

RESPIRATORY DISEASES

1. Acute bronchitis. Etiology and pathogenesis. Clinic, diagnosis, treatment.

inflammation of the bronchi (large and medium-sized airways) of the lungs.
The most common is common cold

Pathogenesis:

During an episode of **acute bronchitis**, the cells of the bronchial-lining tissue are irritated and the mucous membrane becomes hyperemic and edematous, diminishing bronchial mucociliary function. Consequently, the air passages become clogged by debris and irritation increases.

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Quick HIT

It is often difficult to distinguish between a viral and a bacterial infection.

Common Features of Viral Versus Bacterial URIs

Feature	Viral	Bacterial
Rhinorrhea	X	—
Myalgias	X	—
Headache	X	—
Fever	X	X
Cough	X	X
Yellow sputum	—	X

b. May be helpful in the following situations:

- If cause is unknown (and thus specific therapy cannot be given)
 - If specific therapy is not effective
 - If cough serves no useful purpose, such as clearing excessive sputum production or secretions
- c. Medications
- Codeine
 - Dextromethorphan
 - Benzonatate (Tessalon Perles) capsules
- d. Agents used to improve the effectiveness of antitussive medications include expectorants such as guaifenesin and water

••• Acute Bronchitis

A. General characteristics

1. Viruses account for the majority of cases.
2. Laboratory tests are not indicated. Obtain a chest radiograph only if you suspect pneumonia; there is no infiltrate or consolidation in acute bronchitis (presence of fever, tachypnea, crackles, egophony on auscultation, or dullness to percussion suggests pneumonia).

B. Clinical features

1. Cough (with or without sputum) is the predominant symptom—it lasts 1 to 2 weeks. In a significant number of patients, the cough may last for 1 month or longer.
2. Chest discomfort and shortness of breath may be present.
3. Fever may or may not be present.

C. Treatment

1. Antibiotics are usually not necessary—most cases are viral.
2. Cough suppressants (codeine-containing cough medications) are effective for symptomatic relief.
3. Bronchodilators (albuterol) may relieve symptoms.

••• The Common Cold

A. General characteristics

1. The “common cold” is the most common upper respiratory tract infection. Children are more frequently affected than adults. Susceptibility depends on pre-existing antibody levels.
2. Caused by viruses (identification of virus is not important).
 - a. Rhinoviruses are the most common (at least 50% of cases)—there are more than 100 antigenic serotypes, so reinfection with another serotype can lead to symptoms (no cross-immunity among the serotypes).
 - b. Other viruses include coronavirus, parainfluenza viruses (types A, B, and C), adenovirus, coxsackievirus, and RSV.
3. Hand-to-hand transmission is the most common route.
4. Complications include secondary bacterial infection (bacterial sinusitis or pneumonia). These secondary infections (especially pneumonia) are very rare.
5. Most resolve within 1 week, but symptoms may last up to 10 to 14 days.

B. Clinical features

1. Rhinorrhea, sore throat, malaise, nonproductive cough, nasal congestion.
2. Fever is uncommon in adults (suggests a bacterial complication or influenza), but is not unusual in children.

C. Treatment (symptomatic)

1. Adequate hydration
 - a. Loosens secretions and prevents airway obstruction
 - b. Can be achieved by increasing fluid intake and inhaling steam

2. Rest and analgesics (aspirin, acetaminophen, ibuprofen)—for relief of malaise, headache, fever, aches
3. Cough suppressant (dextromethorphan, codeine)
4. Nasal decongestant spray (Neo-Synephrine) for less than 3 days
5. Oral first-generation antihistamines for rhinorrhea/sneezing

2. Chronic bronchitis. Clinic, diagnosis, treatment.

chronic cough productive of sputum
for at least 3 months per year for at least 2 consecutive years.

Chronic bronchitis usually exist with emphysema and form COPD
Pure chronic bronchitis usually is rare.

Risk factors and causes

- a. Tobacco smoke (indicated in almost 90% of COPD cases)
- b. α 1-Antitrypsin deficiency—risk is even worse in combination with smoking c.
Environmental factors (e.g., second-hand smoke)
- d. Chronic asthma—speculated by some to be an independent risk factor

Pathogenesis

- a. Chronic bronchitis
 - Excess mucus production narrows the airways; patients often have a productive cough.
 - Inflammation and scarring in airways, enlargement in mucous glands, and smooth muscle hyperplasia lead to obstruction.

Clinical features

1. Symptoms
 - a. Any combination of cough, sputum production, and dyspnea (on exertion or at rest, depending on severity) may be present. Dyspnea is initially during exertion but eventually becomes progressively worse with less exertion and even at rest.
 - b. Some patients have very sedentary lifestyles but few complaints. They may avoid exertional dyspnea, which is the most common early symptom of COPD by limiting their activity.

Signs—the following may be present:

- a. Prolonged expiratory time.
- b. During auscultation, end-expiratory wheezes on forced expiration, decreased breath sounds, and/or inspiratory crackles
- c. Tachypnea, tachycardia
- d. Cyanosis
- e. Use of accessory respiratory muscles
- f. Hyperresonance on percussion

g. Signs of cor pulmonale

C. Diagnosis

1. Pulmonary function testing (spirometry)—see Table 2-2 and Figure 2-1.
 - a. This is the definitive diagnostic test.
 - b. Obstruction is evident based on the following:
 - Decreased FEV₁ and decreased FEV₁/FVC ratio—GOLD staging is based on FEV₁. FEV₁ ≥80% of predicted value is mild disease, 50% to 80% is moderate disease, 30% to 50% is severe disease, and <30% is very severe disease.

CLINICAL PEARL 2-1

Key Points in Taking History of COPD Patients

General

- History of cardiopulmonary diseases
- Smoking history (duration, intensity, current smoker)
- Family history—COPD, heart disease, asthma
- Occupation—industrial dusts, fumes
- Overall health
- History of respiratory infections—frequency, severity
- Pulmonary medications

Pulmonary Symptoms

- Dyspnea—quantitate severity
- Cough
- Sputum production—quantity, quality, duration, hemoptysis
- Wheezing

Adapted from Burton GG, Hodgkin JE, Ward JJ, eds. *Respiratory Care—A Guide to Clinical Practice*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1997:1026, Table 28-3.

- Increased total lung capacity (TLC), residual volume, and functional reserve capacity (FRC) (indicating air trapping) (see Figure 2-2). Although COPD increases TLC, the air in the lung is not useful because it all becomes residual volume and does not participate in gas exchange.
- Decreased vital capacity.

2. Chest radiograph (CXR)

- a. Low sensitivity for diagnosing COPD; only severe, advanced emphysema will show the typical changes, which include:
 - Hyperinflation, flattened diaphragm, enlarged retrosternal space (see Figure 2-3).
 - Diminished vascular markings.
- b. Useful in an acute exacerbation to rule out complications such as pneumonia or pneumothorax.
3. Measure α_1 -antitrypsin levels in patients with a personal or family history of premature emphysema (≤50 years old).
4. Arterial blood gas (ABG)—chronic PCO₂ retention, decreased PO₂.

D. Treatment

1. Modalities

- a. **Smoking cessation—the most important intervention.**
 - Disease progression is accelerated by continued smoking and can be greatly slowed by its cessation.
 - At around age 35, FEV₁ decreases approximately 25 to 30 mL/yr. In smokers, the rate of decline is faster (threefold to fourfold). If a smoker quits, the *rate of decline* of FEV₁ slows to that of someone of the same age who has never smoked. However, quitting does *not* result in complete reversal.

- **Smoking cessation prolongs the survival rate but does not reduce it to the level of someone who has never smoked** (see Figure 2-4).
- Respiratory symptoms improve within 1 year of quitting.
- b. Inhaled anticholinergic drugs (e.g., ipratropium bromide): bronchodilators.
 - Slower onset of action than the β -agonists, but last longer.
- c. Inhaled β_2 -agonists (e.g., albuterol): bronchodilators.
 - Provide symptomatic relief. Use long-acting agents (e.g., salmeterol) for patients requiring frequent use.
- d. Combination of β -agonist albuterol with ipratropium bromide.
 - More efficacious than either agent alone in bronchodilation.
 - Also helps with adherence to therapy (both medications in one inhaler).
- e. Inhaled corticosteroids (e.g., budesonide, fluticasone): anti-inflammatory.
 - May minimally slow down the decrease in FEV₁ over time; however, many studies have failed to show any benefit in pulmonary function.

- f. Theophylline (oral)—role is controversial.
 - May improve mucociliary clearance and central respiratory drive.
 - Narrow therapeutic index, so serum levels must be monitored.
 - Only modestly effective and has more side effects than other bronchodilators.
 - Occasionally used for patients with refractory COPD.
 - g. Oxygen therapy.
 - Shown to improve survival and quality of life in patients with COPD *and* chronic hypoxemia.
 - Some patients need continuous oxygen, whereas others only require it during exertion or sleep. Get an ABG to determine need for oxygen (see Quick Hit).
 - Long-standing hypoxemia may lead to pulmonary HTN and ultimately cor pulmonale. Continuous oxygen therapy for ≥18 hr/day has been shown to reduce mortality in patients with these complications by controlling pulmonary HTN.
 - h. Pulmonary rehabilitation—education, exercise, physiotherapy: A major goal is to improve exercise tolerance. Pulmonary rehabilitation improves functional status and quality of life.
 - i. Vaccination
 - Influenza vaccination annually for all patients.
 - Vaccination against *Streptococcus pneumoniae* every 5 to 6 years—should be offered to patients with COPD over 65 years old, or under 65 who have severe disease.
 - j. Antibiotics are given for acute exacerbations (see below)—increased sputum production in volume or change in character or worsening shortness of breath.
 - k. Surgery—may be beneficial in selected patients; carefully weigh potential benefits with risks. Options include:
 - Lung resection
 - Lung transplantation
2. Treatment guidelines
 - a. Mild to moderate disease.
 - Begin with a bronchodilator in a metered-dose inhaler (MDI) formulation (with spacer to improve delivery). Anticholinergic drugs and/or β -agonists are first-line agents.
 - Inhaled glucocorticoids may be used as well (see above). Use the lowest dose possible.
 - Theophylline may be considered if the above do not adequately control symptoms.

- b. Severe disease
- Medications as above.
 - Continuous oxygen therapy (if patient is hypoxemic).
 - Pulmonary rehabilitation.
 - Triple inhaler therapy (long-acting β -agonist plus a long-acting anticholinergic plus an inhaled glucocorticoid) is an option for severe disease.
3. Acute COPD exacerbation. Definition: Increased dyspnea, sputum production, and/or cough. Acute COPD exacerbation can lead to acute respiratory failure requiring hospitalization, and possibly mechanical ventilation; potentially fatal.
- Bronchodilators (β_2 -agonist) alone or in combination with anticholinergics are first-line therapy.
 - Systemic corticosteroids are used for patients requiring hospitalization (IV methylprednisolone is a common choice). Taper with oral prednisone on clinical improvement. Do not use inhaled corticosteroids in acute exacerbations.
 - Antibiotics (azithromycin, levofloxacin, doxycycline, etc.; no antibiotic superior to another): Studies have shown that patients who receive broad-spectrum antibiotics do slightly better than a placebo group.
 - Supplemental oxygen is used to keep O₂ saturation 90% to 93%. Start with a nasal cannula; a face mask may need to be used.
 - If SaO₂ is >93%, the patient is at risk of CO₂ retention from worsening V/Q mismatch, loss of hypoxic respiratory drive, and the Haldane effect.
 - Noninvasive positive pressure ventilation (NPPV) (bilevel positive airway pressure [BiPAP] or CPAP): Studies have shown a benefit in acute exacerbations. It may decrease the likelihood of respiratory failure requiring invasive mechanical ventilation.
 - Intubation and mechanical ventilation may be required if the above do not stabilize the patient. Intubate if increasing RR, increasing PaCO₂, and worsening acidosis.

E. Complications

- Acute exacerbations—most common causes are infection, noncompliance with therapy, and cardiac disease
- Secondary polycythemia (Hct >55% in men or >47% in women)—compensatory response to chronic hypoxemia
- Pulmonary HTN and cor pulmonale—may occur in patients with severe, long-standing COPD who have chronic hypoxemia

3. Chronic obstructive pulmonary disease. Definition, epidemiology, risk factors. Pathogenesis. Clinic. Diagnostics.

Diseases of the Pulmonary System

Quick HIT

Pathology

Centrilobular emphysema:

- Most common type, seen in smokers (rarely in nonsmokers)
- Destruction limited to respiratory bronchioles (proximal acini) with little change in distal acini
- Predilection for upper lung zones

Panlobular emphysema:

- Seen in patients with α_1 -antitrypsin deficiency
- Destruction involves both proximal and distal acini
- Predilection for lung bases

Quick HIT

In COPD,

- The FEV₁/FVC ratio is <0.70.
- FEV₁ is decreased.
- TLC is increased.
- Residual volume is increased.

Total lung capacity

Obstructive Lung Diseases

Chronic Obstructive Pulmonary Disease

A. General characteristics

- There are two classic types of chronic obstructive pulmonary disease (COPD): chronic bronchitis and emphysema (see Table 2-1 and Clinical Pearl 2-1).
 - Chronic bronchitis is a clinical diagnosis: chronic cough productive of sputum for at least 3 months per year for at least 2 consecutive years.
 - Emphysema is a pathologic diagnosis: permanent enlargement of air spaces distal to terminal bronchioles due to destruction of alveolar walls.
 - The two often coexist. Pure emphysema or pure chronic bronchitis is rare.
 - COPD is the fourth leading cause of death in the United States.
- Risk factors and causes
 - Tobacco smoke (indicated in almost 90% of COPD cases)
 - α_1 -Antitrypsin deficiency—risk is even worse in combination with smoking
 - Environmental factors (e.g., second-hand smoke)
 - Chronic asthma—speculated by some to be an independent risk factor
- Pathogenesis
 - Chronic bronchitis
 - Excess mucus production narrows the airways; patients often have a productive cough.
 - Inflammation and scarring in airways, enlargement in mucous glands, and smooth muscle hyperplasia lead to obstruction.
 - Emphysema
 - Destruction of alveolar walls is due to relative excess in protease (elastase) activity, or relative deficiency of antiprotease (α_1 -antitrypsin) activity in the lung. Elastase is released from PMNs and macrophages and digests human lung. This is inhibited by α_1 -antitrypsin.
 - Tobacco smoke increases the number of activated PMNs and macrophages, inhibits α_1 -antitrypsin, and increases oxidative stress on the lung by free radical production.

B. Clinical features

- Symptoms
 - Any combination of cough, sputum production, and dyspnea (on exertion or at rest, depending on severity) may be present. Dyspnea is initially during exertion but eventually becomes progressively worse with less exertion and even at rest.
 - Some patients have very sedentary lifestyles but few complaints. They may avoid exertional dyspnea, which is the most common early symptom of COPD by limiting their activity.

TABLE 2-1 COPD—Emphysema and Chronic Bronchitis

Predominant Emphysema ("Pink Puffers")	Predominant Chronic Bronchitis ("Blue Bloaters")
<ul style="list-style-type: none"> Patients tend to be thin due to increased energy expenditure during breathing. When sitting, patients tend to lean forward. Patients have a barrel chest (increased AP diameter of chest). <p>Tachypnea with prolonged expiration through pursed lips is present.</p>	<ul style="list-style-type: none"> Patients tend to be overweight and cyanotic (secondary to chronic hypoxemia and hypoxemia). Chronic cough and sputum production are characteristic. Signs of cor pulmonale may be present in severe or long-standing disease.
Patient is distressed and uses accessory muscles (especially strap muscles in neck).	Patient is in no apparent distress, and there is no apparent use of accessory muscles.

2. Signs—the following may be present:
- Prolonged expiratory time.
 - During auscultation, end-expiratory wheezes on forced expiration, decreased breath sounds, and/or inspiratory crackles
 - Tachypnea, tachycardia
 - Cyanosis
 - Use of accessory respiratory muscles
 - Hyperresonance on percussion
 - Signs of cor pulmonale

C. Diagnosis

- Pulmonary function testing (spirometry)—see Table 2-2 and Figure 2-1.
- This is the definitive diagnostic test.
- Obstruction is evident based on the following:
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Quick HIT

FEV₁ is the amount of air that can be forced out of the lungs in 1 second. The lower the FEV₁, the more difficulty one has breathing.

Diseases of the Pulmonary System

Quick HIT

To diagnose airway obstruction, one must have a normal or increased TLC with a decreased FEV₁.

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TABLE 2-2 Obstructive Versus Restrictive Lung Disease

Measurement	Obstructive	Restrictive
FEV ₁	Low	Normal or slightly low
FEV ₁ /FVC	Low	Normal or high
Peak expiratory flow rate	Low	Normal
Residual volume	High	Low, normal, or high
Total lung capacity	High	Low
Vital capacity	Low	Low

Diseases of the Pulmonary System

Quick HIT

One can measure the peak expiratory flow rate using a peak flow meter. If <350 L/min, one should perform pulmonary function testing, because this is a good screening test for obstruction.

Quick HIT

COPD leads to chronic respiratory acidosis with metabolic alkalosis as compensation.

Quick HIT

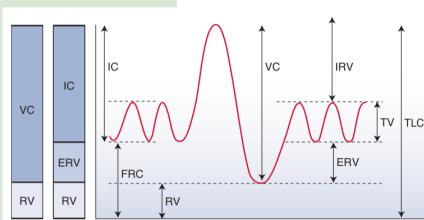
Clinical monitoring of COPD patients entails the following:

- Serial FEV₁ measurements—this has the highest predictive value
- Pulse oximetry
- Exercise tolerance

- Increased total lung capacity (TLC), residual volume, and functional residual capacity (FRC) (indicating air trapping) (see Figure 2-2). Although COPD increases TLC, the air in the lung is not useful because it all becomes residual volume and does not participate in gas exchange.
- Decreased vital capacity.
2. Chest radiograph (CXR)
- Low sensitivity for diagnosing COPD; only severe, advanced emphysema will show the typical changes, which include:
 - Hyperinflation, flattened diaphragm, enlarged retrosternal space (see Figure 2-3).
 - Diminished vascular markings.
 - Useful in an acute exacerbation to rule out complications such as pneumonia or pneumothorax.
 - Measure α_1 -antitrypsin levels in patients with a personal or family history of premature emphysema (≤ 50 years old).
 - Arterial blood gas (ABG)—chronic PCO₂ retention, decreased PO₂.

D. Treatment

1. Modalities
- a. Smoking cessation—the most important intervention.
- Disease progression is accelerated by continued smoking and can be greatly slowed by its cessation.
 - At around age 35, FEV₁ decreases approximately 25 to 30 mL/yr. In smokers, the rate of decline is faster (threefold to fourfold). If a smoker quits, the rate of decline of FEV₁ slows to that of someone of the same age who has never smoked. However, quitting does not result in complete reversal.



1. TLC (total lung capacity) = volume of air in the lungs after maximum inspiration
2. FRC (functional residual capacity) = volume of air in the lungs after a normal expiration
3. RV (residual volume) = volume of air in the lungs at maximal expiration
4. TV (tidal volume) = volume of air breathed in and out of the lungs during quiet breathing
5. VC (vital capacity) = volume of air expired from the lungs during a maximum expiration

FIGURE 2-1 Lung volumes. IC, inspiratory capacity; ERV, expiratory reserve volume.

4. Clinic and variants of the course of COPD, instrumental methods of diagnostics in COPD.

- Stage I: Mild COPD. Lung function is starting to decline but you may not notice it.
- Stage II: Moderate COPD. Symptoms progress, with shortness of breath developing upon exertion.
- Stage III: Severe COPD. Shortness of breath becomes worse and COPD exacerbations are common.
- Stage IV: Very severe COPD.

During the most common **test**, called spirometry, **you** blow into a large tube connected to a small machine to measure how much air your lungs can hold and how fast **you** can blow the air out of your lungs. Other **tests** include measurement of lung volumes and diffusing capacity, six-minute walk **test**, and pulse oximetry.

Pulmonary function testing (spirometry)—see Table 2-2 and Figure 2-1.

a. This is the definitive diagnostic test.

b. Obstruction is evident based on the following:

- Decreased FEV1 and decreased FEV1/FVC ratio—GOLD staging is based on FEV1. FEV1 \geq 80% of predicted value is mild disease, 50% to 80% is moderate disease, 30% to 50% is severe disease, and <30% is very severe disease.

Increased total lung capacity (TLC), residual volume, and functional reserve capacity (FRC) (indicating air trapping) (see Figure 2-2).

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b. Useful in an acute exacerbation to rule out complications such as pneumonia or pneumothorax.

3. Measure α 1-antitrypsin levels in patients with a personal or family history of premature emphysema (\leq 50 years old).

