOPERATIVE CARDIAC RISK ASSESSMENT

#### ACC/AHA PERIOPERATIVE SUMMARY

#### ACTIVE CARDIAC CONDITIONS

- UNSTABLE CORONARY SYNDROMES unstable or severe angina\* (CCS class III or IV), recent MI decompensated heart failure (NYHA functional class IV; worsening or new onset heart failure)
- SIGNIFICANT ARRHYTHMIAS high grade AV block, Mobitz II AV block, 3<sup>rd</sup> degree AV block, symp tomatic ventricular arrhythmias, supraventricu lar 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), sympto matic 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%) intraperito neal and intrathoracic surgery, carotid endarter ectomy, head and neck surgery, orthopedic sur qery, prostate surgery
- Low (cardiac risk <1%) endoscopic proce dures, superficial procedure, cataract surgery, breast surgery, ambulatory surgery

### PERIOPERATIVE CARDIAC RISK ASSESSMENT (CONT'D)

- METABOLIC EQUIVALENT
  - 1 MET ADLs (eat, dress, use toilet)
  - 2–3 MET walk indoors, walk one to two blocks on level ground at 3.2 4.8 km/h [2 3 mi/h]
  - **4** METS climb 1 flight of stairs, light housework such as dusting or washing dishes
  - 5–9 METS recreational activities, walk on level ground at 6.4 km/h [4 mi/h], run a short dis tance, heavy housework such as scrubbing floors or lifting heavy furniture
  - 10 METS strenuous sports such as swimming, tennis, football, basketball, skiing

### OVERALL ALGORITHM

- Need for emergency non cardiac surgery?
   Yes=proceed to operation with perioperative sur
   veillance and postoperative risk stratification and
   risk factor management; no=proceed to step 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
- Functional capacity greater than or equal to four METs without symptoms? Yes=proceed with planned surgery; no or unknown=proceed to step 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
- One to two clinical risk factors: For both vas cular surgery and intermediate risk sur gery, proceed with planned surgery with HR control or consider noninvasive testing if it will change management
- 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 PERCUTA-NEOUS CORONARY INTERVENTION PRIOR TO SUBSE-OUENT SURGERY
  - 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
  - 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 PERCUTA-NEOUS CORONARY INTERVENTION
  - 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
  - Greater than 14 days between balloon angio plasty and planned surgery? Yes=proceed to the operation room with aspirin; no=delay for elective or non urgent surgery
  - Greater than 30 45 days between bare metal stent insertion and planned surgery? Yes=pro ceed 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=pro ceed 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 endarterect omy, head and neck surgery, orthopedic surgery, prostate surgery
- Low (cardiac risk <1%) endoscopic procedures, superficial procedure, cataract surgery, breast sur gery, ambulatory surgery

### Circulation 2007 116:e418 e499 LEE CRITERIA (REVISED CARDIAC RISK INDEX)

 HIGH-RISK SURGERY thoracic surgery, intraperito neal 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%),  $\geq$  **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 peri operatively, upper abdominal, thoracic, and abdom inal aortic aneurysm surgery, surgery >3 h, intrao perative pancuronium, general anesthesia

## AMERICAN SOCIETY OF ANESTHESIOLOGISTS (ASA) CLASSIFICATION

- 1 healthy patient with no disease outside of surgical process (<0.03% mortality)</li>
- 2 mild to moderate systemic disease caused by the surgical condition or other diseases, medically well controlled (0.2% mortality)
- **3** severe disease process which limits activity but is not incapacitating (1.2% mortality)
- 4 severe incapacitating disease process that is a constant threat to life (8% mortality)
- 5 moribund patient not expected to survive 24 h with or without an operation (34% mortality)
- E suffix for emergency surgery for any class

### INVESTIGATIONS FOR PERIOPERATIVE PATIENTS

## **BASIC** CBCD, lytes, urea, Cr, INR, PTT, X match **CARDIAC**

- ECG should be obtained in most patients
- NON-INVASIVE TESTING (exercise stress test, stress MIBI, dobutamine stress echocardiogram, 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 under lying lung disease or unexplained dyspnea. Pro vides baseline but not useful for risk stratification

## INVESTIGATIONS FOR PERIOPERATIVE PATIENTS (CONT'D)

- CXR should be obtained if age >60 or sus pect/known 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 pneu monectomy. 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 VO<sub>2</sub>max >15 mL/kg/min during cardiopulmonary exercise testing will likely tolerate surgery

NEJM 1999 340:12

### MANAGEMENT OF PERIOPERATIVE PATIENTS

 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 Ml. Wait >3 months if severe Ml 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 arrhyth mia will likely be able to go for surgery
- **PREOPERATIVE**  $\beta$  blockers (for Lee score >2, give atenolol 10 mg IV over 15 min prior to surgery, then atenolol 50 100 mg PO daily or bisoprolol 5 10 mg PO daily, titrate to HR 50 60 for a total of 1 month).  $\alpha$ 2 agonists (clonidine 0.1 mg PO BID). **CABG** (indications include poorly controlled angina despite maximal medical ther apy, >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 dys function). 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, con sider balloon valvuloplasty)
- POSTOPERATIVE daily ECG and troponin ×3 days if high risk and patient unable to com municate angina

### MANAGEMENT OF PERIOPERATIVE PATIENTS (CONT'D)

- BACTERIAL ENDOCARDITIS PROPHYLAXIS
   only given to patients with the highest risk of devel
   oping endocarditis, which include the following
  - HIGH-RISK CARDIAC CONDITIONS
    - PROSTHETIC prosthetic cardiac valve, pros thetic 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 region of teeth, perforation of oral mucosa
    - RESPIRATORY TRACT tonsillectomy, adenoi dectomy, 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, cepha lexin 2 g PO, clindamycin 600 mg PO/IM/IV, azithro mycin 500 mg PO, clarithromycin 500 mg PO

AHA Guidelines 2007

### 4. PULMONARY RISK OPTIMIZATION

- PREOPERATIVE smoking cessation for >8 weeks. Manage obstructive lung diseases (ipra tropium 0.25 mg INH QID for all COPD patients, salbutamol 2.5 mg INH Q4h PRN for all COPD/asthma patients with wheezing, and steroids if exacerbations). Antibiotics and delay surgery if respiratory infection is present. Patient education regarding lung expansion maneuvers
- INTRA-OPERATIVE limit duration of surgery to <3 h. Avoid general anesthetics (use spinal or epidural anesthesia). Avoid pancuronium. Laparoscopic procedures when possible. Sub stitute 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 intercos tal nerve blocks)