4. Arterial blood gas (ABG)—chronic PCO₂ retention, decreased PO₂.

5. Complications of COPD and their treatment.

Complications

1. Acute exacerbations—most common causes are infection, noncompliance with therapy, and cardiac disease
2. Secondary polycythemia (Hct >55% in men or >47% in women)—compensatory response to chronic hypoxemia
3. Pulmonary hypertension and cor pulmonale—may occur in patients with severe, long-standing COPD who have chronic hypoxemia

Treatment

1. Modalities

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Disease progression is accelerated by continued smoking and can be greatly slowed by its cessation.

At around age 35, FEV1 decreases approximately 25 to 30 mL/yr. In smokers, the rate of decline is faster (threefold to fourfold). If a smoker quits, the rate of decline of FEV slows to that of someone of the same age who has never smoked. However, quitting does not result in complete reversal.

- Smoking cessation prolongs the survival rate but does not reduce it to the level of someone who has never smoked (see Figure 2-4).

- Respiratory symptoms improve within 1 year of quitting.

b. Inhaled anticholinergic drugs (e.g., ipratropium bromide): bronchodilators.

- Slower onset of action than the β -agonists, but last longer.

c. Inhaled β 2-agonists (e.g., albuterol): bronchodilators.

- Provide symptomatic relief. Use long-acting agents (e.g., salmeterol) for patients requiring frequent use.

d. Combination of β -agonist albuterol with ipratropium bromide.

- More efficacious than either agent alone in bronchodilation.

- Also helps with adherence to therapy (both medications in one inhaler).

e. Inhaled corticosteroids (e.g., budesonide, fluticasone): anti-inflammatory.

- May minimally slow down the decrease in FEV1 over time; however, many

studies have failed to show any benefit in pulmonary function.

Typically used in combination with a long-acting bronchodilator for patients with significant symptoms or repeated exacerbations.

f. Theophylline (oral)—role is controversial.

- May improve mucociliary clearance and central respiratory drive.
- Narrow therapeutic index, so serum levels must be monitored.
- Only modestly effective and has more side effects than other bronchodilators.

Occasionally used for patients with refractory COPD.

g. Oxygen therapy.

- Shown to improve survival and quality of life in patients with COPD and chronic hypoxemia.
- Some patients need continuous oxygen, whereas others only require it during exertion or sleep. Get an ABG to determine need for oxygen (see Quick Hit).
- Long-standing hypoxemia may lead to pulmonary HTN and ultimately cor pul- monale. Continuous oxygen therapy for ≥18 hr/day has been shown to reduce mortality in patients with these complications by controlling pulmonary HTN.

h. Pulmonary rehabilitation—education, exercise, physiotherapy: A major goal is to improve exercise tolerance. Pulmonary rehabilitation improves functional status and quality of life.

i. Vaccination

- Influenza vaccination annually for all patients.
- Vaccination against Streptococcus pneumoniae every 5 to 6 years—should

be offered to patients with COPD over 65 years old, or under 65 who have
severe disease.

j. Antibiotics are given for acute exacerbations (see below)—increased sputum

production in volume or change in character or worsening shortness of breath.

•

- Penicillin VK (Penicillin V)
- Amoxicillin (Amoxil, Moxatag, Trimox)
- Penicillin G benzathine (Bicillin LA, Permapen)
- Cefadroxil (Duricef)
- Erythromycin (E.E.S., Erythrocin, E-Mycin, Eryc)
- Amoxicillin and clavulanate (Augmentin, Augmentin XR)

6. Treatment of COPD. Prevention. Prognosis

Treatment

1. Modalities

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Treatment guidelines

a. Mild to moderate disease.

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- Inhaled glucocorticoids may be used as well (see above). Use the lowest dose possible.
- Theophylline may be considered if the above do not adequately control symptoms.

b. Severe disease

- Medications as above.
- Continuous oxygen therapy (if patient is hypoxemic).
- Pulmonary rehabilitation.
- Triple inhaler therapy (long-acting β-agonist plus a long-acting anticholinergic plus an inhaled glucocorticoid) is an option for severe disease.

3. Acute COPD exacerbation. Definition: Increased dyspnea, sputum production, and/or cough. Acute COPD exacerbation can lead to acute respiratory failure requiring hospitalization, and possibly mechanical ventilation; potentially fatal.

a. Bronchodilators (β₂-agonist) alone or in combination with anticholinergics are first-line therapy.

b. Systemic corticosteroids are used for patients requiring hospitalization (IV methylprednisolone is a common choice). Taper with oral prednisone on clinical improvement. Do not use inhaled corticosteroids in acute exacerbations.

c. Antibiotics (azithromycin, levofloxacin, doxycycline, etc.; no antibiotic superior to another): Studies have shown that patients who receive broad-spectrum antibiotics do slightly better than a placebo group.

d. Supplemental oxygen is used to keep O₂ saturation 90% to 93%. Start with a nasal cannula; a face mask may need to be used.

• If SaO₂ is >93%, the patient is at risk of CO₂ retention from worsening V/Q mismatch, loss of hypoxic respiratory drive, and the Haldane effect.

e. Noninvasive positive pressure ventilation (NPPV) (bilevel positive airway pressure [BIPAP] or CPAP): Studies have shown a benefit in acute exacerbations. It may decrease the likelihood of respiratory failure requiring invasive mechanical ventilation.

f. Intubation and mechanical ventilation may be required if the above do not stabilize the patient. Intubate if increasing RR, increasing PaCO₂, and worsening acidosis.

7. Pneumonia: definition, etiology, pathogenesis, classification. Clinical picture, criteria for the severity of pneumonia. Diagnostics.

Pneumonia is an infection in one or both lungs. Bacteria, viruses, and fungi cause it. The infection causes inflammation in the air sacs in your lungs, which are called alveoli. The alveoli fill with fluid or pus, making it difficult to breathe.

Etiology: bacterial, viral and fungal infection (Candida species, Aspergillus species, **Mucor** specie)

i	17.36 Organisms causing community-acquired pneumonia
Bacteria	<ul style="list-style-type: none"> <i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Legionella pneumophila</i> <i>Chlamydia pneumoniae</i> <i>Haemophilus influenzae</i> <i>Staphylococcus aureus</i> <i>Chlamydia psittaci</i> <i>Coxiella burnetii</i> (Q fever) <i>Klebsiella pneumoniae</i> (Freidländer's bacillus)
Viruses	<ul style="list-style-type: none"> Influenza, parainfluenza Measles Herpes simplex Varicella Adenovirus Cytomegalovirus Coronaviruses (SARS-CoV and MERS-CoV)
(MERS = Middle East respiratory syndrome; SARS = severe acute respiratory syndrome)	

i	17.38 Investigations in community-acquired pneumonia
Blood	<ul style="list-style-type: none"> Full blood count <ul style="list-style-type: none"> Very high ($>20 \times 10^9/L$) or low ($<4 \times 10^9/L$) white cell count: marker of severity Neutrophil leucocytosis $>15 \times 10^9/L$: suggests bacterial aetiology Haemolytic anaemia: occasional complication of <i>Mycoplasma</i>
Urea and electrolytes	<ul style="list-style-type: none"> Urea $>7 \text{ mmol/L}$ ($\sim 20 \text{ mg/dL}$): marker of severity Hyponatraemia: marker of severity
Liver function tests	<ul style="list-style-type: none"> Abnormal if basal pneumonia inflames liver Hypoalbuminaemia: marker of severity
Erythrocyte sedimentation rate/C-reactive protein	<ul style="list-style-type: none"> Non-specifically elevated
Blood culture	<ul style="list-style-type: none"> Bacteraemia: marker of severity
Cold agglutinins	<ul style="list-style-type: none"> Positive in 50% of patients with <i>Mycoplasma</i>
Arterial blood gases	<ul style="list-style-type: none"> Measure when $SaO_2 < 93\%$ or when clinical features are severe, to assess ventilatory failure or acidosis
Sputum	
Sputum samples	<ul style="list-style-type: none"> Gram stain (see Fig. 17.31), culture and antimicrobial sensitivity testing
Oropharynx swab	<ul style="list-style-type: none"> Polymerase chain reaction for <i>Mycoplasma pneumoniae</i> and other atypical pathogens
Urine	<ul style="list-style-type: none"> Pneumococcal and/or <i>Legionella</i> antigen
Chest X-ray	
Lobar pneumonia	<ul style="list-style-type: none"> Patchy opacification evolves into homogeneous consolidation of affected lobe Air bronchogram (air-filled bronchi appear lucent against consolidated lung tissue) may be present (Fig. 17.33)
Bronchopneumonia	<ul style="list-style-type: none"> Typically patchy and segmental shadowing
Complications	<ul style="list-style-type: none"> Para-pneumonic effusion, intrapulmonary abscess or empyema
<i>Staphylococcus aureus</i>	<ul style="list-style-type: none"> Suggested by multilobar shadowing, cavitation, pneumatoceles and abscesses
Pleural fluid	<ul style="list-style-type: none"> Always aspirate and culture when present in more than trivial amounts, preferably with ultrasound guidance

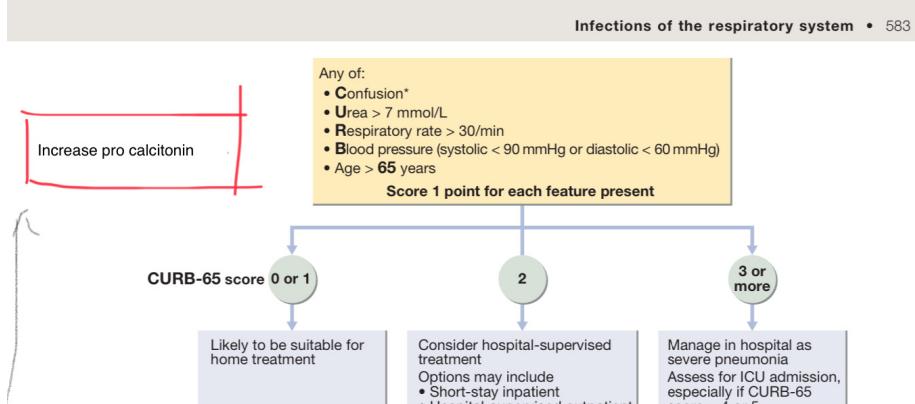
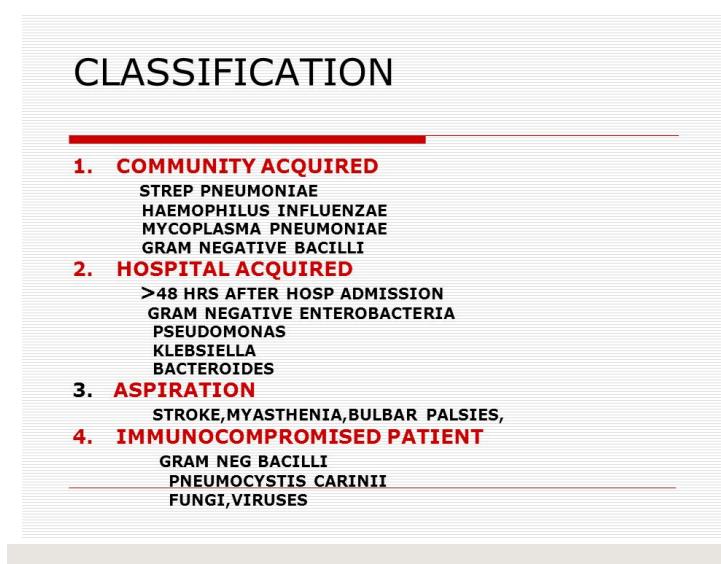


Fig. 17.32 Hospital CURB-65. *Defined as a mental test score of 8 or less, or new disorientation in person, place or time. (ICU = intensive care unit; urea of $7 \text{ mmol/L} \equiv 20 \text{ mg/dL}$)

8. Treatment of pneumonia: indications for hospitalization, antibacterial therapy, stepwise antibacterial therapy, criteria for the effectiveness of antibacterial therapy, antiviral drugs, anti-inflammatory drugs, symptomatic treatment.

- Antibiotics. These medicines are used to **treat** bacterial **pneumonia**. ...
- Cough medicine. ...
- Fever reducers/pain relievers.

i	17.40 Antibiotic treatment for community-acquired pneumonia*
	Uncomplicated CAP
	<ul style="list-style-type: none">• Amoxicillin 500 mg 3 times daily orally
	If patient is allergic to penicillin
	<ul style="list-style-type: none">• Clarithromycin 500 mg twice daily orally or Erythromycin 500 mg 4 times daily orally
	If <i>Staphylococcus</i> is cultured or suspected
	<ul style="list-style-type: none">• Flucloxacillin 1–2 g 4 times daily IV plus• Clarithromycin 500 mg twice daily IV
	If <i>Mycoplasma</i> or <i>Legionella</i> is suspected
	<ul style="list-style-type: none">• Clarithromycin 500 mg twice daily orally or IV or Erythromycin 500 mg 4 times daily orally IV plus• Rifampicin 600 mg twice daily IV in severe cases
	Severe CAP
	<ul style="list-style-type: none">• Clarithromycin 500 mg twice daily IV or Erythromycin 500 mg 4 times daily IV plus• Co-amoxiclav 1.2 g 3 times daily IV or Ceftriaxone 1–2 g daily IV or Cefuroxime 1.5 g 3 times daily IV or• Amoxicillin 1 g 4 times daily IV plus flucloxacillin 2 g 4 times daily IV
	<small>*Antibiotic use in individual patients should take into account local guidance and antibiotic sensitivity patterns.</small>
	<small>Adapted from British Thoracic Society Guidelines.</small>



17.39 Indications for referral to ITU

- CURB score of 4–5 (see Fig. 17.32), failing to respond rapidly to initial management
- Persisting hypoxia ($\text{PaO}_2 < 8 \text{ kPa}$ (60 mmHg)), despite high concentrations of oxygen
- Progressive hypercapnia
- Severe acidosis
- Circulatory shock
- Reduced conscious level

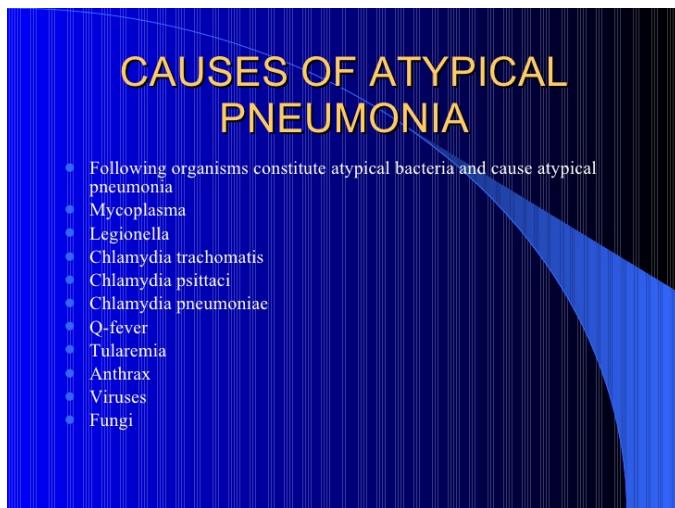
Anti viral drugs:

oseltamivir (Tamiflu®), **zanamivir (Relenza®)**, or **peramivir (Rapivab®)**, to decrease the length and severity of the illness.

Non said drug: ibuprofen

9. Pneumonias caused by atypical microorganisms. Etiology, pathogenesis, clinical features. Diagnostics. Treatment.

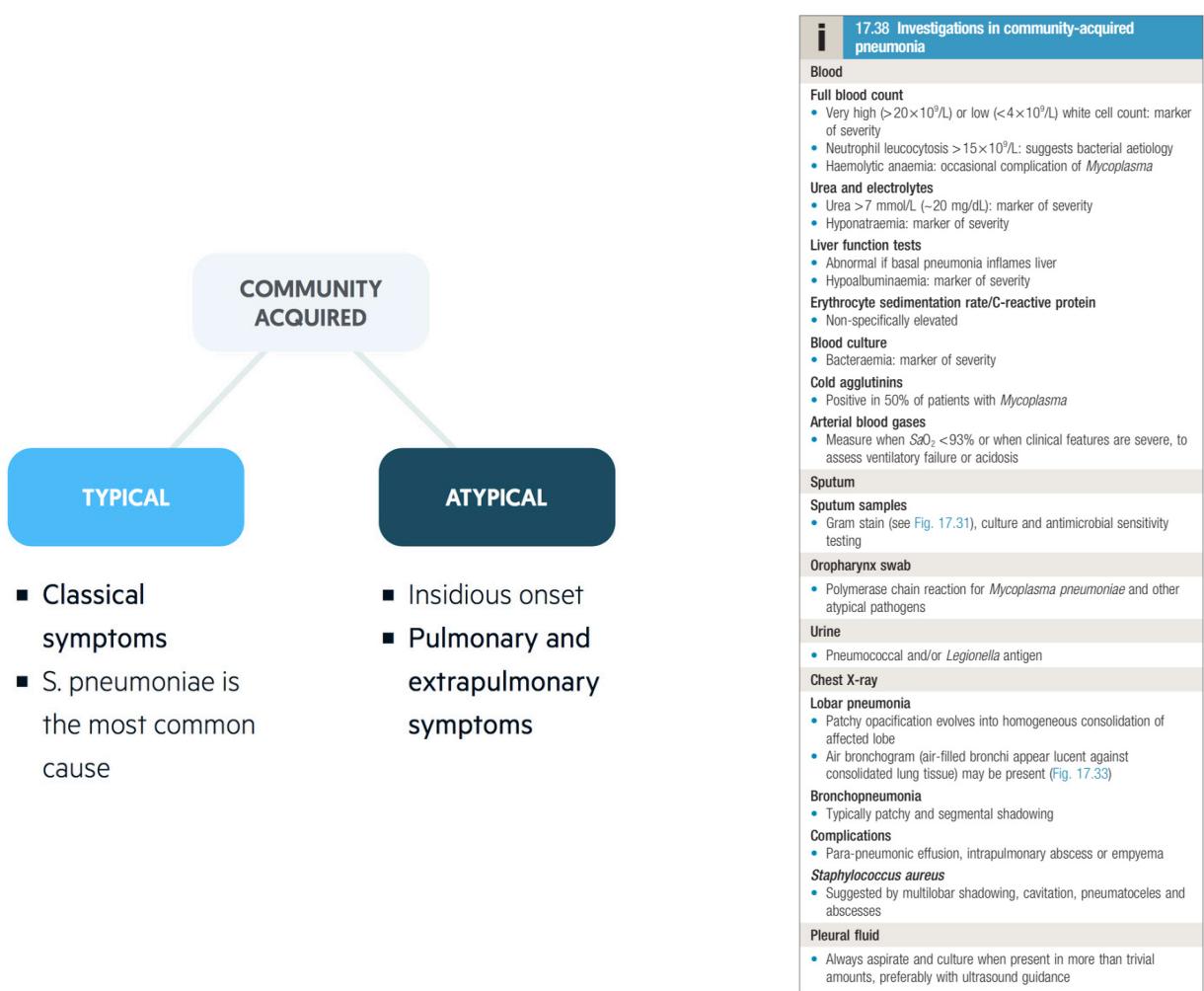
"Atypical pneumonia" is **atypical** in that it is **caused by atypical organisms** (other than *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*). These **atypical organisms** include special **bacteria**, viruses, fungi, and protozoa.



Pathogenesis:

Usually agents produce a protein to attach to epithelium of lung after that it cause stop movement of ciliary of lung which cause irritation and then inflammation.

Symptoms of atypical pneumonia tend to be milder and more persistent than those of typical pneumonia, which appear suddenly, and cause a more serious illness.



antibiotics for **atypical pneumonia**, remembering that **antibiotics** only work against infections caused by bacteria. Also, nonsteroidal anti-inflammatory drugs (NSAIDs) can help reduce symptoms, such as fever, aches, and pain.

i	17.40 Antibiotic treatment for community-acquired pneumonia*
Uncomplicated CAP	
<ul style="list-style-type: none"> Amoxicillin 500 mg 3 times daily orally 	
If patient is allergic to penicillin	
<ul style="list-style-type: none"> Clarithromycin 500 mg twice daily orally or Erythromycin 500 mg 4 times daily orally 	
If <i>Staphylococcus</i> is cultured or suspected	
<ul style="list-style-type: none"> Flucloxacillin 1–2 g 4 times daily IV plus Clarithromycin 500 mg twice daily IV 	
If <i>Mycoplasma</i> or <i>Legionella</i> is suspected	
<ul style="list-style-type: none"> Clarithromycin 500 mg twice daily orally or IV or Erythromycin 500 mg 4 times daily orally IV plus Rifampicin 600 mg twice daily IV in severe cases 	
Severe CAP	
<ul style="list-style-type: none"> Clarithromycin 500 mg twice daily IV or Erythromycin 500 mg 4 times daily IV plus Co-amoxiclav 1.2 g 3 times daily IV or Ceftriaxone 1–2 g daily IV or Cefuroxime 1.5 g 3 times daily IV or Amoxicillin 1 g 4 times daily IV plus flucloxacillin 2 g 4 times daily IV 	
*Antibiotic use in individual patients should take into account local guidance and antibiotic sensitivity patterns.	
Adapted from British Thoracic Society Guidelines.	

10. Complications of pneumonia. Diagnostics. Treatment.

i	17.41 Complications of pneumonia	i	17.38 Investigations in community-acquired pneumonia
	<ul style="list-style-type: none"> Para-pneumonic effusion – common Empyema (p. 564) Retention of sputum causing lobar collapse Deep vein thrombosis and pulmonary embolism Pneumothorax, particularly with <i>Staphylococcus aureus</i> Suppurative pneumonia/lung abscess ARDS, renal failure, multi-organ failure (p. 198) Ectopic abscess formation (<i>Staph. aureus</i>) Hepatitis, pericarditis, myocarditis, meningoencephalitis Arrhythmias (e.g. atrial fibrillation) Pyrexia due to drug hypersensitivity 		Blood <ul style="list-style-type: none"> Full blood count <ul style="list-style-type: none"> Very high ($>20 \times 10^9/L$) or low ($<4 \times 10^9/L$) white cell count: marker of severity Neutrophil leucocytosis $>15 \times 10^9/L$: suggests bacterial aetiology Haemolytic anaemia: occasional complication of <i>Mycoplasma</i> Urea and electrolytes <ul style="list-style-type: none"> Urea $>7 \text{ mmol/L}$ ($>20 \text{ mg/dL}$): marker of severity Hyponatraemia: marker of severity Liver function tests <ul style="list-style-type: none"> Abnormal if basal pneumonia inflames liver Hypoalbuminaemia: marker of severity Erythrocyte sedimentation rate/C-reactive protein <ul style="list-style-type: none"> Non-specifically elevated
	(ARDS = acute respiratory distress syndrome)		Blood culture <ul style="list-style-type: none"> Bacteraemia: marker of severity
			Cold agglutinins <ul style="list-style-type: none"> Positive in 50% of patients with <i>Mycoplasma</i>
			Arterial blood gases <ul style="list-style-type: none"> Measure when $\text{SaO}_2 < 93\%$ or when clinical features are severe, to assess ventilatory failure or acidosis
			Sputum
			Sputum samples <ul style="list-style-type: none"> Gram stain (see Fig. 17.31), culture and antimicrobial sensitivity testing
			Oropharynx swab <ul style="list-style-type: none"> Polymerase chain reaction for <i>Mycoplasma pneumoniae</i> and other atypical pathogens
			Urine <ul style="list-style-type: none"> Pneumococcal and/or <i>Legionella</i> antigen
			Chest X-ray
			Lobar pneumonia <ul style="list-style-type: none"> Patchy opacification evolves into homogeneous consolidation of affected lobe Air bronchogram (air-filled bronchi appear lucent against consolidated lung tissue) may be present (Fig. 17.33)
			Bronchopneumonia <ul style="list-style-type: none"> Typically patchy and segmental shadowing
			Complications <ul style="list-style-type: none"> Para-pneumonic effusion, intrapulmonary abscess or empyema
			<i>Staphylococcus aureus</i> <ul style="list-style-type: none"> Suggested by multilobar shadowing, cavitation, pneumatoceles and abscesses
			Pleural fluid <ul style="list-style-type: none"> Always aspirate and culture when present in more than trivial amounts, preferably with ultrasound guidance

i	17.40 Antibiotic treatment for community-acquired pneumonia
Uncomplicated CAP	
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<ul style="list-style-type: none"> • Flucloxacillin 1–2 g 4 times daily IV <i>plus</i> • Clarithromycin 500 mg twice daily IV 	
If <i>Mycoplasma</i> or <i>Legionella</i> is suspected	
<ul style="list-style-type: none"> • Clarithromycin 500 mg twice daily orally or IV <i>or</i> Erythromycin 500 mg 4 times daily orally IV <i>plus</i> • Rifampicin 600 mg twice daily IV in severe cases 	
Severe CAP	
<ul style="list-style-type: none"> • Clarithromycin 500 mg twice daily IV <i>or</i> Erythromycin 500 mg 4 times daily IV <i>plus</i> • Co-amoxiclav 1.2 g 3 times daily IV <i>or</i> Ceftriaxone 1–2 g daily IV <i>or</i> Cefuroxime 1.5 g 3 times daily IV <i>or</i> • Amoxicillin 1 g 4 times daily IV <i>plus</i> flucloxacillin 2 g 4 times daily IV 	
<p>*Antibiotic use in individual patients should take into account local guidance and antibiotic sensitivity patterns.</p>	
<p>Adapted from British Thoracic Society Guidelines.</p>	

Non steroid anti inflammatory drugs like ibuprofen

Fluid therapy

Cough drugs: dextromethorphan

11. Emergency conditions in pneumonia: acute respiratory failure (acute respiratory distress syndrome). Pathogenesis. Clinical picture. Diagnostics. Treatment.

Acute respiratory distress syndrome (ARDS) is a diffuse neutrophilic alveolitis caused by a range of conditions and characterised by bilateral radiographic infiltrates and hypoxaemia

pathogenesis involves inflammatory injury to the lung endothelium and epithelium, which causes a marked increase in lung vascular and epithelial permeability and the passage of protein-rich edema fluid into the air spaces.

Clinically, it is characterized by dyspnea, profound hypoxemia, decreased lung compliance, and diffuse bilateral infiltrates on chest radiography.

CLINICAL MANIFESTATIONS

- **Early signs/symptoms**
 - Restlessness
 - Dyspnea
 - Low blood pressure
 - Confusion
 - Extreme tiredness
 - Change in patient's behavior
 - Mood swing
 - Disorientation
 - Change in LOC
 - If pneumonia is causing ARDS then client may have
 - Cough
 - Fever

Low blood pressure and low blood oxygen can be signs of ARDS. The doctor may rely on an electrocardiogram and echocardiogram to rule out a heart condition. If a **chest X-ray** or CT scan then reveals fluid-filled air sacs in the lungs, a diagnosis for ARDS is confirmed.

no specific therapy exists for **ARDS**, **treatment** of the underlying condition is essential, along with supportive care, noninvasive ventilation or mechanical ventilation using low tidal volumes, and conservative fluid management.

12. Emergency conditions of pneumonia: septic shock. Pathogenesis. Clinical picture. Diagnostics. Treatment.

Symptoms may include:

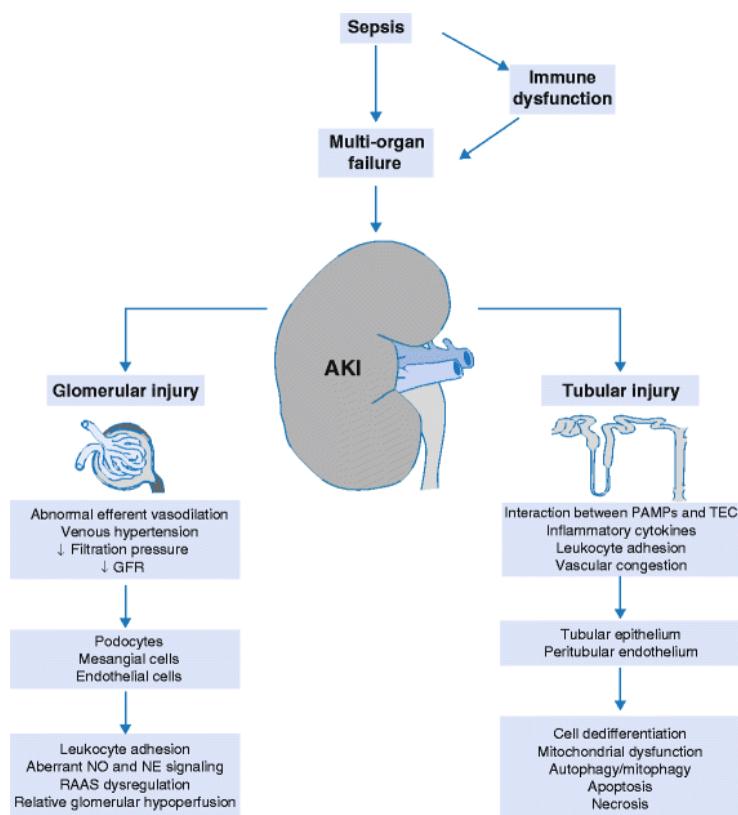
- Cool, pale arms and legs.
- High or very low temperature, chills.
- Lightheadedness.
- Little or no urine.
- Low blood pressure, especially when standing.
- Palpitations.
- Rapid heart rate.
- Restlessness, agitation, lethargy, or confusion.

Blood culture

Antibiotic therapy

Empiric combination **therapy** includes metronidazole plus levofloxacin, aztreonam, or a third- or fourth-generation cephalosporin.

13. Emergency conditions of pneumonia: acute kidney damage. Pathogenesis. Diagnostics. Treatment.



MANAGEMENT

- IV Fluids: Aim BP>100 systolic and urine output>0.5ml/kg/min
- Consider sepsis and treat accordingly
- Stop antihypertensives if hypotensive
- Stop nephrotoxins (e.g. ACEIs, ARBs, NSAIDs), diuretics and metformin
- Avoid contrast if possible

14. Pleural effusion: etiology and pathogenesis. Clinical and laboratory signs of exudate and transudate.

excess fluid between the layers of the **pleura** outside the lungs.

1. Caused by one of the following mechanisms: increased drainage of fluid into pleural space, increased production of fluid by cells in the pleural space, or decreased drainage of fluid from the pleural space (see Figure 2-6)
2. Transudative effusions—pathophysiology is due to either elevated capillary pressure in visceral or parietal pleura (e.g., CHF), or decreased plasma oncotic pressure (e.g., hypoalbuminemia)
3. Exudative effusions
 - a. Pathophysiology: caused by increased permeability of pleural surfaces or decreased lymphatic flow from pleural surface because of damage to pleural membranes or vasculature (see Clinical Pearl 2-4).
 - b. If an exudative effusion is suspected, perform the following tests on the pleural fluid: differential cell count, total protein, LDH, glucose, pH, amylase, triglycerides, microbiology, and cytology.
 - c. Exudative effusions meet at least one of the following of Light's criteria (transudates have none of these):
 - Protein (pleural)/protein (serum) >0.5
 - LDH (pleural)/LDH (serum) >0.6
 - LDH > two-thirds the upper limit of normal serum LDH

B. Causes

1. CHF is most common cause (congestive heart failure)
2. Pneumonia (bacterial)
3. Malignancies: lung (36%), breast (25%), lymphoma (10%)
4. Pulmonary embolism (PE)
5. Viral diseases
6. Cirrhosis with ascites

C. Clinical features

Symptoms (pain on inspiration and coughing) and signs of pleurisy (a pleural rub) often precede the development of an effusion, especially in patients with underlying pneumonia, pulmonary infarction or connective tissue disease.

1. Symptoms
 - a. Dyspnea on exertion
 - b. Peripheral edema
 - c. Orthopnea, paroxysmal nocturnal dyspnea
2. Signs
 - a. Dullness to percussion
 - b. Decreased breath sounds over the effusion
 - c. Decreased tactile fremitus

i**17.14 Light's criteria for distinguishing pleural transudate from exudate**

Exudate is likely if one or more of the following criteria are met:

- Pleural fluid protein:serum protein ratio >0.5
- Pleural fluid LDH:serum LDH ratio >0.6
- Pleural fluid LDH > two-thirds of the upper limit of normal serum LDH

(LDH = lactate dehydrogenase)

D. Diagnosis: Can confirm presence/evaluate size of effusion by the following:

1. CXR (PA and lateral)—look for the following:

a. Blunting of costophrenic angle

b. About 250 mL of pleural fluid must accumulate before an effusion can be detected.

c. Lateral decubitus films: more reliable than PA and lateral CXRs for detecting small pleural effusions; can also determine whether fluid is free flowing or located

2. CT scan—more reliable than CXR for detecting effusions

3. Thoracentesis

a. Thoracentesis is useful if etiology is not obvious. It provides a diagnosis in 75% of patients, and even when it is not diagnostic it provides important clinical information.

b. Therapeutic—drainage provides relief for large effusions.

c. Pneumothorax is a complication seen in 10% to 15% of thoracenteses, but it requires treatment with a chest tube in <5% of cases. Do not perform thoracentesis if effusion is <10-mm thick on lateral internal decubitus CXR.

e. Treatment

1. Transudative effusions

a. Diuretics and sodium restriction (furosemide and indapamide)

b. Therapeutic thoracentesis—only if massive effusion is causing dyspnea

2. Exudative effusions: treat underlying disease

3. Parapneumonic effusions (pleural effusion in presence of pneumonia)

a. Uncomplicated effusions: antibiotics alone (in most cases)

b. Complicated effusions or empyema

• Chest tube drainage

• Intrapleural injection of thrombolytic agents (streptokinase or urokinase); may accelerate the drainage

• Surgical lysis of adhesions may be required

15. Classification of pleurisy. Clinical manifestations, diagnosis, courses of pleural effusion. Indications and methods of puncture of the pleural cavity.

2. Transudative effusions—pathophysiology is due to either elevated capillary pressure in visceral or parenteral pleura (e.g., CHF), or decreased plasma oncotic pressure (e.g., hypoalbuminemia)

3. Exudative effusions

a. Pathophysiology: caused by increased permeability of pleural surfaces or decreased lymphatic flow from pleural surface because of damage to pleural membranes or vasculature (see Clinical Pearl 2-4).

b. If an exudative effusion is suspected, perform the following tests on the pleural fluid: differential cell count, total protein, LDH, glucose, pH, amylase, triglycerides, microbiology, and cytology.

C. Clinical features

Symptoms (pain on inspiration and coughing) and signs of pleurisy (a pleural rub) often precede the development of an effusion, especially in patients with underlying pneumonia, pulmonary infarction or connective tissue disease.

1. Symptoms

- b. Dyspnea on exertion
- c. Peripheral edema
- d. Orthopnea, paroxysmal nocturnal dyspnea

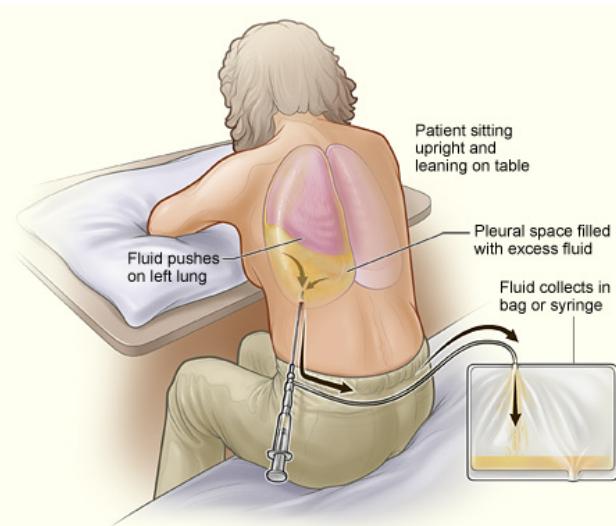
2. Signs

- a. Dullness to percussion
 - b. Decreased breath sounds over the effusion
 - c. Decreased tactile fremitus
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1. CXR (PA and lateral)—look for the following:
 - a. Blunting of costophrenic angle
 - b. About 250 mL of pleural fluid must accumulate before an effusion can be detected.
 - c. Lateral decubitus films: more reliable than PA and lateral CXRs for detecting small pleural effusions; can also determine whether fluid is free flowing or located
 2. CT scan—more reliable than CXR for detecting effusions
 3. Thoracentesis

INDICATIONS

• **Diagnostic:** determination of pleural effusion etiology (e.g. transudative versus exudative) usually requires the removal of 50 to 100mL of pleural fluid for laboratory studies. Most new effusions require diagnostic thoracentesis, an exception being a new effusion with a clear clinical diagnosis (e.g. CHF) with no evidence for superimposed pleural space infection

• **Therapeutic:** reduce dyspnea and respiratory compromise in patients with large pleural effusions. This is typically achieved by removing a much larger volume of fluid compared to the diagnostic thoracentesis



16. Treatment of pleural effusion, indications for surgical treatment. Prevention of pleural effusion.

e. Treatment

1. Transudative effusions
 - a. Diuretics and sodium restriction (furosemide and indapamide)
 - b. Therapeutic thoracentesis—only if massive effusion is causing dyspnea
2. Exudative effusions: treat underlying disease
3. Parapneumonic effusions (pleural effusion in presence of pneumonia)
 - a. Uncomplicated effusions: antibiotics alone (in most cases)
 - b. Complicated effusions or empyema
 - Chest tube drainage
 - Intrapleural injection of thrombolytic agents (streptokinase or urokinase);

may accelerate the drainage

- Surgical lysis of adhesions may be required

There is no established method for primary **prevention of pleural effusion**. However, avoidance of some risk factors, including smoke cessation, alcohol cessation, early treatment of pneumonia, and controlling heart failure, have demonstrated helpfulness.

17. Pulmonary embolism: risk factors, causes and mechanisms of development, classification, clinical manifestations, diagnosis.

••• Pulmonary Embolism

A. General characteristics

1. A PE occurs when a thrombus in another region of the body embolizes to the pulmonary vascular tree via the RV and pulmonary artery. Blood flow distal to the embolus is obstructed.
2. Consider PE and deep venous thrombosis (DVT) as a continuum of one clinical entity (venous thromboembolism)—diagnosing either PE or DVT is an indication for treatment.

Quick HIT

Complications in patients with PE who survive the initial event include:
• Recurrent PE
• Pulmonary HTN (up to two-thirds of patients)

104 • STEP-UP TO MEDICINE

CLINICAL PEARL 2-13

Risk Factors for DVT/PE

- Age >60 years
- Malignancy
- Prior history of DVT, PE
- Hereditary hypercoagulable states (factor V Leiden, protein C and S deficiency, antithrombin III deficiency)
- Prolonged immobilization or bed rest, long-distance travel
- Cardiac disease, especially CHF
- Obesity
- Nephrotic syndrome
- Major surgery, especially pelvic surgery (orthopedic procedures)
- Major trauma
- Pregnancy, estrogen use (oral contraceptives)

Quick HIT

Two important studies to know:

1. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) is a landmark study (*JAMA*. 1990;263:2753). Guides treatment if V/Q is performed.
2. The Christopher Study (*JAMA*. 2006;295:72–179). Guides treatment if spiral CT is performed.

Diseases of the Pulmonary System

3. Sources of emboli
 - a. Lower extremity DVT—PE is the major complication of DVT.
 - Most pulmonary emboli arise from thromboses in the deep veins of lower extremities above the knee (iliofemoral DVT).
 - Pulmonary emboli can also arise from the deep veins of the pelvis.
 - Although calf vein thrombi have a low incidence of embolizing to the lungs, in many patients these thrombi progress into the proximal veins, increasing the incidence of PE.
 - b. Upper extremity DVT is a rare source of emboli (it may be seen in IV drug abusers).
4. Risk factors are those for DVT (see Clinical Pearl 2-13).
5. Pathophysiology
 - a. Emboli block a portion of pulmonary vasculature, leading to increased pulmonary vascular resistance, pulmonary artery pressure, and right ventricular pressure. If it is severe (large blockage), acute cor pulmonale may result.
 - b. Blood flow decreases in some areas of the lung. Dead space is created in areas of the lung in which there is ventilation but no perfusion. The resulting hypoxemia and hypercarbia drive respiratory effort, which leads to tachypnea.
 - c. If the size of the dead space is large (large PE), clinical signs are more overt (SOB, tachypnea).
6. Course and prognosis
 - a. Most often, PE is clinically silent. **Recurrences are common**, which can lead to development of chronic pulmonary HTN and chronic cor pulmonale.
 - b. When PE is undiagnosed, mortality approaches 30%. A significant number of cases are undiagnosed (as many as 50%).
 - c. When PE is diagnosed, mortality is 10% in the first 60 minutes. Of those who survive the initial event, approximately 30% of patients will die of a recurrent PE if left untreated. Most deaths are due to recurrent PE within the first few hours of the initial PE. Treatment with anticoagulants decreases the mortality to 2% to 8%.