### 5. MEDICATION MANAGEMENT

CARDIOVASCULAR AGENTS β blockers (continue up to and including day of surgery. If prolonged NPO, substitute with IV labetalol, propanolol, metoprolol, or esmolol). or 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  $\beta$  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 ticlo pidine (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 discon tinuation of dual antiplatelet therapy increases risk of perioperative cardiac death 5 10×, incidence 30%. Combination clopidogrel+ASA increases absolute risk of major perioperative bleeding by 0.4 1% compared to ASA alone. Generally, most surgeries can be performed without discontinuing antiplatelet therapy for recent coronary stenting. except neurosurgery or posterior chamber eye surgery). NSAIDs (some vascular protective effect but also potential renal failure. Hold 3 days before surgery, substitute with acetaminophen desired). **Statins** (continue up to and including day of sur gery). 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

### MANAGEMENT OF PERIOPERATIVE PATIENTS (CONT'D)

- replacement (hydrocortisone 50 mg IV on call to OR, then 25 mg q8h  $\times$ 24 hours, then normal dose). For **major stress** (intra abdominal, car diac), consider high dose steroid (hydrocortisone 100 mg IV on call to OR, then 50 mg q8h  $\times$ 24 h, then 25 mg q8h  $\times$ 24 h, then resume maintenance)
- DIABETIC AGENTS key principle is to avoid hypo glycemia and hyperglycemia. Oral hypoglyce mics (continue up to day before surgery and discontinue AM dose on day of surgery. If pro longed 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 inter mediate acting insulin dose. For complicated pro cedures, 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, intermit tent pneumatic compression, low dose heparin, LMWH. coumadin
- BLEEDING RISK ASSESSMENT inquire about any recurrent bleeding tendencies and bleeding complications from past surgeries. Review Hb, pla telets, 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 demen tia to assess the risk of postperative delirium

### POSTOPERATIVE COMPLICATIONS

**MAJOR CARDIAC COMPLICATIONS** myocardial infarction, arrhythmia

**MAJOR PULMONARY COMPLICATIONS** pneumo nia, 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 (pul monary 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 antihy pertensive medications, neuroleptic malignant syndrome, malignant hyperthermia

## **POSTOPERATIVE ACUTE RENAL FAILURE** (see p. 68 for more details)

 PRE-RENAL blood loss, fluid loss, ACE inhibitors, NSAIDs, cyclosporin

### POSTOPERATIVE COMPLICATIONS (CONT'D)

- RENAL ATN (ischemic, contrast, aminoglycosides), AIN (penicillins, cephalosporins), microvascular (cholesterol emboli)
- POST-RENAL urinary retention

### POSTOPERATIVE BLEEDING (see p. 153 for more details)

- † INR factor deficiency or inhibitor (VII), liver disease, vitamin K deficiency, DIC, warfarin
- † INR AND PTT factor deficiency (X, V, II, I), liver disease, vitamin K deficiency, DIC, warfarin
- † PTT factor deficiency and inhibitor (VIII, IX, XI), heparin, von Willebrand disease
- PLATELET DISORDER von Willebrand disease, renal failure, liver failure, myeloproliferative disorders

### **POSTOPERATIVE THROMBOCYTOPENIA** (see p. 151 for more details)

- PSEUDOTHROMBOCYTOPENIA platelet clumping
- DILUTIONAL transfusions, bleeding
- DECREASED PRODUCTION less likely but possible
- **SEQUESTRATION** less likely but possible
- DESTRUCTION DIC, drugs (HITT with heparin, GPIIb/IIIa inhibitors, thiazides, sulfonamides, rifam pin, indomethacin), alloimmune (post transfusion)

### **Medical Fitness to Drive**

### GENERAL PRINCIPLES

**DRIVER'S LICENSING AUTHORITY** responsible for issuing/revoking licenses

**PHYSICIANS** responsible for reporting unfit dri vers. In some jurisdictions, it is mandatory to report. The physicians can be held liable for negligence if a patient is involved in a motor vehicle accident

### GENERAL PRINCIPLES (CONT'D)

**UNCERTAINTY** if not sure about medical fitness for driving, advise patient not to drive. Document it and inform the Ministry of Transportation

**BALANCE** interest of public has priority over rights of individual driver

**LICENSE TYPE** class 1 4=professional vehicles, 5=private vehicle, class 6=motorcycle

### **DURATION OF NO DRIVING FOR SPECIFIC DISORDERS**

### Private driver Professional driver

First seizure 3 months 12 months

EtOH withdrawal 6 months (EtOH and seizure free and completed rehabilitation)

seizures

Epilepsy 6 months (seizure free on meds) 5 years (seizure free on/off meds)

 MI
 1 month
 3 months

 PTCA
 48 h
 7 days

 CABG
 1 month
 3 months

 Arrhythmias
 If no symptoms
 If no symptoms

 Pacemaker
 1 week
 1 month

Heart failure No if NYHA >IV No if NYHA >II, EF <35% or >3 VT on Holter

 AAA
 No if >5 cm [>2 in.]
 No if >5 cm [>2 in.]

 TIA
 If no symptoms
 If no symptoms

 Stroke
 1 month
 1 month

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### GENERAL PRINCIPLES (CONT'D)

Private driver

Vision No if poor vision <20/50, hemianopsia, or diplopia

Diabetes No if hypoglycemia ≤6 months

COPD No if on home O<sub>2</sub> (need road test)

**NOTE**: regulations for specific jurisdiction may vary

#### Professional driver

No if poor vision < 20/40, hemianopsia, or diplopia

No if unstable insulin regimen, hypoglycemia, ≤6 months, neuropathy, retinopathy

No if on home O<sub>2</sub>

### **Obtaining Consent for Medical Procedures**

### CONSENTING PROCESS

**CONTEXT** establish an appropriate setting for the discussion

### WHAT DOES THE PATIENT UNDERSTAND?

- 'What do you understand about your illness?"
- 'Have you had any similar procedures before?"
- Obtain a general impression of patient's competence **DISCUSS THE RATIONALE AND POTENTIAL**

## BENEFITS REGARDING THE PROCEDURE EXPLAIN DETAILS OF PROCEDURE

- POSITIONING
- LOCAL ANESTHETIC ask about allergies
- ACTUAL PROCEDURE degree of detail tailored to patient's comprehension and interest. Assess bleed ing risk

### CONSENTING PROCESS (CONT'D)

- ESTIMATED DURATION
- POTENTIAL COMPLICATIONS bleeding, infections, puncture/injury of surrounding tissue, and other specific risks related to procedure

**EXPLAIN ALTERNATIVES** (step by step)

**ASSESS UNDERSTANDING** use simple language and ask the patient to summarize what they understand

**DISCUSS CONSENT FORM** patient may wish to read the consent form carefully and have some time to think about procedure

PROVIDE REASSURANCE AND FOLLOW UP

### **Biomedical Ethics Issues**

### ETHICS JUDGMENT

**MORAL JUDGMENT** the decision making process is based on both ethics principles and facts

- ETHICS PRINCIPLES beneficence, non maleficence, autonomy, and justice
- FACTS patient preference, competence, prog nosis, 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 ben efits), capacity (competence), and voluntariness

### CAPACITY

**EXAMPLE** patient refuses treatment but may not be competent

**REQUIREMENT** ability to understand information and appreciate consequences of *individual* deci sion. Competence assessment may be required (p. 377)

**SUBSTITUTE DECISION MAKING** legally through advance directive proxy (also known as representa tive agreement or personal directive), the court, or court appointed guardian (spouse > children > par ents > 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

428 Biomedical Ethics Issues

### 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
- 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 auton omy. Legally can breach confidentiality if required by court/law, patient consent obtained, or if public inter est 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 auton omy 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

**TYPES** active euthanasia is direct involvement of killing a patient (e.g. injection of KCI), while passive euthanasia is providing the means for the patient to kill himself (e.g. preparing KCI)

**ARGUMENTS FOR** autonomy, the relief of suffer ing, 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 seda tion (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)

- No one disputes that resources are scarce and rationing decisions are required
- It is unfair to ration based on implicit criteria that may vary from physician to physician
- 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
- An alternative to rationing is to augment the availability of the scarce resource

**LEVELS** macro (provincial/national), meso (hospi tal), 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 male ficence, 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 rando mized 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 (appro priate 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 pres sure, 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 ther apy (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

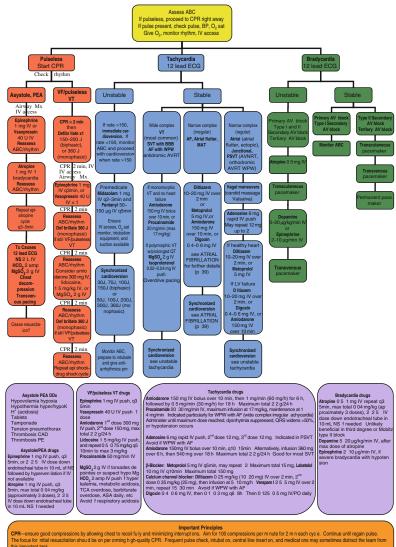
430 Notes

### Notes

## Appendix A

### ADVANCED CARDIAC LIFE SUPPORT

American Heart Association (AHA), European Resuscitation Council (ERC), and International Liaison Committee on Resuscitation (ILCOR) 2005 Guidelines. Circulation 2005; 112[Suppl I]:IV1 211



this important task

Airway—avoid hyperventilat on as this could increase intrathoracic pressure. Initial use of propharynogal airway with bag-valve mask is reasonable, with 2 breaths given after every 30 CPR compress ons. Once switched to advanced airway (language mask airway, combitube, or endotracheal tube), breaths should be given every 6s.

Access—the preferred route is through a perpherial intravenous (IV) I ne, which can usually be estab ished easily. The ritraosseous (IO) route represents a second choice, while central I nes and endotracheal tube should be the last resort for medication access

## LIST OF COMMON ABBREVIATIONS

% sat	Percentage saturation	BAL	Bronchoalveolar lavage
	5-Fluorouracil	BID	Twice per day
5-HIAA	5-Hvdroxvindoleacetic acid	Bili	Bilirubin
5HT	Serotonin	BIPAP	Bilevel positive airway pressure
AAA	Abdominal aortic aneurysm	BL	Burkitt's lymphoma
	Airway, breathing, circulation	BMD	Bone mineral density
	Abdomen	BMI	Body mass index
ABG	Arterial blood gas	BMT	Bone marrow transplant
ABPA	Allergic bronchopulmonary aspergillosis	BNP	B-type natriuretic peptide
ABx	Antibiotics	BOOP	Bronchiolitis obliterans organizing pneumonia
ACE	Angiotensin-converting enzyme	BP	Blood pressure
ACR	American College of Rheumatology	BRBPR	Bright red blood per rectum
ACS	Acute coronary syndrome	BRCA	Breast cancer gene
ACTH	Adrenocorticotropic hormone	BSA	Body surface area
ADL	Activity of daily living	BSE	Breast self-examination
ADP	Adenosine diphosphate	C&S	Culture and sensitivity
AF	Atrial fibrillation	Ca	Calcium
AFB	Acid fast bacilli	CA 125	Cancer antigen 125
AFP	Alpha fetoprotein	CA 15.3	Cancer antigen 15.3
AG	Anion gap	CA 19-9	Cancer antigen 19-9
AIDS	Acquired immunodeficiency syndrome	CABG	Coronary artery bypass graft
AIN	Acute interstitial nephritis	CAD	Coronary artery disease
AJR	Abdominal jugular reflex	CAH	Congenital adrenal hyperplasia
AKI	Acute kidney injury	CA-MRSA	Community-acquired methicillin-resistant
ALI	Acute lung injury		Staphylococcus aureus
ALL	Acute lymphoblastic lymphoma	CAP	Community-acquired pneumonia
ALND	Axillary lymph node dissection	CBC	Complete blood count
ALS	Amyotrophic lateral sclerosis	CBCD	Complete blood count and differential
	Alanine aminotransferase	CBE	Clinical breast examination
	Antimitochondrial antibody	Cbl	Cobalamin
	Acute myelogenous leukemia	CCB	Calcium channel blocker
	Antinuclear antibody	CCP	Cyclic citrullinated peptides
	Absolute neutrophil count	CCS	Canadian Cardiovascular Society
	Anti-neutrophilic cytoplasmic antibody	CEA	Carcinoembryonic antigen
	Anterior–posterior	CHF	Congestive heart failure
	Antiphospholipid antibody	Chol	Cholesterol
	Acute physiology and chronic health evaluation	CK	Creatine kinase
	Adenomatosis polyposis coli	CKD	Chronic kidney disease
	Antiphospholipid antibody syndrome	CKMB	Creatine kinaseMB
	Angiotensin receptor blocker	CI	Chloride
	Acute respiratory distress syndrome	CLL	Chronic lymphocytic leukemia
	Absolute risk reduction	CMA	Canadian Medical Association
	Aortic stenosis	CMC	Carpometacarpal joint
ASA	Acetylsalicylic acid, American Society	CML	Chronic myelogenous leukemia
	of Anesthesiologists	CMML	Chronic myelomonocytic leukemia
	Atrial septal defect	CMV	Cytomegalovirus
	AntiStreptolysin-O	CN	Cranial nerve, cyanide
	Aspartate aminotransferase	CNS	Central nervous system
	Around the clock	СО	Carbon monoxide
	Acute tubular necrosis	COP	Cryptogenic organizing pneumonia
	Atrioventricular or arteriovenous	COPD	Chronic obstructive pulmonary disease
	Arteriovenous malformation	COX	Cyclooxygenase
	Atrioventricular nodal reentry tachycardia	CPAP	Continuous positive airway pressure
	Abdominal X-ray	CPR	Cardiopulmonary resuscitation
BAC	Bronchioloalveolar carcinoma	CR	Controlled release