B. Clinical features

1. Symptoms (frequency per the PIOPED study)
 - a. Dyspnea (73%)
 - b. Pleuritic chest pain (66%)
 - c. Cough (37%)
 - d. Hemoptysis (13%)
 - e. Note that only one-third of patients with PE will have signs and symptoms of a DVT
 - f. Syncope seen in large PE
2. Signs (frequency per the PIOPED study)
 - a. Tachypnea (70%)

CLINICAL PEARL 2-14
Workup of PE

It is often difficult to definitively diagnose or rule out PE. The following tests provide an adequate basis for treating PE with anticoagulation:

- Intraluminal filling defects in central, segmental, or lobular pulmonary arteries on CTA
- DVT diagnosed with ultrasound and clinical suspicion
- Positive pulmonary angiogram (definitely proves PE)

The following can essentially rule out PE:

- Low-probability V/Q scan (or normal helical scan) and low clinical suspicion
- Negative pulmonary angiogram (definite)
- Negative D-dimer assay plus low clinical suspicion

Adapted from PIOPED data. *JAMA*. 1990;263:2753.

- b. Rales (51%)
- c. Tachycardia (30%)
- d. S_4 (24%)
- e. Increased P_2 (23%)
- f. Shock with rapid circulatory collapse in massive PE
- g. Other signs: low-grade fever, decreased breath sounds, dullness on percussion

C. Diagnosis

1. ABG levels are not diagnostic for PE (see Clinical Pearl 2-14).
 - a. PaO_2 and $PaCO_2$ are low (the latter due to hyperventilation) and pH is high; thus, there is typically a respiratory alkalosis.
 - b. The A-a gradient is usually elevated. A normal A-a gradient makes PE less likely, but cannot be relied on to exclude the diagnosis.
2. CXR—usually normal.
 - a. Atelectasis or pleural effusion may be present.
 - b. The main usefulness is in excluding alternative diagnoses.
 - c. Classic radiographic signs such as *Hampton hump* or *Westerman sign* are rarely present.
3. Venous duplex ultrasound of the lower extremities.
 - a. If there is a positive result, treat with IV anticoagulation (heparin); treatment of DVT is the same as for PE. Keep in mind that with this approach, a false positive ultrasound will result in anticoagulation of some patients who do not have DVT or PE. Also, a negative result is not helpful, as patient may still have a PE despite no DVT on ultrasound.
 - b. This test is very helpful when positive, but of little value when negative (negative results occur in 50% of patients with proven PE).
4. V/Q (Ventilation-perfusion lung) scan
 - a. Traditionally, this was the most common test used when PE is suspected, but has been replaced by CT angiography (CTA) as the initial study of choice in many medical centers.
 - b. Plays an important role in diagnosis when there is a contraindication to CTA.
 - May be useful when the chest x-ray is clear and when there is no underlying cardiopulmonary disease.
 - c. Interpretation of results: can be either normal, low-probability, intermediate-probability, or high-probability (treatment guidelines based on PIOPED study).
 - A normal V/Q scan virtually rules out PE—no further testing is needed—but a scan is almost never “normal” in anyone.
 - A high-probability V/Q scan has a very high sensitivity for PE; treat with heparin.
 - If there is low or intermediate probability, clinical suspicion determines the next step. If clinical suspicion is high, pulmonary angiography is indicated. Alternatively, perform a lower extremity duplex ultrasound to avoid

Quick HIT

Signs and symptoms are not a reliable indicator of the presence of PE. This often leads to confusion and delay in diagnosis and treatment. If, however, a patient has symptoms of PE and a DVT is found, one can make the diagnosis of PE without further testing.

Diseases of the Pulmonary System
Quick HIT

If CTA is negative for PE, and clinical probability of PE is high, there is a 5% incidence of PE. So negative results should be interpreted with caution if patient has a high clinical probability of PE.

pulmonary angiography. If the duplex is positive, treatment for DVT is the same as for PE. If the duplex is negative/uncertain, then pulmonary angiography is indicated to exclude PE.

5. CTA
 - a. Has been found to have good sensitivity (>90%) and specificity.
 - b. Can visualize very small clots (as small as 2 mm); may miss clots in small sub-segmental vessels (far periphery).
 - c. The test of choice in most medical centers.
 - d. In combination with clinical suspicion, guides treatment (see Figure 2-14).
 - e. CTA cannot be performed in patients with significant renal insufficiency because of the IV contrast that is required.
6. Pulmonary angiography is the gold standard.
 - a. Definitely diagnoses or excludes PE, but is invasive. Contrast injected into pulmonary artery branch after percutaneous catheterization of femoral vein.
 - b. Consider when noninvasive testing is equivocal and risk of anticoagulation is high, or if the patient is hemodynamically unstable and embolectomy may be required. Angiography is rarely performed because it carries a 0.5% mortality.
7. D-dimer assay
 - a. D-dimer is a specific fibrin degradation product; levels can be elevated in patients with PE and DVT.
 - b. D-dimer assay is a fairly sensitive test (90% to 98%). If results are normal and clinical suspicion is low, PE is very unlikely.

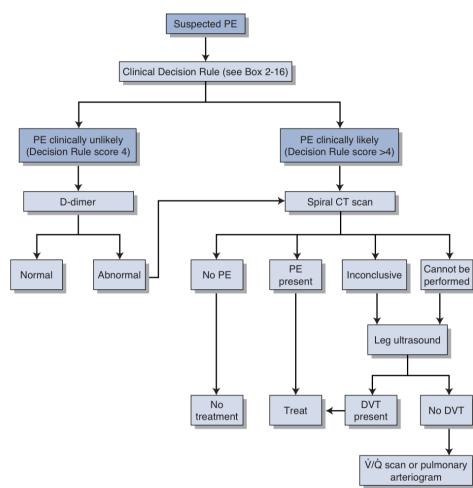


FIGURE 2-14 Workup in a patient with suspected pulmonary embolism.

<http://internalmedicinebook.com>

CLINICAL PEARL 2-15
Dichotomized Clinical Decision Rule for Suspected Acute Pulmonary Embolism (Modified Wells Criteria)

Factor	Points
Symptoms and signs of DVT	3.0
Alternative diagnosis less likely than PE	3.0
Heart rate >100 beats/min	1.5
Immobilization (>3 days) or surgery in previous 4 weeks	1.5
Previous DVT or PE	1.5
Hemoptysis	1.0
Malignancy (current therapy, or in previous 6 months, or palliative)	1.0

Score ≤4 indicates that PE is unlikely; score ≥4 indicates that PE is likely.

Adapted from Van Beur A, Butler HR, Haesman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. *JAMA*. 2006;295:172–179; Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the Simplified D-dimer. *Thromb Haemost*. 2000;83:416–420.

c. Specificity is low—D-dimer results may also be elevated in MI, CHF, pneumonia, and the postoperative state. Any cause of clot or increased bleeding can elevate the D-dimer level.

8. Overall, the workup of suspected PE is based on pretest probability. The Wells criteria (Clinical Pearl 2-15) is a scoring system that takes this into account and helps guide the workup.

a. If PE is unlikely based on the scoring system, then the pretest probability for PE is low and D-dimers can be ordered to exclude PE. If PE is likely, CTA should be performed given its high sensitivity and specificity.

D. Treatment

1. Supplemental oxygen to correct hypoxemia. Severe hypoxemia or respiratory failure requires intubation and mechanical ventilation.
2. Acute anticoagulation therapy with either unfractionated or low-molecular-weight heparin to prevent new PE. Anticoagulation prevents further clot formation, but does not lyse existing emboli or diminish thrombus size.
 - a. Start immediately on a basis of clinical suspicion. Do not wait for studies to confirm PE if clinical suspicion is high.
 - b. Give one bolus, followed by a continuous infusion for 5 to 10 days. The goal is an aPTT of 1.5 to 2.5 times control.
 - Heparin acts by promoting the action of antithrombin III.
 - Contraindications to heparin include active bleeding, uncontrolled HTN, recent stroke, and heparin-induced thrombocytopenia (HIT).
 - Low-molecular-weight heparin has better bioavailability and lower complication rates than unfractionated heparin. It has been shown to be at least as effective or more effective than unfractionated heparin.
 - c. Oral anticoagulation with warfarin or one of the novel oral anticoagulants (e.g., rivaroxaban) for long-term treatment.
 - a. Can start with heparin on day 1
 - b. Therapeutic INR is 2 to 3.
 - c. Continue for 3 to 6 months or more, depending on risk factors. Some patients at significant risk for recurrent PE (e.g., malignancy, hypercoagulable state) may be considered for lifelong anticoagulation.
 - d. Thrombolytic therapy—for example, streptokinase, tissue plasminogen activator (tPA).
 - a. Speeds up the lysis of clots.
 - b. There is no evidence that thrombolysis improves mortality rates in patients with PE. Therefore, its use is not well defined at this point.

Quick HIT

If pretest probability of PE is low, D-dimer test is a good noninvasive test to rule out PE. So if D-dimer is negative, you can rule out a clot. But if it is positive, this does not help you.

Quick HIT

Start therapeutic heparin as initial treatment. Also start warfarin at same time. Goal is therapeutic INR of 2 to 3.

Quick HIT

Why PE and DVT are problematic for physicians:

- Both are common diseases.
- Both are sometimes subtle in both.
- Noninvasive imaging tests do not always detect either condition.
- Anticoagulation carries significant risk.

18. Principles of risk stratification of early death in pulmonary embolism. Treatment. Primary and secondary prevention of pulmonary embolism.

Almost same as 17

19. Pulmonary hypertension: concept, mechanisms of development, risk factors. Clinical classification. Diagnostics. Treatment.

●●● Pulmonary Hypertension

A. General characteristics

1. Defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest
2. There are multiple pathophysiologic processes that can cause pulmonary hypertension (Clinical Pearl 2-12):
 - a. Passive due to resistance in the pulmonary venous system (e.g., left heart failure, mitral stenosis, atrial myxoma)

CLINICAL PEARL 2-12

How to Determine the Cause of Pulmonary HTN

- Perform a series of tests (CXR, PFTs, ABGs, serology, echocardiogram, cardiac catheterization). These tests will give you enough information to recognize heart disease or lung disease as the cause of pulmonary HTN.
- If the cause is not revealed (neither heart nor lung), then obtain a V/Q scan: this indicates either PE or primary pulmonary hypertension (pulmonary arterial hypertension, PAH). Note that PAH is a diagnosis of exclusion.

- b. Hyperkinetic (left-to-right cardiac shunts such as ASD or PDA)
 - c. Obstruction (e.g., PE, pulmonary artery stenosis)
 - d. Pulmonary vascular obliteration (e.g., collagen vascular diseases)
 - e. Pulmonary vasoconstriction (e.g., chronic hypoxemia, COPD, OSA)
3. Classification of pulmonary hypertension is based on the revised WHO classification system:
 - a. Group 1: Pulmonary arterial hypertension (PAH)
 - Idiopathic, familial, veno-occlusive disease, and PAH with associated conditions (connective tissue disorders, congenital shunting, HIV)
 - An abnormal increase in pulmonary arteriolar resistance leads to thickening of pulmonary arteriolar walls. This worsens the pulmonary HTN, which in turn causes further wall thickening, thus leading to a vicious cycle.
 - The cause is unknown; it usually affects young or middle-aged women.
 - The prognosis is poor. Mean survival is 2 to 3 years from the time of diagnosis.
 - b. Group 2: Left heart disease
 - Secondary to any cause of left heart failure, including mitral stenosis and mitral regurgitation
 - c. Group 3: Lung disease and/or chronic hypoxemia
 - Causes include ILD, COPD, OSA, and any other cause of chronic hypoxemia
 - d. Group 4: Chronic thromboembolic disease
 - Recurrent PE (many patients do not have symptoms of PE), including non-thrombotic etiologies (e.g., tumor emboli)
 - e. Group 5: Miscellaneous
 - Pulmonary vascular compression (e.g., tumors or lymphadenopathy), sarcoidosis, histiocytosis X, etc.

B. Clinical features

1. Symptoms
 - a. Dyspnea on exertion
 - b. Fatigue
 - c. Chest pain—exertional
 - d. Syncope—exertional (with severe disease)
2. Signs
 - a. Loud pulmonic component of the second heart sound (P_2) and subtle lift of sternum (sign of RV dilatation)—These may be the only findings, and yet the patient may still have a devastating disease!
 - b. When right ventricular failure occurs, the corresponding signs and symptoms appear (JVD, hepatomegaly, ascites, peripheral edema).

C. Diagnosis

1. ECG: Often suggests right ventricular hypertrophy—specifically, right axis deviation and right atrial abnormality are frequently present
2. CXR: Enlarged pulmonary arteries with or without clear lung fields based on the cause of pulmonary hypertension
3. Echocardiogram
 - a. Dilated pulmonary artery
 - b. Dilatation/hypertrophy of RA and RV
 - c. Abnormal movement of IV septum (due to increased right ventricular volume)
4. Right heart catheterization: reveals increased pulmonary artery pressure

Treatment:

Diuretic therapy should be prescribed for patients with right heart failure. Supplemental oxygen should be given to maintain resting PaO₂

Anticoagulation should be considered unless there is an increased risk of bleeding.

Digoxin may be useful in patients who develop atrial tachyarrhythmias.

Excessive physical activity that leads to distressing symptoms should be avoided but otherwise patients should be encouraged to remain active.

Nitrates should be avoided owing to the risk of hypotension, and β-blockers are poorly tolerated.

Cyclizine can aggravate PH and should also be avoided.

20. Acute pulmonary heart: definition, pathogenesis, diagnosis, treatment.

The initial pathophysiologic event in the production of **cor pulmonale** is an elevation of pulmonary vascular resistance. As the resistance increases, the pulmonary arterial pressure rises, and the right ventricular work increases leading to right ventricular enlargement.

••• Cor Pulmonale

A. General characteristics

1. Cor pulmonale is defined as right ventricular hypertrophy with eventual RV failure resulting from pulmonary HTN, **secondary to pulmonary disease**.
2. The definition does not encompass any of the causes of pulmonary HTN due to left-sided heart disease (such as mitral stenosis or left-to-right shunts).

B. Causes

1. It is most commonly secondary to COPD.
2. Other causes include recurrent PE, ILD, asthma, CF, sleep apnea, and pneumococcoses.

C. Clinical features

1. Decrease in exercise tolerance
2. Cyanosis and digital clubbing
3. Signs of right ventricular failure: hepatomegaly, edema, JVD
4. Parasternal lift

D. Diagnosis

1. CXR: enlargement of the RA, RV, and pulmonary arteries
2. ECG: right axis deviation, P pulmonale (peaked P waves), right ventricular hypertrophy
3. Echocardiogram: right ventricular dilatation, but normal LV size and function; useful in excluding LV dysfunction

E. Treatment

1. Treat the underlying pulmonary disorder.
2. Use diuretic therapy cautiously because patients may be preload-dependent.
3. Apply continuous long-term oxygen therapy if the patient is hypoxic.
4. Administer digoxin only if there is coexistent LV failure.
5. A variety of vasodilators have been studied; no definite improvement has been shown with their use.

21. Chronic pulmonary heart: definition, pathogenesis, diagnosis, treatment.

Chronic pulmonary heart disease happens when the right ventricle has to work too hard to pump blood to lungs that have been damaged. The lungs may have been damaged by a condition like COPD (**chronic obstructive pulmonary** disease), blood clots in the lung, or sleep apnea.

The initial pathophysiologic event in the production of **cor pulmonale** is an elevation of pulmonary vascular resistance. As the resistance increases, the pulmonary arterial pressure rises, and the right ventricular work increases leading to right ventricular enlargement.

Diagnosis:

Echo

Ecg

CXR

Treatment:

Treat the underlying disorder

Use diuretic therapy

Long term oxygen therapy

Digoxin

Vasodilators

22. Bronchiectasis. Etiology and pathogenesis. Factors contributing to the development of bronchiectasis. Clinical manifestations. Complications.

Sulbutamol and ipratropium

- d. Supplemental oxygen (keep oxygen saturation >90%).
- e. Antibiotics if severe exacerbation or suspicion of infection.
- f. Intubation for patients in respiratory failure or impending respiratory failure.
- 3. Guidelines for treatment are based on severity.

••• Bronchiectasis

A. General characteristics

- 1. There is permanent, abnormal dilation and destruction of bronchial walls with chronic inflammation, airway collapse, and ciliary loss/dysfunction leading to impaired clearance of secretions.
- 2. Less common today because modern antibiotics are used for respiratory infections.

B. Causes

- 1. Recurrent infections (airway obstruction, immunodeficiency, allergic bronchopulmonary aspergillosis, mycobacterium)
- 2. Cystic fibrosis (CF) is most common cause of bronchiectasis (accounts for half of all cases)
- 3. Primary ciliary dyskinesia (e.g., Kartagener syndrome)
- 4. Autoimmune disease (rheumatoid arthritis, systemic lupus erythematosus, Crohn disease, etc.)
- 5. Humoral immunodeficiency (abnormal lung defense), airway obstruction

C. Clinical features

- 1. Chronic cough with large amounts of mucopurulent, foul-smelling sputum
- 2. Dyspnea
- 3. Hemoptysis—due to rupture of blood vessels near bronchial wall surfaces; usually mild and self-limited, but sometimes can be brisk and present as an emergency
- 4. Recurrent or persistent pneumonia

D. Diagnosis

- 1. High-resolution CT scan is the diagnostic study of choice.
- 2. PFTs reveal an obstructive pattern.
- 3. CXR is abnormal in most cases, but findings are nonspecific.
- 4. Bronchoscopy applies in certain cases.

E. Treatment

- 1. Antibiotics for acute exacerbations—superimposed infections are signaled by change in quality/quantity of sputum, fever, chest pain, etc.
- 2. Bronchial hygiene is very important.
 - a. Hydration
 - b. Chest physiotherapy (postural drainage, chest percussion) to help remove the mucus
 - c. Inhaled bronchodilators

Quick HIT

A variety of infections can cause bronchiectasis by destroying and damaging the bronchial walls and interfering with ciliary action.

Quick HIT

The main goal in treating bronchiectasis is to prevent the complications of pneumonia and hemoptysis.

23. Treatment of bronchiectasis. Antibacterial therapy. Improvement of bronchial drainage: expectorants, mucolytics, postural drainage, therapeutic bronchoscopy. Physiotherapy. Indications for surgical treatment. Prevention of exacerbations.

E. Treatment

1. Antibiotics for acute exacerbations—superimposed infections are signaled by change in quality/quantity of sputum, fever, chest pain, etc.
2. Bronchial hygiene is very important.
 - a. Hydration
 - b. Chest physiotherapy (postural drainage, chest percussion) to help remove the mucus
 - c. Inhaled bronchodilators

amoxicillin, 500–1,000 mg three times a day for *Streptococcus pneumoniae* and *Haemophilus influenzae*; co-amoxiclav, 625 mg three times a day, for *Moraxella catarrhalis*; flucloxacillin, 500–1,000 mg four times a day, for *Staphylococcus aureus*; rifampicin, 400–600 mg once daily, fucidin, 500 mg three times a day, and ciprofloxacin, 750 mg twice a day, for *Pseudomonas aeruginosa* and coliforms (a rod-shaped bacteria normally present in the intestine).

Expectorants or mucus clearance agents, include hypertonic saline and inhaled mannitol, that keeps the airways hydrated and enhance clearance and

mucolytics, such as bromhexine, N-acetylcysteine, erdosteine and fudosteine and dornase alfa.

Postural drainage is essential in treating bronchiectasis and patients must receive physiotherapy to learn to tip themselves into a position in which the lobe can be drained. It is done at least three times daily for up to 30 minutes.

24. Abscess and gangrene of the lung. Etiology and pathogenesis. Clinical manifestations. Complications. Treatment. Indications for surgical treatment. Primary and secondary prevention.

● ● ● Lung Abscess

A. General characteristics

1. Abscess in the lung parenchyma results when infected lung tissue becomes necrotic and forms suppurative cavitary lesions. The typical case is aspiration of a large volume of oropharyngeal contents or food, with resulting pneumonia and necrosis when adequate treatment is not administered. Most patients who have aspiration pneumonia are treated promptly, thereby avoiding abscess formation.
2. By definition, a lung abscess is formed by one or more cavities, each >2 cm in diameter.
3. Lung abscesses can be complications of the following:
 - a. Aspiration of organisms.

- b. Acute necrotizing pneumonia (gram-negative rods).
 - c. Hematogenous spread of infection from distant site.
 - d. Direct inoculation with contiguous spread.
4. Microbiologic causes are mainly bacteria that colonize the oropharynx.
- a. Oral anaerobes: *Prevotella*, *Peptostreptococcus*, *Fusobacterium*, *Bacteroides* spp.
 - b. Other bacteria: *S. aureus*, *S. pneumoniae*, and aerobic gram-negative bacilli
5. Epidemiology/risk factors.
- a. The main risk factor is predisposition to aspiration. This may be seen in patients with alcoholism, drug addition, CVA, seizure disorders, general anesthesia, or a nasogastric or endotracheal tube.
 - b. Poor dental hygiene increases the content of oral anaerobes.
 - c. Edentulous patients are less likely to aspirate oropharyngeal secretions.