CrCl	Creatinine clearance	FTA-ABS	Fluorescent treponemal antibody-absorption
CRF	Chronic renal failure	FUO	Fever of unknown origin
CRH	Corticotropin-releasing hormone	FVC	Forced vital capacity
CRP	C-reactive protein	G6PD	Glucose-6-phosphate dehydrogenase deficiency
CRT	Cardiac resynchronization therapy	GBM	Glomerular basement membrane, glioblastoma
CT	Computed tomography		multiforme
CVA	Cerebral vascular disease, costovertebral angle	GBS	Guillain-Barre syndrome
CVD	Cerebral vascular disease	GCS	Glasglow coma scale
CVP	Central venous pressure	GCSF	Granulocyte colony-stimulating factor
CVVHD	Continuous veno-venous hemodialysis	GERD	Gastroesophageal reflux disease
CXR	Chest X-ray	GFR	Glomerular filtration rate
D5W	5% dextrose water	GGT	Gamma-glutamyl transpeptidase
DAT	Direct antiglobulin test	GI	Gastrointestinal
DBP	Diastolic blood pressure	Gm	Gram stain
DC DCIS	Direct current	GN GU	Glomerulonephritis
DDAVP	Ductal carcinoma in situ	GVHD	Genitourinary Graft vs. host disease
DEXA	Desmopressin acetate Dual-energy X-ray absorptiometry	GYN	Gynecological
DHEA	Dehydroepiandrosterone	H&N	Head and neck
DHEAS	Dehydroepiandrosterone sulfate	Hb	Hemoglobin
DI	Diabetes insipidus	HBV	Hepatitis B virus
DIC	Disseminated intravascular coagulation	HCL	Hairy cell leukemia
DIP	Distal interphalangeal joint	HCO₃	Bicarbonate
DKA	Diabetic ketoacidosis	Hct	Hematocrit
DLBCL	Diffuse large B-cell lymphoma	HCV	Hepatitis C virus
DLCO	Diffusion capacity of lung for carbon monoxide	HD	Hemodialysis
DM	Diabetes mellitus	HDL	High density lipoprotein
DM1	Type 1 diabetes mellitus	HF	Heart failure
DM2	Type 2 diabetes mellitus	HHV8	Human herpes virus 8
<b>DMARDs</b>	Disease-modifying agents of rheumatoid disease	HITT	Heparin-induced thrombocytopenia with associated
DOT	Directly observed treatment		thrombosis
DPI	Dry powder inhaler	HIV	Human immunodeficiency virus
DPT	Diphtheria, pertussis, tetanus	HLA	Human leukocyte antigen
dsDNA	Double-stranded DNA	HMG-CoA	3-Hydroxy-3-methylglutaryl coenzyme A
DT	Delirium tremens	HNPCC	Hereditary non-polyposis colorectal cancer
DVT	Deep vein thrombosis	HR	Heart rate
Dx	Disease	HSP	Henoch–Schonlein purpura
EBV ECG	Epstein–Barr virus	HSV HTLV	Herpes simplex virus
EEG	Electrocardiogram Electroencephalography	HU	Human T-cell lymphoma virus Hounsfield unit
EF	Ejection fraction	HUS	Hemolytic uremic syndrome
EGFR	Epidermal growth factor receptor	IADL	Instrumental activities of daily living
EHEC	Enterohemorrhagic Escherichia coli	IBD	Inflammatory bowel disease
EIEC	Enteroinvasive Escherichia coli	IBS	Irritable bowel syndrome
EMG	Electromyography	IBW	Ideal body weight
ENA	Extractable nuclear antigen	ICD	Implantable cardioverter-defibrillators
EPO	Erythropoietin	ICH	Intracerebral hemorrhage
ER	Estrogen receptor, emergency room	ICP	Intracranial pressure
ERCP	Endoscopic retrograde cholangiopancreatography	ICU	Intensive care unit
ESAS	Edmonton symptom assessment scale	IDU	Injection drug use
ESBL	Extended spectrum β-lactamase	IL	Interleukin
ESR	Erythrocyte sedimentation rate	INF	Interferon
ESRD	End-stage renal disease	INH	Inhaler
ET	Essential thrombocytosis	INR	International normalized ratio
ETEC	Enteropathogenic Escherichia coli	IPF	Idiopathic pulmonary fibrosis
FAP	Familial adenomatous polyposis	IPI	International prognostic index
Fe	Iron	IR	Immediate release
FEV1	Forced expiratory volume (1 second)	ITP	Idiopathic thrombocytopenic purpura
FFP	Fresh frozen plasma	IV	Intravenous
FH	Family history	IVC	Inferior vena cava
FHF	Fulminant hepatic failure	IVP	Intravenous pyelogram
FISH	Fluorescence in situ hybridization	JVP	Jugular venous pressure
FL FNA	Follicular lymphoma Fine needle aspirate	KOH KPS	Potassium hydroxide Karnofsky performance status
FNH	Focal nodular hyperplasia	KUB	Kidney, ureter, and bladder X-ray study
FOB	Fecal occult blood	LAA	Left atrial abnormality
FSGS	Focal segmental glomerulosclerosis	LAD	Left anterior descending
FSH	Follicle-stimulating hormone	LAE	Left atrial enlargement
			J

LAHB	Left anterior hemiblock	MZL	Marginal zone lymphoma
LAP	Leukocyte alkaline phosphatase	N&V	Nausea and vomiting
LBBB	Left bundle branch block	Na	Sodium
I CIS	Lobular carcinoma in situ	NAAT	Nucleic acid amplification test
ICX	Left circumflex artery	NCS	Nerve conduction studies
IDH	Lactate dehydrogenase	NF	Norepinephrine
LDL	Low-density lipoprotein	NEB	Nebulizer
LES		NG	
	Lambert–Eaton syndrome		Nasogastric
LFT	Liver function test	NMDA	N-methyl-p-aspartic acid
LH	Luteinizing hormone	NMS	Neuroleptic malignant syndrome
Li	Lithium	NNT	Number needed to treat
LLL	Left lower lobe	NPH	Normal pressure hydrocephalus, insulin
LLQ	Left lower quadrant	NPO	Nothing by mouth
LLSB	Left lower sternal border	NPV	Negative predictive value
LML	Left middle lobe	NS	Normal saline
LMN	Lower motor neuron	NSAID	Non-steroidal anti-inflammatory drug
LMWH	Low molecular weight heparin	NSCLC	Non-small cell lung cancer
LN	Lymph node	NSIP	Nonspecific interstitial pneumonia
LOC	Level of consciousness	NSTF	Non-ST elevation
LPHB		NYD	
	Left posterior hemiblock		Not yet diagnosed
LR-	Negative likelihood ratio	NYHA	New York Heart Association
LR+	Positive likelihood ratio	O&P	Ovum and parasites
LSD	Lysergic acid diethylamide	OHS	Obesity hypoventilation syndrome
LTBI	Latent tuberculosis infection	OHS	Obesity hypoventilation syndrome
LUL	Left upper lobe	OR	Odds ratio
LUQ	Left upper quadrant	OSA	Obstructive sleep apnea
LUSB	Left upper sternal border	Osmo	Osmolality
LV	Left ventricular	PA	Posterior—anterior
LVEF	Left ventricular ejection fraction	PAC	Paroxysmal atrial contraction
LVH	Left ventricular hypertrophy	$P_{\alpha}CO_2$	Arterial carbon dioxide pressure
MAC	Mycobacterium avium complex	PAN	Polyarteritis nodosa
MALT	Mucosa-associated lymphoid tissue	$P_aO_2$	Arterial oxygen pressure
MAO	Monoamine oxidase	PAOP	Pulmonary artery occlusion pressure
MAP	Mean arterial pressure	PaP	Palliative prognostic score
MCA	Middle cerebral artery	PAP	Pulmonary artery pressure
MCD	Minimal change disease	PBC	Primary biliary sclerosis
MCL	Mantle cell lymphoma	PCOS	Polycystic ovarian syndrome
MCP	Metacarpal joint	PCR	Polymerase chain reaction
MCV	Mean corpuscular volume	PCWP	Pulmonary capillary wedge pressure
MDI	Metered dose inhaler	PDA	Patent ductus arteriosus
MDS	Myelodysplastic syndrome	PE	Pulmonary embolism
MEDD	Morphine equivalent daily dose	PEA	Pulseless electrical activity
MELD	Model for end-stage liver disease	PEEP	Positive end expiratory pressure
MEN	Multiple endocrine neoplasia	PEF	Peak expiratory flow
MF	·	PFT	• •
*****	Myelofibrosis, mycosis fungoides		Positron emission tomography
Mg	Magnesium	PFO	Patent foramen ovale
MGN	Membranous glomerulopathy	PFT	Pulmonary function test
MGUS	Monoclonal gammopathy of uncertain significance	PIP	Proximal interphalageal joint
MHA-TP	Microhemagglutination assay for antibody to	PJP	Pneumocystis jirovecii pneumonia
	Treponema pallidum	PML	Progressive multifocal leukoencephalopathy
MI	Myocardial infarction	PMN	Polymorphonuclear neutrophil
MIBG	lodine-131-meta-iodobenzylguanidine	PND	Paroxysmal nocturnal dyspnea
MIBI	Methoxyisobutyl isonitrile	PNH	Paroxysmal nocturnal hemoglobinuria
MM	Multiple myeloma	PO	Oral
MMR	Measles, mumps, and rubella	PPS	Palliative performance scale
MMSF	Mini-mental state examination	PPV	Positive predictive value
MPA	Microscopic polyangiitis	PR	Progesterone receptor
MPGN	Membranoproliferative glomerulopathy	PRV	Polycythemia ruba vera
MPS		PSA	
MPS MRCP	Myeloproliferative syndrome	PSA PSC	Prostate-specific antigen
	Magnetic resonance cholangiopancreatography		Primary sclerosing cholangitis
MRI	Magnetic resonance imaging	PSI	Pneumonia severity of illness score
MRSA	Methicillin-resistant Staphylococcus aureus	PSV	Pressure support ventilation
MS	Mitral stenosis, multiple sclerosis	PTCA	Percutaneous transluminal coronary angioplasty
MSI	Microsatellite instability	PTCL	Peripheral T-cell lymphoma
MSK	Musculoskeletal	PTH	Parathyroid hormone
MSSA	Methicillin-sensitive Staphylococcus aureus	PTLD	Post-transplant lymphoproliferative disease
MTC	Medullary thyroid cancer	PTP	Post transfusion purpura
MTP	Metatarsophalangeal joint	PTT	Partial thromboplastin time
	,		

PTU	Propylthiouracil	TB	Tuberculosis
PUD	Peptic ulcer disease	TBI	Total body irradiation
PVC	Paroxysmal ventricular contraction	TCA	Tricyclic antidepressants
PVD	Peripheral vascular disease	TD	Transdermal
OID	Four times per day	TEF	Transesophageal echocardiogram
RA	Rheumatoid arthritis	TGL	Triglyceride
RAA	Right atrial abnormality	TIA	Transient ischemic attack
RAF	Right atrial enlargement	TIBC	Total iron-binding capacity
RAS	Renal artery stenosis	TID	Three times per day
RBBB	Right bundle branch block	TIMI	Thrombolysis in myocardial infarction
RBC	Red blood cell	TIPS	Transjugular intrahepatic portosystemic shunt
RCA	Right coronary artery	TLC	Total lung capacity
RDW	Red blood cell distribution width	TNF	Tumor necrosis factor
RF	Rheumatoid factor	TP-FIA	Treponema pallidum enzyme immunoassay
RLL	Right lower lobe	TPN	Total parenteral nutrition
RLO	Right lower quadrant	TPO	Thyroid peroxidase
RPGN	Rapidly progressive glomerulonephritis	TPPA	Treponema pallidum particle agglutination assay
RR	Respiratory rate, relative risk	TRH	Thyrotropin releasing hormone
RRR	Relative risk reduction	TSH	Thyroid stimulating hormone
RSV	Respiratory syncytial virus	TST	Tuberculin skin test
RSVP	Right ventricular systolic pressure	TTE	Transthoracic echocardiogram
RTA	Renal tubular acidosis	TTP	Thrombotic thrombocytopenic purpura
RT-PCR	Reverse transcriptase polymerase chain reaction	TUR	Transurethral resection
RUL	Right upper lobe	TURP	Transurethral resection of prostate
RUO	Right upper quadrant	U/A	Urinalysis
RUSB	Right upper sternal border	UGI	Upper gastrointestinal
SAH	Subarachnoid hemorrhage	UIP	Usual interstitial pneumonia
SBP	Systolic blood pressure, spontaneous bacterial	UMN	Upper motor neuron
SUF	peritonitis	UNC	Urine net charge
SCLC	Small cell lung cancer	US	Ultrasound
SCT	Stem cell transplant	UTI	Urinary tract infection
Sens	Sensitivity	UV	Ultraviolet
SIADH	Syndrome of inappropriate antidiuretic hormone	V/O	Ventilation/perfusion
SIRS	Systemic inflammatory response syndrome	VAP	Ventilator-associated pneumonia
SK	Streptokinase	VC	Vital capacity
SLE	Systemic lupus erythematosus	VDRL	Venereal Disease Research Laboratory
SLL	Chronic lymphocytic lymphoma	VF	Ventricular fibrillation
Spc	Specificity	VHL	Von Hippel–Lindau syndrome
SPN	Solitary pulmonary nodule	VIDI	Very low density lipoprotein
SR	Slow release	VRF	Vancomycin-resistant enterococci
SSRI	Selective serotonin reuptake inhibitor	VSD	Ventricular septal defect
SSS	Sick sinus syndrome	VT	Ventricular septal defect  Ventricular tachycardia
SSSS	Staphylococcal scalded skin syndrome	vWD	Von Willebrand disease
STE	ST elevation	VVD VZV	Varicella zoster virus
SVC	Superior vena cava	WBC	White blood cell
SVR	Systemic vascular resistance	WPW	Wolff-Parkinson-White
SVT	Supraventricular tachycardia	***	Wom randibon-wille
541	Supraventicular tueriyearala		