B. Clinical features

1. The majority of cases have an indolent onset; some present more acutely.
2. Common symptoms and signs.
 - a. Cough—Foul-smelling sputum is consistent with anaerobic infection. It is sometimes blood tinged.
 - b. Shortness of breath.
 - c. Fever, chills.
 - d. Constitutional symptoms: fatigue, malaise, weight loss.

C. Diagnosis

1. CXR
 - a. This reveals thick-walled cavitation with air–fluid levels.
 - b. Look for abscess in dependent, poorly ventilated lobes.
2. CT scan may be necessary to differentiate between abscess and empyema.
3. Sputum Gram stain and culture has low sensitivity and specificity.
4. Consider obtaining cultures via bronchoscopy or transtracheal aspiration rather than simple expectoration to avoid contamination with oral flora.

D. Treatment

1. Hospitalization is often required if lung abscess is found. Postural drainage should be performed.
2. Antimicrobial therapy.
 - a. Antibiotic regimens include coverage for the following:
 - Gram-positive cocci—ampicillin or amoxicillin/clavulanic acid, ampicillin/sulbactam, or vancomycin for *S. aureus*.
 - Anaerobes—clindamycin or metronidazole.
 - If gram-negative organisms are suspected, add a fluoroquinolone or ceftazidime.
 - b. Continue antibiotics until the cavity is gone or until CXR findings have improved considerably—this may take months!

Complications of pulmonary abscess include the following:

- Rupture into pleural space causing empyema.
- Pleural fibrosis.
- Trapped lung.
- Respiratory failure.
- Bronchopleural fistula.
- Pleural cutaneous fistula.

Indications for surgical resection of lung abscess can be divided on acute and chronic. Acute indications are: hemoptysis, prolonged sepsis and febricity, bronchopleural fistula, rupture of abscess in pleural cavity with pyopneumothorax/empyema.

Lung Abscess - Classification

- May be *primary* or *secondary*
- **Primary** = abscess in previously healthy patient or in a patient at risk for aspiration
- **Secondary** = associated bronchogenic neoplasm or immunocompromised patient

25. Bronchial asthma. Definition Prevalence. Etiology and pathogenesis. Classification. The severity of bronchial asthma. Complications.

● ● ● Asthma

A. General characteristics

1. Characteristically defined by the following triad:
 - a. Airway inflammation
 - b. Airway hyperresponsiveness
 - c. Reversible airflow obstruction
2. **Asthma can begin at any age**
3. Extrinsic versus intrinsic asthma
 - a. Extrinsic asthma (most cases)
 - Patients are atopic, that is, produce immunoglobulin E (IgE) to environmental antigens. May be associated with eczema and hay fever
 - Patients become asthmatic at a young age
 - b. Intrinsic asthma—not related to atopy or environmental triggers
4. Triggers include pollens, house dust, molds, cockroaches, cats, dogs, cold air, viral infections, tobacco smoke, medications (β -blockers, aspirin), and exercise.

B. Clinical features

1. Characterized by intermittent symptoms that include **SOB, wheezing, chest tightness, and cough**. Symptoms have variable severity and may not be present simultaneously. Usually occur within 30 minutes of exposure to triggers.
2. Symptoms are typically worse at night.
3. Wheezing (during both inspiration and expiration) is the most common finding on physical examination (see Clinical Pearl 2-2).

C. Diagnosis

1. Pulmonary function tests (PFTs) are required for diagnosis. They show an obstructive pattern: decrease in expiratory flow rates, decreased FEV₁, and decreased FEV₁/FVC ratio (<0.70).
2. Spirometry before and after bronchodilators can confirm diagnosis by proving reversible airway obstruction. If inhalation of a bronchodilator (β_2 -agonist) results in an increase in FEV₁ or FVC by at least 12%, airflow obstruction is considered reversible.
3. Peak flow (peak expiratory flow rate)—useful measure of airflow obstruction. Patients should self-monitor their peak flow:
 - a. Mild persistent asthma: Periodic monitoring is sufficient. Increase the dose of inhaled steroid if the peak flow decreases.
 - b. Moderate persistent asthma: Daily monitoring is required. Increase the dose of inhaled steroid if the peak flow decreases.
 - c. Severe persistent asthma: Daily monitoring is required. Initiate prednisone if the peak flow decreases.
4. Bronchoprovocation test.
 - a. May be useful when asthma is suspected but PFTs are nondiagnostic.
 - b. Measures ease with which airways narrow in response to stimuli.
 - c. Measures lung function before and after inhalation of increasing doses of methacholine (muscarinic agonist); hyperresponsive airways develop obstruction at lower doses.
5. Chest x-ray
 - a. Normal in mild cases; severe asthma reveals hyperinflation
 - b. Only necessary in severe asthma to exclude other conditions (e.g., pneumonia, pneumothorax, pneumomediastinum, foreign body).
6. ABGs
 - a. ABGs should be considered if the patient is in significant respiratory distress. Hypocapnia is common. Hypoxemia may be present.
 - b. If the PaCO₂ is normal or increased, respiratory failure may ensue.
 - Remember that patients with an asthma attack have an increased respiratory rate, which should cause the PaCO₂ to decrease. Increased PaCO₂ is a sign of respiratory muscle fatigue or severe airway obstruction.
 - The patient should be hospitalized and mechanical ventilation considered.

D. Treatment

1. Available modalities (see Table 2-3).
 - a. Inhaled β_2 -agonists.
 - Short-acting β_2 -agonists (e.g., albuterol) are used for acute attacks (rescue). Onset is 2 to 5 minutes, duration is 4 to 6 hours.
 - Long-acting versions (e.g., salmeterol) are especially good with nighttime asthma and exercise-induced asthma.
 - b. Inhaled corticosteroids for moderate to severe asthma.
 - Preferred over oral steroids due to fewer systemic side effects. (Oral steroids are reserved for severe, persistent asthma.)

TABLE 2-3 Chronic Treatment of Asthma

Severity	Long-term Control Medications
Mild intermittent (symptoms two or fewer times per week)	None
Mild persistent (symptoms two or more times per week but not every day)	Low dose inhaled corticosteroid
Moderate persistent (daily symptoms; frequent exacerbations)	Daily inhaled corticosteroid (low dose) with long-acting inhaled β_2 -agonist, or daily inhaled corticosteroid (medium dose). Alternatives include adding a leukotriene modifier or theophylline to the daily inhaled corticosteroid (low dose)
Severe persistent (continual symptoms, frequent exacerbations, limited physical activity)	Daily inhaled corticosteroid (medium or high dose) and long-acting inhaled β_2 -agonists. Omalizumab (anti-IgE) may be considered additionally. If poor control, systemic corticosteroids should be considered.

Note: All patients should have intermittent short-acting inhaled β_2 -agonists as needed plus long-term control medications based on the severity of their asthma.

From The National Asthma Education and Prevention Program, *Expert Panel Report 2*, 1997.

- If used on a regular basis, airway hyperresponsiveness decreases, and the number of asthma exacerbations decreases.
- c. Montelukast—leukotriene modifiers—less efficacious than inhaled steroids but useful for prophylaxis of mild exercise-induced asthma and for control of mild to moderate persistent disease. They may allow reductions in steroid and bronchodilator requirements.
- d. Cromolyn sodium/nedocromil sodium.
 - Only for prophylaxis (e.g., before exercise); rarely used in adults.
- 2. Treatment of acute severe asthma exacerbation (hospital admission).
 - a. Inhaled β_2 -agonist (first-line therapy).
 - Via nebulizer or MDI (see Clinical Pearl 2-3).
 - Mainstays of emergency treatment—have an onset of action of minutes.
 - Assess patient response to bronchodilators (clinically and with peak flows).
 - b. Corticosteroids
 - Traditionally given intravenously initially, but may also be given orally if given in equivalent doses.
 - Taper IV or oral corticosteroids, but only when clinical improvement is seen.
 - Initiate inhaled corticosteroids at the beginning of the tapering schedule.
 - c. Third-line agent includes IV magnesium—not as effective as β -agonists, magnesium helps with bronchospasm but only used in acute severe exacerbation that has not responded to above medications (albuterol, steroids, oxygen).

CLINICAL PEARL

2-3

MDIs and Nebulizers

- An MDI with a spacer is just as effective as a nebulizer. A spacer is a holding chamber that obviates the need to coordinate inhalation and depression of the canister, and thus makes the use of an MDI easier. Its use leads to a greater bronchodilator effect because more of the drug is deposited in smaller airways and less accumulates in the oropharynx.
- A nebulizer is no more effective than an MDI, but patients may report greater relief of symptoms simply because it provides more medication. It may be preferred by patients with very severe asthma unresponsive to MDIs.

- d. Supplemental oxygen (keep oxygen saturation >90%).
- e. Antibiotics if severe exacerbation or suspicion of infection.
- f. Intubation for patients in respiratory failure or impending respiratory failure.
- 3. Guidelines for treatment are based on severity.

Complications of asthma

- fatigue.
- underperformance or absence from work.
- inability to exercise, leading to other health problems such as high blood pressure or weight gain.
- permanent problems with your lungs.
- repeated visits to hospital.
- psychological problems including stress, anxiety and depression.
- learning problems in children.

26. Clinical symptoms and diagnosis of exogenous and endogenous asthma. The role of allergy testing. Differential diagnosis.

Asthma

A. General characteristics

1. Characteristically defined by the following triad:
 - a. Airway inflammation
 - b. Airway hyperresponsiveness
 - c. Reversible airflow obstruction
2. **Asthma can begin at any age**
3. Extrinsic versus intrinsic asthma
 - a. Extrinsic asthma (most cases)
 - Patients are atopic, that is, produce immunoglobulin E (IgE) to environmental antigens. May be associated with eczema and hay fever
 - Patients become asthmatic at a young age
 - b. Intrinsic asthma—not related to atopy or environmental triggers
4. Triggers include pollens, house dust, molds, cockroaches, cats, dogs, cold air, viral infections, tobacco smoke, medications (β -blockers, aspirin), and exercise.

B. Clinical features

1. Characterized by intermittent symptoms that include **SOB, wheezing, chest tightness, and cough**. Symptoms have variable severity and may not be present simultaneously. Usually occur within 30 minutes of exposure to triggers.
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C. Diagnosis

C. Diagnosis

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 - c. Severe persistent asthma: Daily monitoring is required. Initiate prednisone if the peak flow decreases.
4. Bronchoprovocation test.
 - a. May be useful when asthma is suspected but PFTs are nondiagnostic.
 - b. Measures ease with which airways narrow in response to stimuli.
 - c. Measures lung function before and after inhalation of increasing doses of methacholine (muscarinic agonist); hyperresponsive airways develop obstruction at lower doses.
5. Chest x-ray
 - a. Normal in mild cases; severe asthma reveals hyperinflation
 - b. Only necessary in severe asthma to exclude other conditions (e.g., pneumonia, pneumothorax, pneumomediastinum, foreign body).
6. ABGs
 - a. ABGs should be considered if the patient is in significant respiratory distress. **Hypocarbia** is common. Hypoxemia may be present.
 - b. If the PaCO₂ is normal or increased, respiratory failure may ensue.
 - Remember that patients with an asthma attack have an increased respiratory rate, which should cause the PaCO₂ to decrease. Increased PaCO₂ is a sign of respiratory muscle fatigue or severe airway obstruction.
 - The patient should be hospitalized and mechanical ventilation considered.

Strategy for the diagnosis-1

- **History of asthma development**

(age of onset, atopy, response to treatment, smoking)

- **Severity of disease**

(exacerbations, hospitalisations, ICU admissions)

- **Exogenous aggravating factors**

(allergens, occupationnal agents, drugs, foods..)

- **Endogenous aggravating factors**

(Rhinosinusitis, GER, OSA, influence of menstruation, psychiatric disease..)

- **Miscellaneous**

(adherence, aduers effect, psychosocial circumstances)

- **Physical examination (specific points of attention)**

(Body mass index, Nasal polypes, cardiac failure, adverse effects of treatment)

27. The mechanism of a bronchial asthma attack. Arresting an attack of bronchial asthma. Indications for hospitalization of patients.

During an **asthma** episode, inflamed airways react to environmental triggers such as smoke, dust, or pollen. The airways narrow and produce excess mucus, making it difficult to breathe. In essence, **asthma** is the result of an immune response in the **bronchial** airways.

Almost same as 26

28. Asthmatic status (acute severe asthma), predisposing factors. Criteria for diagnosis and stage of the course. Relief of asthmatic status and its prevention.

Acute severe asthma, formerly known as status asthmaticus, is defined as severe asthma unresponsive to repeated courses of beta-agonist therapy such as inhaled albuterol, levalbuterol, or subcutaneous epinephrine. It is a medical emergency that requires immediate recognition and treatment.

risk factors responsible for acute severe asthma were poor drug compliance (68%), which was statistically significant (p -value <0.0001), exposure to house dust (61%) and smoke (42%) (p <0.0001).

MILD/MODERATE	SEVERE	LIFE THREATENING
<ul style="list-style-type: none">• SpO₂ >92%• RR: <30 (over 5's) <40 (under 5's)• No or minimal accessory muscle use• Feeding well or talking in full sentences• Wheeze (may only be audible with stethoscope)	<ul style="list-style-type: none">• SpO₂ <92%• PEFR 33-50% predicted• RR: >30 (over 5's) >40 (under 5's)• Too breathless to feed or talk• HR: >125 (over 5's) >140 (under 5's)• Use of accessory muscles• Audible wheeze	<ul style="list-style-type: none">• SpO₂ <92%• PEFR <33% predicted• Silent chest• Poor respiratory effort• Altered consciousness• Agitation/confusion• Exhaustion• Cyanosis

C. Diagnosis

1. Pulmonary function tests (PFTs) are required for diagnosis. They show an obstructive pattern: decrease in expiratory flow rates, decreased FEV₁, and decreased FEV₁/FVC ratio (<0.70).
2. Spirometry before and after bronchodilators can confirm diagnosis by proving reversible airway obstruction. If inhalation of a bronchodilator (β_2 -agonist) results in an increase in FEV₁ or FVC by at least 12%, airflow obstruction is considered reversible.
3. Peak flow (peak expiratory flow rate)—useful measure of airflow obstruction. Patients should self-monitor their peak flow:
 - a. Mild persistent asthma: Periodic monitoring is sufficient. Increase the dose of inhaled steroid if the peak flow decreases.
 - b. Moderate persistent asthma: Daily monitoring is required. Increase the dose of inhaled steroid if the peak flow decreases.
 - c. Severe persistent asthma: Daily monitoring is required. Initiate prednisone if the peak flow decreases.
4. Bronchoprovocation test.
 - a. May be useful when asthma is suspected but PFTs are nondiagnostic.
 - b. Measures ease with which airways narrow in response to stimuli.
 - c. Measures lung function before and after inhalation of increasing doses of methacholine (muscarinic agonist); hyperresponsive airways develop obstruction at lower doses.
5. Chest x-ray
 - a. Normal in mild cases; severe asthma reveals hyperinflation
 - b. Only necessary in severe asthma to exclude other conditions (e.g., pneumonia, pneumothorax, pneumomediastinum, foreign body).
6. ABGs
 - a. ABGs should be considered if the patient is in significant respiratory distress.
Hypocapnia is common. Hypoxemia may be present.
 - b. If the PaCO₂ is normal or increased, respiratory failure may ensue.
 - Remember that patients with an asthma attack have an increased respiratory rate, which should cause the PaCO₂ to decrease. Increased PaCO₂ is a sign of respiratory muscle fatigue or severe airway obstruction.
 - The patient should be hospitalized and mechanical ventilation considered.

rapid administration of oxygen, inhalations with bronchodilators and systemic corticosteroids. Inhaled bronchodilators may include selective b₂-agonists, adrenaline and anticholinergics.

DISEASES OF CIRCULATORY ORGANS

29. Arterial hypertension. The global prevalence of hypertension. Risk factors. Etiology and pathogenesis. The scheme of examination for arterial hypertension.

C. Definitions

1. Classification
 - a. Normal—Systolic BP <120 and diastolic BP <80
 - b. Prehypertension—Systolic BP 120 to 139 or diastolic BP 80 to 89
 - c. Stage I—Systolic BP 140 to 159 or diastolic BP 90 to 99
 - d. Stage II—Systolic BP \geq 160 or diastolic BP \geq 100
2. Hypertensive urgency—Severe HTN (typically systolic BP \geq 180 or diastolic BP \geq 120) in an asymptomatic patient
3. Hypertensive emergency—Severe HTN with end organ damage (e.g., neurologic changes, myocardial ischemia, aortic dissection, etc.)

B. Risk factors

1. Age—both systolic and diastolic BP increase with age.
2. Gender—more common in men (gap narrows over age 60); men have higher complication rates.
3. Race—it is twice as common in African-American patients as in Caucasian patients; African-American patients have higher complication rates (stroke, renal failure, heart disease).
4. Obesity, sedentary lifestyle, dyslipidemia.
5. Family history.
6. Increased sodium intake—this correlates with increased prevalence in large populations, although not in individuals; individual susceptibility to the effects of high salt intake varies.
7. Alcohol—intake of more than 2 oz (8 oz of wine or 24 oz of beer) per day is associated with HTN.

••• Hypertension

A. General characteristics

1. Essential hypertension (HTN) (i.e., there is no identifiable cause) applies to more than 95% of cases of HTN.
2. Secondary HTN has many identifiable causes.
 - a. Renal/renovascular disease—renal artery stenosis (most common cause of secondary HTN), chronic renal failure, polycystic kidneys.
 - b. Endocrine causes—hyperaldosteronism, thyroid or parathyroid disease, Cushing syndrome, pheochromocytoma, hyperthyroidism, acromegaly.
 - c. Medications—oral contraceptives, decongestants, estrogen, appetite suppressants, chronic steroids, tricyclic antidepressants (TCAs), nonsteroidal anti-inflammatory drugs (NSAIDs).
 - d. Coarctation of the aorta.
 - e. Cocaine, other stimulants.
 - f. Obstructive sleep apnea (OSA).

E. Diagnosis

1. BP measurement
 - a. Unless the patient has severe HTN or evidence of end-organ damage, never diagnose HTN on the basis of one BP reading. Establish the diagnosis on the basis of at least two readings over a span of 4 or more weeks
 - b. Observe the following to obtain an accurate BP reading
 - The arm should be at heart level, and the patient should be seated comfortably
 - Have the patient sit quietly for at least 5 minutes before measuring BP
 - Make sure the patient has not ingested caffeine or smoked cigarettes in the past 30 minutes (both elevate BP temporarily)
 - Use a cuff of adequate size (a cuff that is too small can falsely elevate BP readings). The bladder within the cuff should encircle at least 80% of the arm
2. Order the following laboratory tests to evaluate target organ damage and assess overall cardiovascular risk
 - a. Urinalysis
 - b. Chemistry panel: serum K¹, BUN, Cr
 - c. Fasting glucose (if patient is diabetic, check for microalbuminuria)
 - d. Lipid panel
 - e. ECG
3. If the history and physical examination (H&P) or laboratory tests suggest a secondary cause of HTN, order appropriate tests

30. Classification of primary arterial hypertension. Clinical picture. Complications of arterial hypertension.

C. Definitions

1. Classification
 - a. Normal—Systolic BP <120 and diastolic BP <80
 - b. Prehypertension—Systolic BP 120 to 139 or diastolic BP 80 to 89
 - c. Stage I—Systolic BP 140 to 159 or diastolic BP 90 to 99
 - d. Stage II—Systolic BP \geq 160 or diastolic BP \geq 100
2. Hypertensive urgency—Severe HTN (typically systolic BP \geq 180 or diastolic BP \geq 120) in an asymptomatic patient

Complications

- Heart attack or stroke. ...
- Aneurysm. ...
- Heart failure. ...
- Weakened and narrowed blood vessels in your kidneys. ...
- Thickened, narrowed or torn blood vessels in the eyes. ...
- Metabolic syndrome. ...
- Trouble with memory or understanding. ...
- Dementia.

31.The protection of the hypertension-mediated organ damage. Risk stratification and prognosis for AH.

2. Lifestyle changes, listed in order of effect on BP reduction:
 - a. Weight loss lowers BP significantly. In patients with central obesity (who often have coexisting diabetes, hyperlipidemia, and other risk factors), weight loss is particularly important because multiple risk factors are reduced concomitantly.
 - b. Follow a low-saturated-fat diet rich in fruits, vegetables, and low-fat dairy products (DASH diet).
 - c. Exercise regularly. Regular aerobic exercise can lower BP (and reduces overall cardiovascular risk).
 - d. Reduce salt intake. Reduction in dietary salt has been shown to reduce BP. Recommend either a no-added-salt diet (4 g sodium/day) or a low-sodium diet (2 g/day).
 - e. Avoid excessive alcohol consumption. Alcohol has a pressor action, and excessive use can increase BP.
 - f. Others—stop unnecessary medications that may contribute to HTN. Engage in appropriate stress management practices.
3. Pharmacologic treatment (seven classes of drugs) (Table 12-2).
 - a. Thiazide diuretics.
 - Because “salt-sensitive” HTN is more common in African-American patients, diuretics are a good initial choice for these patients (though a calcium channel blocker is equally recommended as a first-line option).
 - A good option in patients with osteoporosis (increases calcium reabsorption in the nephron).
 - b. β -Blockers—decrease HR and cardiac output and decrease renin release.
 - A good option in patients with CHF, CAD, or atrial fibrillation; a poor option in patients with obstructive lung disease, heart block, or depression.
 - c. ACE inhibitors.
 - Inhibit the renin–angiotensin–aldosterone system by inhibiting the conversion of angiotensin I to angiotensin II. Angiotensin II normally causes vasoconstriction, aldosterone release, and ventricular remodeling.
 - ACE also acts to degrade bradykinin, so inhibition results in excess levels in the lung that can cause a chronic dry cough.
 - Preferred in all diabetic patients because of their protective effect on kidneys; also a good option for patients with CHF, CAD.
 - d. Angiotensin II receptor blockers (ARBs).
 - Also inhibit renin–angiotensin–aldosterone system.
 - ARBs have the same beneficial effects on the kidney in diabetic patients as ACE inhibitors and do not cause a chronic cough; ACE inhibitors and ARBs should not be used in combination.
 - e. Calcium channel blockers—cause vasodilation of arteriolar vasculature.
- f. α -Blockers—decrease arteriolar resistance.
 - May be of benefit if the patient has concurrent benign prostatic hyperplasia (BPH) but these are not considered first- or second-line agents.
- g. Vasodilators (hydralazine and minoxidil)—not commonly used; typically given in combination with β -blockers and diuretics to patients with refractory HTN.
4. General principles of treatment.
 - a. BP should be lowered to <140/90 mm Hg for patients <60 years old, and <150/90 mm Hg for patients \geq 60 years old. If patients \geq 60 years old previously tolerated a BP goal <140/90 mm Hg, their treatment does not need to be changed.
 - b. Each of the antihypertensive agents is roughly equally effective in lowering BP. But there is great variability in how patients respond to each drug. The three classes of drugs that are used for initial monotherapy are thiazide diuretics, long-acting calcium channel blockers (most often a dihydropyridine), and ACE inhibitors or ARBs. β -Blockers are not commonly used as initial monotherapy in the absence of a specific indication because of adverse effects on some cardiovascular outcomes especially in elderly patients.
 - c. Drug treatment is often lifelong. However, patients with very mild HTN may be able to be weaned off medication if their BP can be lowered and controlled with nonpharmacologic measures. However, these patients need frequent BP checks.
 - d. ALLHAT trial compared chlorthalidone, amlodipine, lisinopril, and doxazosin in patients with essential HTN and at least one CAD risk factor. The doxazosin arm was terminated early because of an increased risk of CHF compared to chlorthalidone. The other three agents were similar in regards to rates of fatal CAD and nonfatal MI, however chlorthalidone reduced rates of CAD, stroke, CHF, and angina when compared to lisinopril.
 - e. ACCOMPLISH trial showed that treatment with antihypertensive combination therapy—the ACE inhibitor benazepril plus the calcium channel blocker amlodipine—was more effective than treatment with the ACE inhibitor plus diuretic. Based on this trial, it makes sense to start monotherapy with either a calcium channel blocker or an ACE inhibitor, so that the other can be added if combination therapy is needed. Despite the findings of this trial, thiazide diuretics remain a common initial drug choice.
 - f. If the patient's response to one agent is not adequate, there are two options:
 - Increase the dose of the first agent to the maximum dose.
 - Add a second medication (thiazide, calcium channel blocker, ACE inhibitor, or ARB); if target BP not achieved, increase the dose of each as necessary until the maximum dose is achieved.
 - g. If a patient's response is still inadequate with two agents, consider a third agent and referral to a HTN specialist.
 - h. When to start treatment.
 - The decision of when to start pharmacologic treatment is based on the patient's total cardiovascular risk, not just the elevation in BP.

32.The main groups of antihypertensive drugs. Differential use of antihypertensive drugs of various mechanisms of action. Principles of combined pharmacotherapy.

Same as 31

33. Hypertensive crises: definition, classification and causes. Treatment of hypertensive crises.

A **hypertensive crisis** is a severe increase in blood pressure that can lead to a stroke. Extremely high blood pressure — a top number (systolic pressure) of 180 millimeters of mercury (mm Hg) or higher or a bottom number (diastolic pressure) of 120 mm Hg or higher — can damage blood vessels.

Classification:

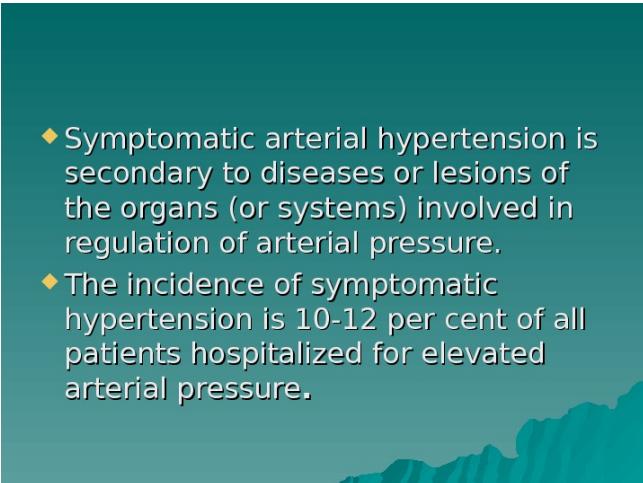
hypertensive urgency when there is no end-organ damage, and as **hypertensive emergency** when there is a risk of death evidenced by end-organ damage.

Causes:

- Stroke.
- Heart attack.
- Heart failure.
- Kidney failure.
- Rupture of your body's main artery (aorta)
- Interaction between medications.
- Convulsions during pregnancy (eclampsia)

The drugs of choice in treating patients with a **hypertensive crisis** and eclampsia or pre-eclampsia are hydralazine, labetalol, and nicardipine (5,6). **Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, direct renin inhibitors, and sodium nitroprusside** are **contraindicated in treating these patients**.

34. Symptomatic arterial hypertension. Classification.

- 
- ◆ Symptomatic arterial hypertension is secondary to diseases or lesions of the organs (or systems) involved in regulation of arterial pressure.
 - ◆ The incidence of symptomatic hypertension is 10-12 per cent of all patients hospitalized for elevated arterial pressure.

Classification of symptomatic/secondary HTN

- nephrogenic hypertension (with chronic kidney disease);
- vasorenal hypertension (associated with renal artery disease)
- endocrine hypertension
- AH, caused by the lesion of large arterial vessels
- Neurogenic or central hypertension
- medicines and exogenous substances that can cause hypertension

35. Renal arterial hypertension. Clinics, diagnostics and treatment.

Renal hypertension is caused by a narrowing in the **arteries** that deliver blood to the **kidney**. One or both kidneys' **arteries** may be narrowed. This is a condition called **renal artery stenosis**. When the kidneys receive low blood flow, they act as if the low flow is due to dehydration.

Symptoms of renal artery stenosis

- continued high blood pressure (hypertension) despite taking medications to help lower it.
- decreased kidney function.
- fluid retention.
- edema (swelling), especially in your ankles and feet.
- decreased or abnormal kidney function.
- an increase of proteins in your urine.

If renovascular **hypertension** is suspected, ultrasonography, magnetic resonance angiography (MRA), or radionuclide imaging may be done to identify patients who should have **renal angiography**, the definitive test.

Treatments for Renal Hypertension

Medications are used first to try to control high blood pressure in renal hypertension. The most important blood pressure medications to treat renal hypertension include:

- **ACE inhibitors** (angiotensin converting enzyme inhibitors). These include **ramipril**, **benazepril**, **captopril**, **lisinopril**, and others.
- ARBs (angiotensin II receptor blockers). Examples include **candesartan**, **losartan**, **olmesartan** and **valsartan**.

36. Endocrine arterial hypertension (Itsenko-Cushing syndrome and disease, pheochromocytoma, primary hyperaldosteronism, thyrotoxicosis).

Endocrine arterial hypertension (EAH) a condition in which hormone excess results in clinically significant hypertension is a rare cause of hypertension. However in the last years its prevalence has increased, mostly due to the improvement of diagnostic work-up.

Cushing's disease is a specific type of **Cushing's syndrome** caused by a pituitary tumor leading to excessive production of ACTH (adrenocorticotrophic hormone). Excessive ACTH stimulates the adrenal cortex to produce high levels of cortisol, producing the **disease** state.

Other names: Hypercortisolism, Itsenko-Cushing ...

Symptoms: [High blood pressure](#), abdominal o...

Causes: Prolonged exposure to [cortisol](#)

Treatment: Based on underlying cause

Pheochromocytoma is a rare tumor of adrenal gland tissue. It results in the release of too much epinephrine and norepinephrine, hormones that control heart rate, metabolism, and blood pressure.

Primary aldosteronism (PA), also known as **primary hyperaldosteronism** or Conn's syndrome, refers to the excess production of the hormone aldosterone from the adrenal glands, resulting in low renin levels. This abnormality is caused by hyperplasia or tumors.

Causes: [Enlargement of both adrenal glands](#), ...

Diagnostic method: Blood test for aldosterone....

Other names: Primary hyperaldosteronism, Co...

Symptoms: [High blood pressure](#), poor vision, h...

Thyotoxicosis means an excess of thyroid hormone in the body. Having this condition also means that you have a low level of thyroid stimulating hormone, TSH, in your bloodstream, because the pituitary gland senses that you have “enough” thyroid hormone. If you are thyrotoxic, you may feel nervous or irritable, because all of your body’s functions are speeding up.

Hyperthyroidism, also referred to as an overactive thyroid is the most common cause of thyrotoxicosis and, occurs when your thyroid gland produces too much thyroid hormone.

37. Atherosclerosis. The social significance of the problem. Epidemiology.

Pathogenesis. Risk factors.

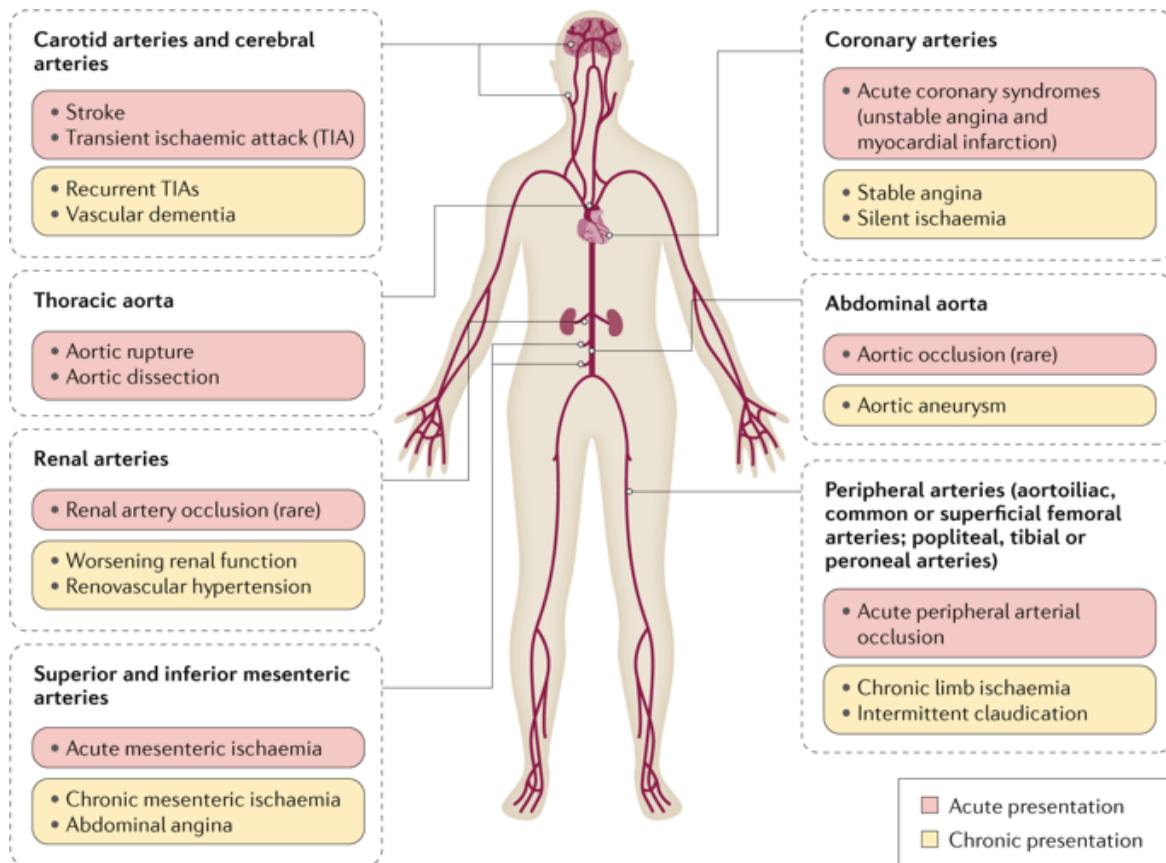
Atherosclerosis refers to the buildup of fats, cholesterol and other substances in and on your artery walls (plaque), which can restrict blood flow. The plaque can burst, triggering a blood clot. Although atherosclerosis is often considered a heart problem, it can affect arteries anywhere in your body.

Atherogenesis can be divided into five key **steps**, which are 1) endothelial dysfunction, 2) formation of lipid layer or fatty streak within the intima, 3) migration of leukocytes and smooth muscle cells into the vessel wall, 4) foam cell formation and 5) degradation of extracellular matrix.

Major Risk Factors

- Unhealthy blood cholesterol levels. This includes high LDL cholesterol (sometimes called "bad" cholesterol) and low HDL cholesterol (sometimes called "good" cholesterol).
- High blood pressure. ...
- Smoking. ...
- Insulin resistance. ...
- Diabetes. ...
- Overweight or obesity. ...
- Lack of physical activity. ...
- Unhealthy diet.
- Age
- Family history of heart disease

38. Features of clinical manifestations of different localizations of atherosclerosis (aorta, brain arteries, mesenteric arteries). The value of laboratory and instrumental research methods in the diagnosis of atherosclerosis.



include an angiogram (Arteriogram), cholesterol tests, a chest x-ray, a CT (computed tomography) scan, Duplex scanning, an echocardiogram, an electrocardiogram (ECG or EKG), an exercise stress test .

39. Principles of treatment of atherosclerosis, depending on the degree of risk of developing cardiovascular diseases and the type of hyperlipidemia: lifestyle modification, lipid-lowering diet, exercise, drugs.

Treatment

Lifestyle changes, such as eating a healthy diet and exercising, are often the most appropriate treatment for atherosclerosis. Sometimes, medication or surgical procedures may be recommended as well.

Medications

Various drugs can slow — or even reverse — the effects of atherosclerosis. Here are some common choices:

- **Cholesterol medications.** Aggressively lowering your low-density lipoprotein (LDL) cholesterol, the "bad" cholesterol, can slow, stop or even reverse the buildup of fatty deposits in your arteries. Boosting your high-density lipoprotein (HDL) cholesterol, the "good" cholesterol, may help, too.
Your doctor can choose from a range of cholesterol medications, including drugs known as statins and fibrates. In addition to lowering cholesterol, statins have additional effects that help stabilize the lining of your heart arteries and prevent atherosclerosis.
- **Anti-platelet medications.** Your doctor may prescribe anti-platelet medications, such as aspirin, to reduce the likelihood that platelets will clump in narrowed arteries, form a blood clot and cause further blockage.
- **Beta blocker medications.** These medications are commonly used for coronary artery disease. They lower your heart rate and blood pressure, reducing the demand on your heart and often relieve symptoms of chest pain. Beta blockers reduce the risk of heart attacks and some heart rhythm problems.
- **Angiotensin-converting enzyme (ACE) inhibitors.** These medications may help slow the progression of atherosclerosis by lowering blood pressure and producing other beneficial effects on the heart arteries. ACE inhibitors can also reduce the risk of recurrent heart attacks.
- **Calcium channel blockers.** These medications lower blood pressure and are sometimes used to treat angina.
- **Water pills (diuretics).** High blood pressure is a major risk factor for atherosclerosis. Diuretics lower blood pressure.
- **Other medications.** Your doctor may suggest certain medications to control specific risk factors for atherosclerosis, such as diabetes. Sometimes specific medications to treat symptoms of atherosclerosis, such as leg pain during exercise, are prescribed.

Surgical procedures

Sometimes more aggressive treatment is needed to treat atherosclerosis. If you have severe symptoms or a blockage that threatens muscle or skin tissue survival, you may be a candidate for one of the following surgical procedures:

- **Angioplasty and stent placement.** In this procedure, your doctor inserts a long, thin tube (catheter) into the blocked or narrowed part of your artery. A second catheter with a deflated balloon on its tip is then passed through the catheter to the narrowed area. The balloon is then inflated, compressing the deposits against your artery walls. A mesh tube (stent) is usually left in the artery to help keep the artery open.
- **Endarterectomy.** In some cases, fatty deposits must be surgically removed from the walls of a narrowed artery. When the procedure is done on arteries in the neck (the carotid arteries), it's called a carotid endarterectomy.
- **Fibrinolytic therapy.** If you have an artery that's blocked by a blood clot, your doctor may use a clot-dissolving drug to break it apart.
- **Bypass surgery.** Your doctor may create a graft bypass using a vessel from another part of your body or a tube made of synthetic fabric. This allows blood to flow around the blocked or narrowed artery.

40. Primary and secondary prevention of atherosclerosis.

Prevention of Atherosclerotic Vascular Disease

Primary prevention of atherosclerosis

- Cessation of cigarette smoking
- Control of hypertension
- Weight loss
- Exercise, and lowering total and LDL blood cholesterol levels while increasing HDL (e.g., by diet or through statins).
- Statin use may also modulate the inflammatory state of the vascular wall.
- Risk factor stratification and reduction should even begin in childhood.

Prevention of Atherosclerotic Vascular Disease

Secondary prevention involves use of –

- Aspirin (anti-platelet agent),
- Statins, and beta blockers (to limit cardiac demand),
- Surgical interventions (e.g., coronary artery bypass surgery, carotid endarterectomy).
- These can successfully reduce recurrent myocardial or cerebral events.

QUESTION

ANSWER

ANSWER

41. Ischemic (coronary) heart disease. The urgency of the problem, social significance, epidemiology. Classification of CHD.

Coronary heart disease (CHD), or **coronary artery disease**, develops when the **coronary** arteries become too narrow. The **coronary** arteries are the blood vessels that supply oxygen and blood to the **heart**. CHD tends to develop when cholesterol builds up on the **artery** walls, creating plaques.

Types include stable angina, unstable angina, myocardial infarction, and sudden **cardiac** death.

42. Risk factors for CHD.

- Premature family history
- Smoking
- Hypertension
- Dyslipidemia
 - Elevated low-density lipoprotein cholesterol
 - Low levels of high-density lipoprotein cholesterol
 - Elevated triglycerides
 - Elevated lipoprotein (a)
 - Elevated apolipoprotein B
 - High number of small dense particles
- Metabolic syndrome
- Diabetes
- Obesity
- Physical inactivity (and reduced fitness)
- Psychological risk factors

43. CHD: atherosclerotic cardiosclerosis. Diagnostic criteria. Principles of treatment.

Coronary heart disease (CHD), or **coronary artery disease**, develops when the **coronary** arteries become too narrow. The **coronary** arteries are the blood vessels that supply oxygen and blood to the **heart**. CHD tends to develop when cholesterol builds up on the **artery** walls, creating plaques.

Cardiosclerosis: induration of the heart caused by formation of fibrous tissue in the cardiac muscle.

1. electrocardiogram (ECG)
2. exercise stress tests.
3. X-rays.
4. echocardiogram.
5. blood tests.
6. coronary angiography.
7. radionuclide tests.
8. MRI scans.