## **Appendix C**

# COMMON LABORATORY VALUES AND UNIT CONVERSION

Note: normal ranges are provided for general refer ence only. The normal values for individual institu tion 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. 10<sup>th</sup> ed. New York, NY: Oxford University Press; 2007

BLOOD COUNTS				
	SI units	US units	SI→US ratio	US→SI ratio
Hematocrit				
Male	0.41-0.50	41-50%	100	0.01
Female	0.35-0.45	35-45%	100	0.01
Hemoglobin				
Male	140-175 g/L	14-17.5 g/dL	0.1	10
Female	120-160 g/L	12-16 g/dL	0.1	10
RBC count				
Male	4.5-5.9×10 <sup>12</sup> /L	$4.5-5.9\times10^{6}/\mu$ L	1	1
Female	4.0-5.2×10 <sup>12</sup> /L	$4.0-5.2\times10^{6}/\mu$ L	1	1
Platelet count	140-440×10 <sup>9</sup> /L	$140-440\times10^{3}/\mu$ L	1	1
WBC count	4.5-11.0×10 <sup>9</sup> /L	$4.5-11.0\times10^{3}/\mu$ L	1	1
Neutrophil	1.7-7.3×10 <sup>9</sup> /L	$1.7 - 7.3 \times 10^3 / \mu L$	1	1
Lymphocyte	1.0-4.8×10 <sup>9</sup> /L	$1.0-4.8\times10^{3}/\mu$ L	1	1
Monocyte	$0.08 - 0.70 \times 10^9 / L$	$0.08 - 0.70 \times 10^3 / \mu L$	1	1
Eosinophil	$0.04 - 0.40 \times 10^9$ /L	$0.04 - 0.40 \times 10^{3} / \mu L$	1	1
Basophil	$0-0.10\times10^{9}/L$	$0-0.10\times10^{3}/\mu L$	1	1
CD4 count	0.64-1.18×10 <sup>9</sup> /L	640-1175/mm <sup>3</sup>	1000	0.001
CD8 count	0.34-0.88×10 <sup>9</sup> /L	335-875/mm <sup>3</sup>	1000	0.001
CD4:CD8 ratio	1.0-4.0	1.0-4.0	1	1
Reticulocyte count	0.005-0.025	0.5-2.5%	100	0.01

COAGULATION STUDIES				
	SI units	US units	SI→US ratio	US→SI ratio
aPTT	22.1-35.1 s	22.1-35.1 s	1	1
Bleeding time	2-9.5 min	2-9.5 min	1	1
D-dimer	<0.5 mg/L	<0.5 μg/mL	1	1
INR	0.8-1.2	0.8-1.2	1	1
PT	10-13 s	10-13 s	1	1
Thrombin time	16-24 s	16-24 s	1	1

TUMOR MARKERS				
	SI units	US units	SI→US ratio	US→SI ratio
AFP	<15 μg/L	<15 ng/mL	1	1
β2 microglobulin	0-2 mg/L	0-2 mg/L	1	1
CA 19-9	<37 kU/L	<37 U/mL	1	1
CA 27.29	<32 kU/L	<32 U/mL	1	1
CA 125	<35 kU/L	<35 U/mL	1	1
CEA	<4 μg/L	<4 ng/mL	1	1
HCG	<5 IU/L	<5 mIU/mL	1	1
PSA	<4 μg/L	<4 ng/mL	1	1

Appendix C

TUMOR MARKERS (CONT'D)	SI units	US units	SI→US ratio	US→SI ratio
Serum protein electrophoresis				
Total protein	60-80 g/L	6-8 g/dL	0.1	10
Globulins	25-35 g/L	2.5-3.5 g/dL	0.1	10
Alpha1	2-4 g/L	0.2-0.4 g/dL	0.1	10
Alpha2	5-9 g/L	0.5-0.9 g/dL	0.1	10
Beta	6-11 g/L	0.6-1.1 g/dL	0.1	10
Gamma	7-17 g/L	0.7-1.7 g/dL	0.1	10

CHEMISTRY				
	SI units	US units	SI→US ratio	US→SI ratio
Albumin	35-50 g/L	3.5-5 g/dL	0.1	10
Calcium				
Regular	2.05-2.55 mmol/L	8.2-10.2 mg/dL	4	0.25
lonized	1.1-1.4 mmol/L	4.5-5.6 mg/dL	4	0.25
Cardiac enzymes				
CK	40-150 U/L	40-150 U/L	1	1
Troponin				
Troponin I	0-0.4 μg/L	0.4 ng/mL	1	1
Troponin T	0-0.1 μg/L	0.1 ng/mL	1	1
CRP (high sens)	<8 mg/L	<8 mg/L	1	1
Electrolytes panel				
Na	136-142 mmol/L	136-142 mEq/L	1	1
K	3.5-5.0 mmol/L	3.5-5.0 mEq/L	1	1
CI	96-106 mmol/L	96-106 mEq/L	1	1
HCO <sub>3</sub>	22-30 mmol/L	22-30 mEq/L	1	1
Urea (BUN)	2.9-8.2 mmol/L	8-23 mg/dL	2.78	0.36
Creatinine	53-106 μmol/L	0.6-1.2 mg/dL	0.011	88.4
Cr clearance	1.24-2.08 mL/s	75-125 mL/min	59.9	0.017
Glucose				
Fasting	4.2-6.4 mmol/L	75-115 mg/dL	18.02	0.0555
Postprandial 2 h	<6.7 mmol/L	<120 mg/dL	18.02	0.0555
ESR				
Male	0-17 mm/h	0-17 mm/h	1	1
Female	1-25 mm/h	1-25 mm/h	1	1
Folate	7.0-39.7 nmol/L	3.1-17.5 ng/mL	0.44	2.27
Iron studies				
Ferritin				
Male	30-300 μg/L	30-300 ng/mL	1	1
Female	100-20 μg/L	100-200 ng/mL	1	1
Iron	5.4-28.7 μmol/L	30-160 μg/dL	5.56	0.18
TIBC	40.8-76.7 μmol/L	228-428 μg/dL	5.56	0.18
Transferrin	0-0.4 μg/L	0-0.4 ng/mL	1	1
Lipid profile				
LDL				
Optimal	<2.59 mmol/L	<100 mg/dL	38.5	0.026
Near normal	2.59-3.34 mmol/L	100-129 mg/dL	38.5	0.026
Borderline high	3.36-4.12 mmol/L	130-159 mg/dL	38.5	0.026
High	4.13-4.99 mmol/L	160-189 mg/dL	38.5	0.026
Very high	≥4.91 mmol/L	≥190 mg/dL	38.5	0.026
HDL			38.5	0.026
Low	<1.03 mmol/L	<40 mg/dL	38.5	0.026
High	≥1.55 mmol/L	≥60 mg/dL		
Total cholesterol				
Desirable	<5.17 mmol/L	<200 mg/dL	38.5	0.026
Borderline high	5.17-6.17 mmol/L	200-239 mg/dL	38.5	0.026
High	≥6.18 mmol/L	≥240 mg/dL	38.5	0.026
Triglycerides	<1.8 mmol/L	<160 mg/dL	90.9	0.011
Liver function tests				
AST	20-48 U/L	20-48 U/L	1	1
ALT	10-40 U/L	10-40 U/L	1	1
ALP	50-120 U/L	50-120 U/L	1	1
Bilirubin				
Total	5-21 μmol/L	0.3-1.2 mg/dL	0.058	17.1
Direct	<3.4 μmol/L	<0.2 mg/dL	0.058	17.1