- Cholesterol-modifying medications. ...
- Aspirin. ...
- Beta blockers. ...
- Calcium channel blockers. ...
- Ranolazine. ...
- Nitroglycerin. ...
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

44. Angina pectoris. Clinical variants: stable and unstable. Treatment.

Stable angina occurs predictably. It happens when you exert yourself physically or feel considerable stress. Stable angina doesn't typically change in frequency and it doesn't worsen over time. Unstable angina is chest pain that occurs at rest or with exertion or stress.

Stable angina usually at rest will be relieved but unstable angina at rest occur

Stable duration is 2-5 min but unstable angina more than 10 min

The unstable angina is more severe

Stable:

Unstable:

D. Treatment

1. Risk factor modification
 - a. Smoking cessation cuts coronary heart disease (CHD) risk in half by 1 year after quitting.
 - b. HTN—vigorous BP control reduces the risk of CHD, especially in diabetic patients.
 - c. Hyperlipidemia—reduction in serum cholesterol with lifestyle modifications and HMG-CoA reductase inhibitors (statins) reduce CHD risk.
 - d. DM—type II diabetes is considered to be a cardiovascular heart disease equivalent, and strict glycemic control should be strongly emphasized.
 - e. Obesity—weight loss modifies other risk factors (diabetes, HTN, and hyperlipidemia) and provides other health benefits.
 - f. Exercise is critical; it minimizes emotional stress, promotes weight loss, and helps reduce other risk factors.
 - g. Diet: Reduce intake of saturated fat (<7% total calories) and cholesterol (<200 mg/day).
2. Medical therapy
 - a. Aspirin
 - Indicated in all patients with CAD
 - Decreases morbidity—reduces risk of MI
 - b. β -Blockers—block sympathetic stimulation of heart. First-line choices include atenolol and metoprolol.
 - Reduce HR, BP, and contractility, thereby decreasing cardiac work (i.e., β -blockers lower myocardial oxygen consumption)
 - Have been shown to reduce the frequency of coronary events
 - c. Nitrates—cause generalized vasodilation
 - Relieve angina; reduce preload myocardial oxygen demand
 - May prevent angina when taken before exertion

C. Treatment

1. Hospital admission on a floor with continuous cardiac monitoring. Establish IV access and give supplemental oxygen. Provide pain control with nitrates (below) and morphine.
2. Aggressive medical management is indicated—treat as in MI except for fibrinolysis.
 - a. Aspirin
 - b. Clopidogrel—shown to reduce the incidence of MI in patients with USA compared with aspirin alone in the CURE trial. This benefit persists whether the patient undergoes revascularization with PCI or not. Patients presenting with USA should generally be treated with aspirin and clopidogrel for 9 to 12 months, in accordance with the CURE trial. This may be altered however, according to the bleeding risk of each patient
 - c. β -Blockers—first-line therapy if there are no contraindications
 - d. Low-molecular-weight heparin (LMWH) is superior to unfractionated heparin. Goal is to prevent progression or development of a clot
 - Should be continued for at least 2 days
 - Enoxaparin is the drug of choice based on clinical trials (see Quick Hit on ESSENCE trial).
 - e. Nitrates are first-line therapy
 - f. Oxygen if patient is hypoxic
 - g. Glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban) can be helpful adjuncts in USA, especially if patient is undergoing PTCA or stenting
 - h. Morphine is controversial—provides good pain relief but may mask worsening symptoms
 - i. Replacement of deficient electrolytes, especially K^+ and Mg^{2+}
3. Cardiac catheterization/revascularization
 - a. More than 90% of patients improve with the above medical regimen within 1 to 2 days.
 - b. The choice of invasive management (early catheterization/revascularization within 48 hours) versus conservative management (catheterization/revascularization only if medical therapy fails) is controversial.
 - No study has shown a significant difference in outcomes between these two approaches.

- Effect on prognosis is unknown; main benefit is symptomatic relief
 - Can be administered orally, sublingually, transdermally, intravenously, or in paste form. For chronic angina, oral or transdermal patches are used. For acute coronary syndromes (see below), either sublingual, paste, or IV forms are used
 - d. Calcium channel blockers
 - Cause coronary vasodilation and afterload reduction, in addition to reducing contractility.
 - Now considered a **secondary treatment** when β -blockers and/or nitrates are not fully effective. None of the calcium channel blockers have been shown to lower mortality in CAD. In fact, they may increase mortality because they raise heart rates. Do not routinely use these drugs in CAD.
 - e. If congestive heart failure (CHF) is also present, treatment with ACE inhibitors and/or diuretics may be indicated as well.
3. Revascularization
- May be preferred for high-risk patients, although there is some controversy whether revascularization is superior to medical management for a patient with stable angina and stenosis >70%
 - Two methods—PCI and CABG—see Clinical Pearl 1-4
 - Revascularization does **not** reduce incidence of MI, but does result in significant improvement in symptoms
4. Management decisions (general guidelines)—risk factor modification and aspirin are indicated in all patients. Manage patients according to overall risk
- Mild disease (normal EF, mild angina, single-vessel disease)
 - Nitrates (for symptoms and as prophylaxis) and a β -blocker are appropriate
 - Consider calcium channel blockers if symptoms continue despite nitrates and β -blockers
 - Moderate disease (normal EF, moderate angina, two-vessel disease)
 - If the above regimen does not control symptoms, consider coronary angiography to assess suitability for revascularization (either PCI or CABG)
 - Severe disease (decreased EF, severe angina, and three-vessel/left main or left anterior descending disease)
 - Coronary angiography and consider for CABG

45. Functional classes of angina pectoris.

Canadian cardiovascular society functional classification of angina

CLASS	Characteristic
Class I	No angina with ordinary activity. Angina with strenuous activity
Class II	Angina during ordinary activity, e.g. walking up hills, walking rapidly upstairs, with mild limitation of activities
Class III	Angina with low levels of activity, e.g. walking 50–100 yards on the flat, walking up one flight of stairs, with marked restriction of activities
Class IV	Angina at rest or with any level of exercise

46. Diagnosis of angina pectoris. Characteristics of an angina attack.

C. Diagnosis (of CAD)

1. Note that physical examination in most patients with CAD is normal (see Clinical Pearl 1-1)
2. Resting ECG
 - a. Usually normal in patients with stable angina
 - b. Q waves are consistent with a prior MI
 - c. If ST segment or T-wave abnormalities are present during an episode of chest pain, then treat as unstable angina (USA)
3. Stress test—useful for patients with an intermediate pretest probability of CAD based upon age, gender, and symptoms.
 - a. Stress ECG
 - Highest sensitivity if patients have normal resting ECG, such that changes can be noted.
 - Test involves recording ECG before, during, and after exercise on a treadmill.
 - 75% sensitive if patients are able to exercise sufficiently to increase heart rate to 85% of maximum predicted value for age. A person's maximum heart rate is calculated by subtracting age from 220 (220—age).
 - Exercise-induced ischemia results in subendocardial ischemia, producing ST segment depression. So the detection of ischemia on an ECG stress test is based on presence of ST segment depression.
 - Other positive findings include onset of heart failure or ventricular arrhythmia during exercise or hypotension.
 - *Patients with a positive stress test result should undergo cardiac catheterization.*
 - b. Stress echocardiography
 - Performed before and immediately after exercise. Exercise-induced ischemia is evidenced by wall motion abnormalities (e.g., akinesis or dyskinesis) not present at rest.
 - Favored by many cardiologists over stress ECG. It is more sensitive in detecting ischemia, can assess LV size and function, can diagnose valvular disease, and can be used to identify CAD in the presence of pre-existing ECG abnormalities (see Clinical Pearl 1-2).
 - *Again, patients with a positive test result should undergo cardiac catheterization.*

CLINICAL PEARL 1-2

Types of Stress Tests

Test	Method of Detecting Ischemia
Exercise ECG	ST segment depression
Exercise or dobutamine echocardiogram	Wall motion abnormalities
Exercise or dipyridamole perfusion study (thallium/technetium)	Decreased uptake of the nuclear isotope during exercise

How is unstable angina diagnosed?

1. blood tests, to check for creatine kinase and cardiac biomarkers (troponin) that leak from your heart muscle if it's been damaged.

Angina symptoms include chest pain and discomfort, possibly described as pressure, squeezing, burning or fullness. You may also have pain in your arms, neck, jaw, shoulder or back. Other symptoms that you may have with angina include: Dizziness.

- c. Information gained from a stress test can be enhanced by stress myocardial perfusion imaging after IV administration of a radioisotope such as thallium 201 during exercise.
 - Viable myocardial cells extract the radioisotope from the blood. No radioisotope uptake means no blood flow to an area of the myocardium.
 - *It is important to determine whether the ischemia is reversible*, that is, whether areas of hypoperfusion are perfused over time as blood flow eventually equalizes. Areas of *reversible* ischemia may be rescued with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG). Irreversible ischemia, however, indicates infarcted tissue that cannot be salvaged.
 - Perfusion imaging increases the sensitivity and specificity of exercise stress tests, but is also more expensive, subjects the patient to radiation, and is often not helpful in the presence of a left bundle branch block.
4. If the patient cannot exercise, perform a *pharmacologic stress test*.
 - a. IV adenosine, dipyridamole, or dobutamine can be used. The cardiac stress induced by these agents takes the place of exercise. This can be combined with an ECG, an echocardiogram, or nuclear perfusion imaging.
 - b. IV adenosine and dipyridamole cause generalized coronary vasodilation. Since diseased coronary arteries are already maximally dilated at rest to increase blood flow, they receive relatively less blood flow when the entire coronary system is pharmacologically vasodilated.
 - c. Dobutamine increases myocardial oxygen demand by increasing heart rate, blood pressure, and cardiac contractility.
5. Holter monitoring (ambulatory ECG) can be useful in detecting silent ischemia (i.e., ECG changes not accompanied by symptoms). The Holter monitor is also used for evaluating arrhythmias, heart rate variability, and to assess pacemaker and implantable cardioverter-defibrillator (ICD) function.
 - a. Continuously examines patient's cardiac rhythm over 24 to 72 hours during normal activity
 - b. Useful for evaluating unexplained syncope and dizziness as well
6. Cardiac catheterization with coronary angiography (see Clinical Pearl 1-3, Figure 1-1)
 - a. Coronary angiography—definitive test for CAD. Often performed with concurrent PCI or for patients being considered for revascularization with CABG.

CLINICAL PEARL 1-3

Cardiac Catheterization

1. Most accurate method of determining a specific cardiac diagnosis.
2. Provides information on hemodynamics, intracardiac pressure measurements, cardiac output, oxygen saturation, etc.
3. Coronary angiography (see below) is almost always performed as well for visualization of coronary arteries.
4. There are many indications for cardiac catheterization (generally performed when revascularization or other surgical intervention is being considered):
 - After a positive stress test.
 - Acute MI with intent of performing angiogram and PCI.
 - In a patient with angina in any of the following situations: When noninvasive tests are nondiagnostic, angina that occurs despite medical therapy, angina that occurs soon after MI, and any angina that is a diagnostic dilemma.
 - If patient is severely symptomatic and urgent diagnosis and management are necessary.
 - For evaluation of valvular disease, and to determine the need for surgical intervention.

Coronary Arteriography (Angiography)

1. Most accurate method of identifying the presence and severity of CAD; the standard test for delineating coronary anatomy.
2. Main purpose is to identify patients with severe coronary disease to determine whether revascularization is needed. Revascularization with PCI involving a balloon and/or a stent can be performed at the same time as the diagnostic procedure.
3. Coronary stenosis >70% may be significant (i.e., it can produce angina).

Figure 6-8: Courtesy of Dr. William Daley.)

- b. Contrast is injected into coronary vessels to visualize any stenotic lesions. This defines the location and extent of coronary disease.
- c. Angiography is the most accurate test for detecting CAD.
- d. If CAD is severe (e.g., left main or three-vessel disease), refer patient for surgical revascularization (CABG).

47. Vasospastic stenocardia (Prinzmetal's stenocardia).

Pathogenesis. Diagnostics. Treatment.

Definition. **Vasospastic** angina indicates a form of angina caused by coronary artery spasm, which consists of a sudden occlusive vasoconstriction of a segment of an epicardial artery, resulting in a dramatic reduction of coronary blood flow¹.

Pathogenesis:

Vascular smooth muscle hyper-reactivity is thought to be central to the **pathogenesis** of **vasospastic** angina [1,4,5]. Spasm may occur in the absence of any preceding increase in myocardial oxygen demand (eg, exercise) and in normal or diseased vessels.

Vasospastic angina diagnostic criteria elements

1. Nitrate-responsive angina—during spontaneous episode, with at least one of the following:
 - Rest angina—especially between night and early morning
 - Marked diurnal variation in exercise tolerance—reduced in morning
 - Hyperventilation can precipitate an episode
 - Calcium channel blockers (but not β -blockers) suppress episodes
- 2.
3. Transient ischaemic ECG changes—during spontaneous episode, including any of the following in at least two contiguous leads:
 - ST segment elevation ≥ 0.1 mV
 - ST segment depression ≥ 0.1 mV
 - New negative U waves
- 4.
5. Coronary artery spasm—defined as transient total or subtotal coronary artery occlusion ($>90\%$ constriction) with angina and ischaemic ECG changes either spontaneously or in response to a provocative stimulus (typically acetylcholine, ergot, or hyperventilation)

Nitrates(nitroglycerin and isorbid) and calcium channel blockers(nifedipine , amlodipine , verapamil) are the mainstays of medical therapy for vasospastic angina. Other agents have been tried with variable success, including endothelin antagonists such as bosentan.

48. Silent myocardial ischemia. Causes, diagnosis, treatment.

Silent myocardial ischemia is defined as the presence of objective evidence of **myocardial ischemia** in the absence of chest discomfort or another anginal equivalent symptom (eg, dyspnea, nausea, diaphoresis, etc).

Most **silent ischemia** occurs when one or more coronary arteries are narrowed by plaque. It can also occur when the heart is forced to work harder than normal. People who have diabetes or who have had a heart attack are most likely to develop **silent ischemia**.

Patient classification is as one of three types of silent ischemia:

- Type I: This is the least common form and occurs in completely asymptomatic patients with CAD (which may be severe) in the absence of anginal symptoms.
- Type II: This type occurs in patients with documented previous myocardial infarction.
- Type III: This is the most common form and occurs in patients with the usual forms of chronic stable angina, unstable angina, and vasospastic angina.

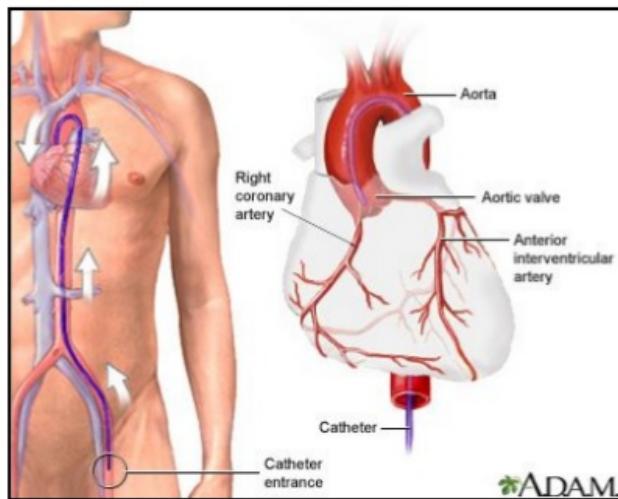
Medical Therapy: Beta blockers appear to be most effective and also improve outcomes. Although beta-blockers produce the greatest reduction in the number and duration of ischemic episodes, calcium channel blockers are also effective. Monotherapy with calcium channel blockers should primarily be used in patients with a specific identified pathogenic mechanism which is expected to respond better to calcium channel blockers (e.g., vasospastic angina), or if a patient is intolerant of beta blockers. Aspirin (antiplatelet therapy) and statin (lipid-lowering therapy) are also used.

The **diagnosis of silent ischemia** in asymptomatic patients with known coronary artery disease is adequately achieved by stress testing. 24 hour monitoring allows to assess the total **ischemic** burden which has prognostic implications.

49. The role of ECG in the detection of coronary insufficiency (ECG with pharmacological and stress tests, myocardial scintigraphy).

50. The role of invasive methods in the diagnosis and treatment of coronary artery disease (coronary angiography).

Coronary Angiography - Heart Test



This is a real time invasive contrast imaging of the coronary arteries. Special catheters are introduced via femoral or radial artery and contrast is injected directly into the coronary arteries. Continuous simultaneous fluoroscopy is done. The imaging is 2D and assessment of the blocks is by assessing the diameter reduction of the artery.

Method of Coronary Angiography (CAG)

The special catheter needs to be guided into the coronary artery to perform CAG. The access can be from femoral artery (in the groin) or Radial artery (at the wrist). Traditionally CAG was done through femoral route. It is often uncomfortable for the patient and needs overnight stay at hospital. However, femoral artery being a larger vessel, this approach is easier and versatile.

51.Treatment of CHD. Relief and prevention of an angina attack.

Indications for surgical treatment. Prevention (primary and secondary). Prognosis.

- Cholesterol-modifying medications.
- Aspirin.
- Beta blockers.
- Calcium channel blockers.
- Ranolazine.
- Nitroglycerin.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).

Prevention:

- Eat lots of fruits, vegetables, whole grains, and low-fat sources of protein such as nuts and fish.
- Exercise regularly.
- Maintain a healthy weight and keep diabetes under control.
- Quit smoking.

clear **indications for surgical** revascularization exist in patients with unstable **angina pectoris**, i.e., progressive **angina** and onset of rest **pain** and nocturnal **angina** in spite of adequate medical **therapy**.

Primary prevention: control diet, exercise regular, weight control , stop smoking

Secondary prevention: medication control by statin , aspirin,...

Prognosis: depend on god 😅

52. Acute coronary syndrome without ST segment elevation: definition, clinic, diagnostics. Treatment. Indications for coronary angiography.

Acute coronary syndrome (ACS) is a **syndrome** (set of **signs** and **symptoms**) due to decreased **blood flow** in the **coronary arteries** such that part of the **heart muscle** is unable to function properly or **dies**.^[1] The most common symptom is **chest pain**, often radiating to the left shoulder^[2] or angle of the jaw, crushing, central and associated with **nausea** and **sweating**. Many people with acute coronary syndromes present with symptoms other than chest pain, particularly, women, older patients, and patients with **diabetes mellitus**.^[3]

Symptoms:

The cardinal symptom of critically decreased blood flow to the heart is chest pain, experienced as tightness around or over the chest and (often, but not always) radiating to the left arm and the left angle of the jaw. This may be associated with **diaphoresis** (sweating), **nausea** and **vomiting**, as well as **shortness of breath**. In many cases, the sensation is "atypical", with pain experienced in different ways or even being completely absent (which is more likely in female patients and those with **diabetes**). Some may report **palpitations**, anxiety or a sense of impending doom (**angor animi**) and a feeling of being acutely ill. The description of the chest discomfort as a pressure has little utility in aiding a diagnosis as it is not **specific** for ACS.^[7]

Though ACS is usually associated with **coronary thrombosis**, it can also be associated with **cocaine use**.^[8] Chest pain with features characteristic of cardiac origin (angina) can also be precipitated by profound **anemia**, **brady-** or **tachycardia** (excessively slow or rapid heart rate), **low** or **high blood pressure**, severe **aortic valve stenosis** (narrowing of the valve at the beginning of the aorta), **pulmonary artery hypertension** and a number of other conditions.^[9]

Diagnosis:

Electrocardiogram[edit]

In the setting of acute chest pain, the [electrocardiogram](#) is the investigation that most reliably distinguishes between various causes.^[12] The ECG should be done as early as practicable, including in the ambulance if possible.^[13] If this indicates acute heart damage (elevation in the *ST segment*, new **left bundle branch block**), treatment for a heart attack in the form of [angioplasty](#) or [thrombolysis](#) is indicated immediately (see below). In the absence of such changes, it is not possible to immediately distinguish between unstable angina and NSTEMI.

Imaging and blood tests[edit]

As it is only one of the many potential causes of [chest pain](#), the patient usually has a number of tests in the [emergency department](#), such as a [chest X-ray](#), [blood tests](#) (including [myocardial markers](#) such as [troponin I](#) or [T](#), and [H-FABP](#) and/or a [D-dimer](#) if a [pulmonary embolism](#) is suspected), and [telemetry](#) (monitoring of the heart rhythm).