CHEMISTRY (CONT'D)				
	SI units	US units	SI→US ratio	US→SI ratio
LDH	50-200 U/L	50-200 U/L	1	1
Magnesium	0.8-1.2 mmol/L	1.8-3.0 mg/dL	2.4	0.41
Phosphate	0.97-1.45 mmol/L	3-45 mg/dL	3.1	0.32
Uric acid	240-510 μmol/L	4.0-8.5 mg/dL	0.017	60
Vitamin B12				
Normal	>185 pmol/L	>250 pg/mL	1.35	0.74
Deficient	<92 pmol/L	<125 pg/mL	1.35	0.74
Amylase	25-100 U/L	25-100 U/L	1	1
Lipase	0-160 U/L	0-160 U/L	1	1

SI units	US units	SI→US ratio	US→SI ratio
<26 pmol/L	<120 pg/mL	4.54	0.22
		0.036	27.7
$2-5 \times$ supine value	2-5× supine value		
0.8-7.6 pmol/L	3-26 pg/mL	3.42	0.292
0.58-5.0 pmol/L	2-17 pg/mL	3.42	0.292
138-690 nmol/L	5-25 μg/dL	0.036	27.6
138-414 nmol/L	5—15 μg/dL	0.036	27.6
0-276 nmol/L	0-10 μg/dL	0.036	27.6
5-36 U/L	5-36 U/L	1	1
20-100 ng/L	20-100 pg/mL	1	1
14-140 pmol/L	2-20 μU/mL	0.14	6.95
<0.5 nmol/L	<0.5 nmol/L	1	1
<5 μmol	<1 mg	0.20	5.1
89-473 nmol	15—80 μg	0.17	5.9
0—20 μg/L	0-20 ng/mL	1	1
0-15 μg/L	0-15 ng/mL	1	1
10-60 ng/L	10-60 pg/mL	1	1
0.7-1.0 pmol/L	30-40 pg/mL	42.2	0.024
9.4-37.1 nmol/L	270-1070 ng/dL	28.6	0.035
0.21-2.98 nmol/L	6-86 ng/dL	28.6	0.035
0-60 μg/L	0-60 ng/mL	1	1
0.5-5.0 mU/L	0.5-5.0 μU/mL	1	1
3.5-6.5 pmol/L	230-420 pg/dL	65	0.015
0.92-2.78 nmol/L		65	0.015
	J		
10.3-35 pmol/L	0.8-2.7 ng/dL	0.078	13
58-140 nmol/L	4.5—10.9 μg/dL	0.078	13
	1.5		
60-108 pmol/L	25-45 pg/mL	0.42	2.4
35—150 nmol/L	14-60 ng/mL	0.4	2.5
	26 pmol/L  55—250 pmol/L  2–5× supine value  0.8—7.6 pmol/L  0.58—5.0 pmol/L  138—690 nmol/L  138—414 nmol/L  0–276 nmol/L  5–36 U/L  20—100 ng/L  14—140 pmol/L  <0.5 nmol/L  <5 μmol  89—473 nmol  0–20 μg/L  0–15 μg/L  10–60 ng/L  0.7—1.0 pmol/L  9.4—37.1 nmol/L  0.21-2.98 nmol/L  0.5—6.5 pmol/L  0.5—5.0 mU/L  3.5—6.5 pmol/L  0.92—2.78 nmol/L  10.3—35 pmol/L  58—140 nmol/L	<26 pmol/L	<26 pmol/L

DRUG LEVELS				
	SI units	US units	SI→US ratio	US→SI ratio
Acetaminophen				
Therapeutic range	66-199 μmol/L	10-30 μg/mL	0.15	6.6
Toxic range	>1324 µmol/L	>200 μg/mL	0.15	6.6
Amitriptyline				
Therapeutic range	433-903 nmol/L	120-250 ng/mL	0.28	3.6
Toxic range	>1805 nmol/L	>500 ng/mL	0.28	3.6
Carbamazepine				
Therapeutic range	26-51 μmol/L	6—12 μg/mL	0.24	4.2
Toxic range	>63 µmol/L	>15 μg/mL	0.24	4.2

Appendix C

DRUG LEVELS (CONT'D)				
	SI units	US units	SI→US ratio	US→SI ratio
Clonazepam				
Therapeutic range	48-190 nmol/L	15-60 ng/mL	0.31	3.2
Toxic range	>254 nmol/L	>80 ng/mL	0.31	3.2
Clozapine Therapeutic range	0.6-1.0 μmol/L	200-350 ng/mL	333	0.003
Cocaine	υ.b— I.U μΠΟΙ/L	200—350 fig/filL	333	0.005
Toxic dose	>3300 nmol/L	>1000 ng/mL	0.30	3.3
Diazepam	/3300 IIII0// L	>1000 Hg/HL	0.50	5.5
Therapeutic range	0.35-3.51 μmol/L	100-1000 ng/mL	285	0.0035
Toxic range	>17.55 µmol/L	>5000 ng/mL	285	0.0035
Digoxin		<b>3</b>		
Therapeutic range	1.0-2.6 nmol/L	0.8-2.0 ng/mL	0.78	1.28
Toxic range	>3.2 nmol/L	>2.5 ng/mL	0.78	1.28
Ethanol				
Toxic dose	>65 mmol/L	>300 mg/dL	4.6	0.22
Gentamicin				
Peak	16.7-20.9 μmol/L	8—10 μg/mL	0.48	2.1
Trough	<4.2-8.4 μmol/L	<2-4 μg/mL	0.48	2.1
Imipramine				
Therapeutic range	446-893 nmol/L	125-250 ng/mL	0.28	3.57
Toxic range	>1784 nmol/L	>500 ng/mL	0.28	3.57
Lidocaine				
Therapeutic	6.4-26 μmol/L	1.5—6.0 μg/mL	0.23	4.3
Lithium	06.12.1/	06.13.5.8		
Therapeutic	0.6—1.2 nmol/L	0.6—1.2 mEq/L	1	1
Toxic range Methadone	>2 mmol/L	>2 mEq/L	1	ı
Therapeutic range	0.32-1.29 μmol/L	100-400 ng/mL	313	0.0032
Toxic range	>6.46 µmol/L	>2000 ng/mL	313	0.0032
Morphine	>0.40 μποι/L	/2000 flg/fliL	515	0.0032
Therapeutic range	35-280 nmol/L	10-80 ng/mL	0.29	3.5
Toxic range	>700 nmol/L	>200 ng/mL	0.29	3.5
Nortriptyline		J		
Therapeutic range	0.19-0.65 nmol/L	50-170 ng/mL	263	0.0038
Toxic range	>1.9 µmol/L	>500 ng/mL	263	0.0038
Phenytoin				
Therapeutic range	40-79 μmol/L	10-20 μg/mL	0.25	3.95
Toxic range	>79 µmol/L	>20 μg/mL	0.25	3.95
Salicylates				
Therapeutic range	1086-2172 μmol/L	150—300 μg/mL	0.14	7.24
Toxic range	>2172 μmol/L	>300 μg/mL	0.14	7.24
Theophylline				
Therapeutic range	44-111 μmol/L	8—20 μg/mL	0.18	5.5
Toxic range	>110 μmol/L	>20 μg/mL	0.18	5.5
<b>Tobramycin</b> Peak	17-21 μmol/L	8—10 μg/mL	0.44	2.25
Trough	•		0.44	2.25
Valproic acid	<9 μmol/L	<4 μg/mL	0.44	2.23
Therapeutic range	347-1040 μmol/L	50-150 μg/mL	0.14	6.9
Toxic range	>1040 μmol/L	>150 μg/mL	0.14	6.9
Vancomycin	> 10-10 μπιοι/ Ε	> 130 μg/111L	0.11	0.5
Peak	12-18 μmol/L	18-26 μg/mL	1.67	0.6
Trough	3—7 μmol/L	5—10 μg/mL	1.67	0.6
Amikacin		- F-3,		
Peak	43-60 μmol/L	25-35 μg/mL	0.59	1.7
Trough	6.8-13.7 μmol/L	4-8 μg/mL	0.59	1.7
-	·			

## **Appendix D**

## HISTORY TEMPLATE

BASIC SCHEME		REVIEW O	F SYSTEMS	
CHIEF COMPLAINT:	CONSTITUTIONAL:	11211211 0	RHEUMATOLOGIC:	
	□ Weight ∆	□ Energy	☐ Joint pain, swe	lling, redness
	□ Fever, chills	□ Night sweats	□ AM stiffness	□ Back pain
HISTORY OF PRESENT ILLNESS:	□ Appetite Δ	□ Sleep	□ Myalgia	□ Arthralgia
Onset	□ Mood Δ		□ Skin rash	□ Raynaud's
Position/posture			□ Dry eyes	□ Dry mouth
Previous history	HEAD AND NECK:		□ Oral ulcers	☐ Hair loss
Progression Quality	□ Vision Δ	□ Diplopia Δ	□ Photosensitivity	
Radiating	□ Smell	□ Rhinorrhea	□ Psoriasis	□ IBD
Severity	□ Sinusitis	□ Epistaxis		
Temporal factors	☐ Hearing ∆	□ Discharge	OBS/GYN:	
Treatment	☐ Tinnitus	□ Vertigo	☐ Menarche age	□ LMP
Understanding	□ Sore throat	□ Teeth	□ Cycle regular	□ Period length
	□ Tongue	□ Oral lesions	□ Periods freq.	□ Period volume
Aggravating	□ Neck pain	□ Neck mass	☐ Menopause age	
Alleviating	CARDIAC:		☐ Abnormal bleed	•
Associated symptoms	□ Chest pain	□ Dyspnea	☐ No. of preg.	□ Difficult preg.
Etiologies	□ Syncope	□ Palpitations	□ Contraception	□ STDs
Risk factors	□ Orthopnea		☐ Vaginal dryness	or discharge
Complications	□ Claudication	□ Leg edema	□ Dyspareunia	
Complications	□ Murmurs	☐ Hypertension	BREASTS:	
How has illness affected your life	□ Rheumatic feve		□ Masses	□ Swelling
Support systems	- I III culliano leve	•	□ Nipple discharg	
Worries, fears	RESPIRATORY:		□ Pain	,0
Expectations	□ Dyspnea	□ Cough	□ Self breast exam	1
	□ Sputum	☐ Hemoptysis	- Och breast exam	'
PAST MEDICAL HISTORY:	☐ Pleuritic chest	pain	ENDOCRINE:	
Hospitalization (time, tx, recovery) Medical illnesses (time, tx, recovery)		•	□ Polydipsia	□ Polyphagia
Injuries (time, tx, recovery)	GASTROINTESTINAL		□ Polyuria	□ Galactorrhea
injuries (time, tx, recovery)	<ul> <li>Dysphagia</li> </ul>	□ Odynophagia	☐ Heat or cold tol	erance
MEDICATIONS:	☐ Heartburn	□ Reflux		
drug name, dose, route, frequency	□ N&V	☐ Hematemesis	NEUROPSYCHIATRIC	
	□ Melena	□ Abd pain	□ Unconscious	□ Syncope
ALLERGIES:	□ Diarrhea	□ Constipation	□ Vertigo	□ Dizziness
	□ Bowel habits	☐ Hematochezia	☐ Memory loss	□ Dysphasia
IMMUNIZATIONS:	□ Bloating	□ Flatus	☐ Head trauma	□ Strokes
Occur Hemony	☐ Pale stool	□ Jaundice	☐ Headaches	□ Seizures
SOCIAL HISTORY:	□ Hemorrhoid		□ Weakness	□ Paresis
☐ Living arrangement, marital	GENITOURINARY:		☐ Clumsiness	□ Balance/gait
□ Support system □ Hobbies	□ Dysuria	□ Frequency	- Denvession	□ Suicidal
□ ADLs □ IADLs	□ Urgency	□ Hesitancy	<ul> <li>□ Depression</li> <li>□ Anxiety</li> </ul>	□ Previous w hx
	□ Incontinence	☐ Slow stream	□ Alixiety	□ Previous ψ πx
□ Education □ Occupation	□ Hematuria	□ Nocturia	SKIN:	
□ Smoking □ Alcohol	□ Discharge	- Noctaria	□ Rashes	□ Lumps
□ Smoking □ Alcohol □ Illicit drugs □ Diet	□ Libido	□ Impotence	□ Pruritus	□ Pigment Δ
inicit drugs in blet		= impotence		•
Francisco de la constanta de l				
FAMILY HISTORY:				
Father Mother Siblings Children				
Siblings Children  Cancer Heart disease				
☐ Diabetes ☐ Genetic disease				
□ Diabetes □ Genetic disease				
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## Selected Internal Medicine Topics

## Integrated Symptom-Based and Issue-Based Approach

from *Approach to Internal Medicine*, 3<sup>rd</sup> Edition David Hui, MD, M.Sc., FRCPC

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