Combination of troponin levels (less than 5 ng/l) with low [TIMI](#) scores can help to predict those with low possibility of myocardial infarction and discharge them safely from the emergency department.^[10] [Coronary CT angiography](#) combined with Troponin levels is also helpful to [triage](#) those who are susceptible to ACS. F-fluoride [positron emission tomography](#) is also helpful in identifying those with high risk, lipid-rich coronary plaques.^[10]

Prediction scores

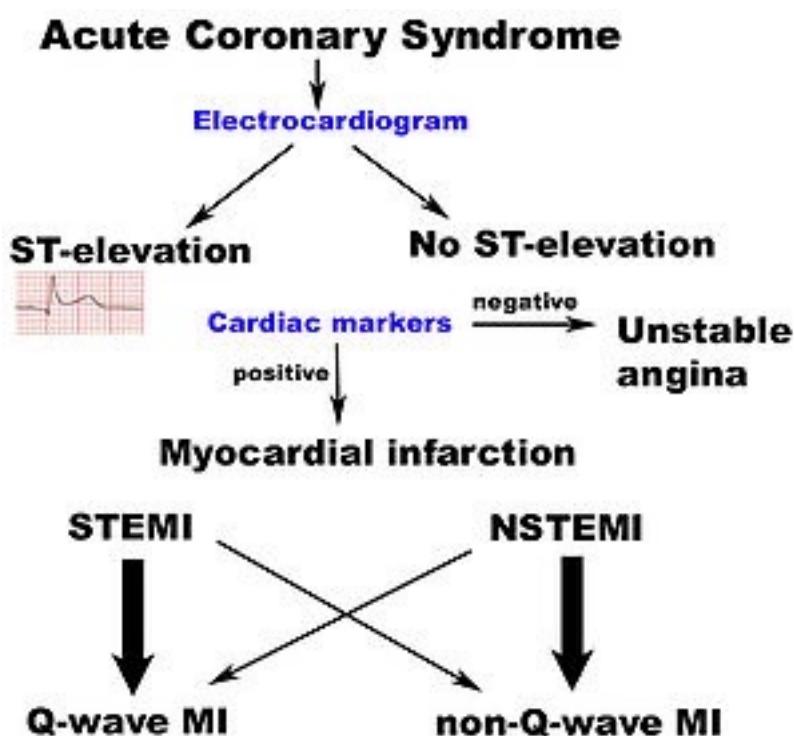
Treatment:

aspirin, a second [platelet inhibitor](#) such as clopidogrel, prasugrel or ticagrelor, and heparin (usually a [low-molecular weight heparin](#)), with intravenous [nitroglycerin](#) and [opioids](#) if the pain persists. The heparin-like drug known as [fondaparinux](#) appears to be better than [enoxaparin](#).^[23]

Indication of angio:

A blood test is generally performed for cardiac troponins twelve hours after onset of the pain. If this is positive, [coronary angiography](#) is typically performed on an urgent basis, as this is highly predictive of a heart attack in the near-future. If the troponin is negative, a treadmill exercise test or a thallium scintigram may be requested.

If there is no evidence of ST segment elevation on the [electrocardiogram](#), delaying urgent [angioplasty](#) until the next morning is not inferior to doing so immediately.^[24] Using [statins](#) in the first 14 days after ACS reduces the risk of further ACS.^[25]



53. Acute coronary syndrome with ST-segment elevation: definition, clinic, diagnostics. Treatment.

Acute coronary syndrome (ACS) is a **syndrome** (set of signs and symptoms) due to decreased blood flow in the **coronary arteries** such that part of the **heart muscle** is unable to function properly or dies.[1] The most common symptom is **chest pain**, often radiating to the left shoulder[2] or angle of the jaw, crushing, central and associated with **nausea** and **sweating**. Many people with acute coronary syndromes present with symptoms other than chest pain, particularly, women, older patients, and patients with **diabetes mellitus**.[3]

Symptoms:

The cardinal symptom of critically decreased blood flow to the heart is chest pain, experienced as tightness around or over the chest and (often, but not always) radiating to the left arm and the left angle of the jaw. This may be associated with **diaphoresis** (sweating), **nausea** and **vomiting**, as well as **shortness of breath**. In many cases, the sensation is "atypical", with pain experienced in different ways or even being completely absent (which is more likely in female patients and those with **diabetes**). Some may report **palpitations**, anxiety or a sense of impending doom (**angor animi**) and a feeling of being acutely ill. The description of the chest discomfort as a pressure has little utility in aiding a diagnosis as it is not **specific** for ACS.[7]

Though ACS is usually associated with **coronary thrombosis**, it can also be associated with **cocaine use**.[8] Chest pain with features characteristic of cardiac origin (angina) can also be precipitated by profound **anemia**, **brady-** or **tachycardia** (excessively slow or rapid heart rate), **low** or **high blood pressure**, severe **aortic valve stenosis** (narrowing of the valve at the beginning of the aorta), **pulmonary artery hypertension** and a number of other conditions.[9]

Diagnosis:

Electrocardiogram[edit]

In the setting of acute chest pain, the **electrocardiogram** is the investigation that most reliably distinguishes between various causes.[12] The ECG should be done as early as practicable, including in the ambulance if possible.[13] If this indicates acute heart damage (elevation in the **ST segment**, new **left bundle branch block**), treatment for a heart attack in the form of **angioplasty** or **thrombolysis** is indicated immediately (see below). In the absence of such changes, it is not possible to immediately distinguish between unstable angina and NSTEMI.

Imaging and blood tests[edit]

As it is only one of the many potential causes of **chest pain**, the patient usually has a number of tests in the **emergency department**, such as a **chest X-ray**, **blood tests** (including **myocardial markers** such as **troponin I** or **T**, and **H-FABP** and/or a **D-dimer** if a **pulmonary embolism** is suspected), and **telemetry** (monitoring of the heart rhythm).

Combination of troponin levels (less than 5 ng/l) with low **TIMI** scores can help to predict those with low possibility of myocardial infarction and discharge them safely from the emergency department. [10] **Coronary CT angiography** combined with Troponin levels is also helpful to **triage** those who are susceptible to ACS. F-fluoride **positron emission tomography** is also helpful in identifying those with high risk, lipid-rich coronary plaques.[10]

Prediction scores

Treatment:

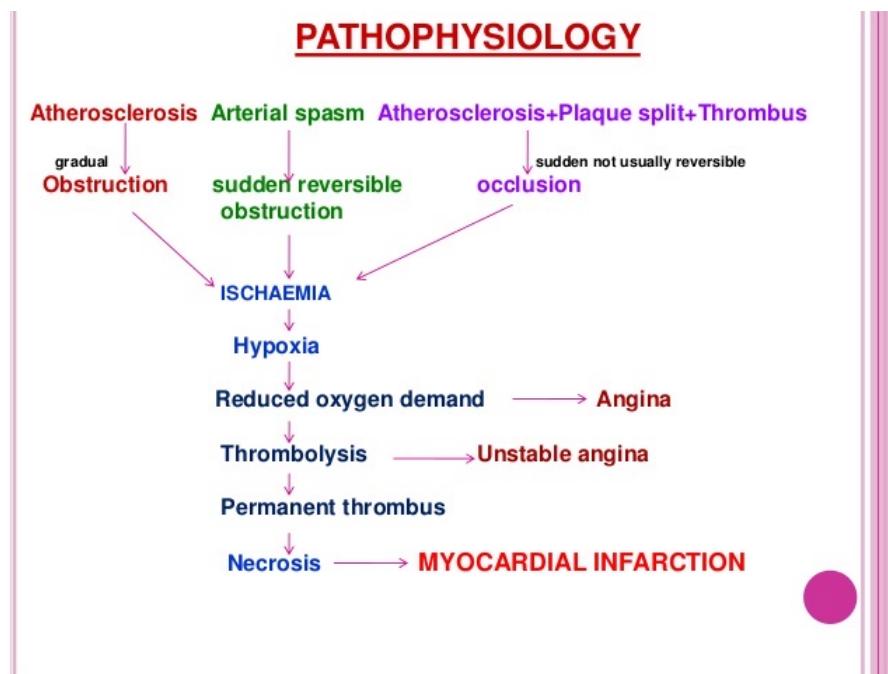
If the ECG confirms changes suggestive of **myocardial infarction** (ST elevations in specific leads, a new left bundle branch block or a true posterior MI pattern), **thrombolytics** may be administered or **primary coronary angioplasty** may be performed. In the former, medication is injected that stimulates **fibrinolysis**, destroying blood clots obstructing the **coronary arteries**.

54. Myocardial infarction: etiology, pathogenesis, clinic, diagnostics.

MI is due to necrosis of myocardium as a result of an interruption of blood supply (after a thrombotic occlusion of a coronary artery previously narrowed by atherosclerosis).

Etiology:a. Most cases are due to acute coronary thrombosis: Atheromatous plaque ruptures into the vessel lumen, and thrombus forms on top of this lesion, which causes occlusion of the vessel.

- Coronary occlusion secondary to vasculitis
- Ventricular hypertrophy (eg, left ventricular hypertrophy, hypertrophic cardiomyopathy)
- Coronary artery emboli, secondary to cholesterol, air, or the products of sepsis
- Coronary trauma
- Primary coronary vasospasm (variant angina)
- Drug use (eg, cocaine, amphetamines, ephedrine)
- Arteritis
- Coronary anomalies, including aneurysms of coronary arteries
- Factors that increase oxygen requirement, such as heavy exertion, fever, or hyperthyroidism
- Factors that decrease oxygen delivery, such as hypoxemia of severe anemia
- **Aortic dissection**, with retrograde involvement of the coronary arteries
- Respiratory infections, particularly influenza



Clinical features

1. Chest pain
 - a. Intense substernal pressure sensation; often described as “crushing” and “an elephant standing on my chest.”
 - b. Radiation to neck, jaw, arms, or back, commonly to the left side.
 - c. Similar to angina pectoris in character and distribution but much more severe and lasts longer. Unlike in angina, pain typically does not respond to nitroglycerin.
 - d. Some patients may have epigastric discomfort.
2. Can be asymptomatic in up to one-third of patients; painless infarcts or atypical presentations more likely in postoperative patients, the elderly, diabetic patients, and women.
3. Other symptoms
 - a. Dyspnea
 - b. Diaphoresis
 - c. Weakness, fatigue
 - d. Nausea and vomiting
 - e. Sense of impending doom
 - f. Syncope
4. Sudden cardiac death—usually due to ventricular fibrillation (VFib)

Diagnosis

1. ECG (Figure 1-2; see also Table 1-1 and Clinical Pearl 1-5)
 - a. Markers for ischemia/infarction include:
 - Peaked T waves: Occur very early and may be missed
 - ST segment elevation indicates transmural injury and can be diagnostic of an acute infarct
 - Q waves: Evidence for necrosis (specific)—Q waves are usually seen late; typically not seen acutely
 - T-wave inversion is sensitive but not specific
 - ST segment depression: Subendocardial injury
 - b. Categories of infarcts
 - ST segment elevation infarct: Transmural (involves entire thickness of wall); tends to be larger
 - Non-ST segment elevation infarct: Subendocardial (involves inner one-third to one-half of the wall); tends to be smaller, and presentation is similar to USA—cardiac enzymes differentiate the two
2. Cardiac enzymes—currently the diagnostic gold standard for myocardial injury (Figure 1-3)
 - a. Troponins (Troponin I and T)—most important enzyme test to order
 - Increases within 3 to 5 hours and returns to normal in 5 to 14 days; reaches a peak in 24 to 48 hours.
 - Greater sensitivity and specificity than CK-MB for myocardial injury.
 - Obtain serum levels of either troponin T or troponin I on admission, and again every 8 hours for 24 hours.
 - Troponin I can be falsely elevated in patients with renal failure; thus following trend of levels is important.
 - b. CK-MB—less commonly used
 - Increases within 4 to 8 hours and returns to normal in 48 to 72 hours; reaches a peak in 24 hours.
 - When measured within 24 to 36 hours of onset of chest pain, has greater than 95% sensitivity and specificity.
 - Levels of total CK and CK-MB should be measured on admission and every 8 hours thereafter for 24 hours.
 - Most helpful in detecting recurrent infarction given quicker return to baseline than troponin.

55. Atypical forms of myocardial infarction.

atypical presentation includes the absence of chest pain and the presence of non-chest pain, particularly localized in the neck, back, jaw, or head, followed by non-pain **symptoms** such as weakness, sweating, nausea, dyspnoea, or cough.

- in the throat (laryngeal-pharyngeal form)
- in the left-hand end of the left little finger (left-hand form)
- left shoulder blade (left shoulder blade form)
- in the cervical-thoracic spine (upper vertebral)
- lower jaw (mandibular form)

The intensity of pain varies. Sometimes it is enhanced, and not relieved by nitroglycerin.

56. Treatment of myocardial infarction: relief of pain, reperfusion of the affected artery, limitation of ischemia, prevention of complications.

D. Treatment

1. Admit patient to a cardiac monitored floor (CCU) and establish IV access. Give supplemental oxygen and analgesics (nitrates, morphine—see below).
2. Medical therapy
 - a. Aspirin
 - Antiplatelet agent reduces coronary reocclusion by inhibiting platelet aggregation on top of the thrombus
 - **Has been shown to reduce mortality and should be part of long-term maintenance therapy**
 - b. β -Blockers
 - Block stimulation of HR and contractility to reduce oxygen demand and decrease the incidence of arrhythmias
 - Reduce remodeling of the myocardium post-MI
 - **Have been shown to reduce mortality and should be part of maintenance therapy**
 - c. ACE inhibitors
 - Initiate within hours of hospitalization if there are no contraindications
 - **Have been shown to reduce mortality and should be part of long-term maintenance therapy**
 - d. Statins
 - **Reduce risk of further coronary events**
 - Stabilize plaques and lower cholesterol
 - The PROVE IT-TIMI 22 trial showed the superiority of starting atorvastatin 80 mg over other statins before discharging a STEMI patient
 - **Should be part of maintenance therapy**
 - e. Oxygen
 - May limit ischemic myocardial injury
 - f. Nitrates
 - Dilate coronary arteries (increase supply)
 - Venodilation (decrease preload and thus demand)
 - Reduce chest pain, although not as effective as narcotics
 - g. Morphine sulfate
 - Analgesia
 - Causes venodilation, which decreases preload and thus oxygen requirements

- h. Heparin**
- Initiate in all patients with MI; prevents progression of thrombus; however, has not been shown to decrease mortality
 - LMWH, specifically enoxaparin, is preferred over unfractionated heparin, as shown in the ExTRACT TIMI 25 trial as well as a recent meta-analysis. Enoxaparin was shown to decrease the risk of another MI versus unfractionated heparin
- 3. Revascularization**
- Benefit highest when performed early (within 90 minutes of hospital arrival).
 - Should be considered in all patients.
 - Revascularization options include thrombolysis, PCI, or CABG—see Clinical Pearl 1-6.
 - Several studies have shown enhanced survival and lower rates of recurrent MI and intracranial bleeding when PCI performed by skilled personnel is chosen over thrombolysis. For patients with a delayed presentation, fibrinolysis alone may be a better option.
 - Urgent/emergent CABG is typically performed only in the setting of mechanical complications of an acute MI, cardiogenic shock, life-threatening ventricular arrhythmias, or after failure of PCI. It is almost never performed in the acute setting on a stable patient.
 - Clopidogrel—evidence suggests that benefits of clopidogrel is additive to the effects of aspirin. Clopidogrel therapy should be initiated in all patients who
- g. Sinus tachycardia**
- May be caused by pain, anxiety, fever, pericarditis, medications, etc.
 - Worsens ischemia (increases myocardial oxygen consumption)
 - Treat underlying cause (analgesics for pain, aspirin for fever, etc.)
- h. Sinus bradycardia**
- A common occurrence in early stages of acute MI, especially right-sided/inferior MI
 - May be a protective mechanism (reduces myocardial oxygen demand)
 - No treatment is required other than observation. If bradycardia is severe or symptomatic (hemodynamic compromise), atropine may be helpful in increasing HR
- i. Asystole**
- Very high mortality.
 - Treatment should begin with electrical defibrillation for VFib, which is more common in cardiac arrest and may be difficult to clearly differentiate from asystole.
 - If asystole is clearly the cause of arrest, transcutaneous pacing is the appropriate treatment.
- j. AV block**
- Associated with ischemia involving conduction tracts.
 - First-degree and second-degree (type I) blocks do not require therapy.
 - Second-degree (type II) and third-degree blocks: Prognosis is dire in the setting of an anterior MI—emergent placement of a temporary pacemaker is indicated (with later placement of a permanent pacemaker). In inferior MI, prognosis is better, and IV atropine may be used initially. If conduction is not restored, a temporary pacemaker is appropriate.
- 3. Recurrent infarction (extension of existing infarction or reinfarction of a new area)**
- Both short-term and long-term mortality are increased.
 - Diagnosis is often difficult.
 - Cardiac enzymes are already elevated from the initial infarction. Troponin levels remain elevated for a week or more, so are not useful here. CK-MB returns to normal faster, and so a reelevation of CK-MB after 36 to 48 hours may be due to recurrent infarction.
 - If there is repeat ST segment elevation on ECG within the first 24 hours after infarction, suspect recurrent infarction.
 - Treatment: Repeat thrombolysis or urgent cardiac catheterization and PCI. Continue standard medical therapy for MI.
- 4. Mechanical complications**
- Free wall rupture**
 - A catastrophic, usually fatal event that occurs during the first 2 weeks after MI (90% within 2 weeks, most commonly 1 to 4 days after MI)
 - 90% mortality rate
 - Usually leads to hemopericardium and cardiac tamponade
 - Treatment: Hemodynamic stabilization, immediate pericardiocentesis, and surgical repair
 - Rupture of interventricular septum**
 - Greater potential for successful therapy than with a free wall rupture, although this is also a critical event; emergent surgery is indicated
 - Occurs within 10 days after MI
 - Likelihood of survival correlates with size of defect
 - Papillary muscle rupture**
 - Produces MR (presents with new murmur)
 - If suspected, obtain an echocardiogram immediately
 - Emergent surgery is needed (mitral valve replacement is usually necessary), as well as afterload reduction with sodium nitroprusside or intra-aortic balloon pump (IABP)
 - Ventricular pseudoaneurysm**
 - Incomplete free wall rupture (myocardial rupture is contained by pericardium)
 - Bedside echocardiogram may show the pseudoaneurysm
- 5. Acute pericarditis**
- The incidence has decreased sharply since the introduction of revascularization techniques.
 - Treatment consists of aspirin (which is already standard in treatment of MI).
 - NSAIDs and corticosteroids are contraindicated (may hinder myocardial scar formation).
- 6. Dressler syndrome (“postmyocardial infarction syndrome”)**
- Immunologically based syndrome consisting of fever, malaise, pericarditis, leukocytosis, and pleuritis, occurring weeks to months after an MI
 - Aspirin is the most effective therapy. Ibuprofen is a second option
- E. Complications of acute MI**
- Pump failure (CHF) (Figure 1-4)
 - Most common cause of in-hospital mortality
 - If mild, treat medically (ACE inhibitor, diuretic)
 - If severe, may lead to cardiogenic shock; invasive hemodynamic monitoring may be indicated (see Cardiogenic Shock on page 64)
 - Arrhythmias
 - Premature ventricular contractions (PVCs)—conservative treatment (observation) indicated; no need for antiarrhythmic agents
 - Atrial fibrillation (AFib)
 - Ventricular tachycardia (VT)-sustained VT requires treatment: If patient is hemodynamically unstable, electrical cardioversion is indicated. If patient is hemodynamically stable, start antiarrhythmic therapy (IV amiodarone)—see treatment of VT
 - VFib—immediate unsynchronized defibrillation and CPR are indicated (see Arrhythmias on page 22)
 - Accelerated idioventricular rhythm does not affect prognosis; no treatment needed in most cases
 - Paroxysmal supraventricular tachycardia (PSVT)—for treatment, see Arrhythmias

57. Complications of myocardial infarction: cardiogenic shock. Diagnosis. Treatment.

Cardiogenic shock is a condition in which your heart suddenly can't pump enough blood to meet your body's needs. The condition is most often caused by a severe heart attack, but not everyone who has a heart attack has **cardiogenic shock**. **Cardiogenic shock** is rare, but it's often fatal if not treated immediately.

●●● Cardiogenic Shock

A. General characteristics

1. Occurs when heart is unable to generate a cardiac output sufficient to maintain tissue perfusion
2. Can be defined as a systolic BP <90 with urine output <20 mL/hr and adequate left ventricular filling pressure

B. Causes

1. After acute MI—most common cause
2. Cardiac tamponade (compression of heart)
3. Tension pneumothorax (compression of heart)
4. Arrhythmias
5. Massive PE leading to RVF
6. Myocardial disease (cardiomyopathies, myocarditis)
7. Mechanical abnormalities (valvular defects, ventricular septal defect)

C. Clinical features

1. Typical findings seen in shock (altered sensorium, pale cool skin, hypotension, tachycardia, etc.)
2. Engorged neck veins—Venous pressure is usually elevated
3. Pulmonary congestion

D. Diagnosis

1. ECG—ST segment elevation suggesting acute MI or arrhythmia are the most common findings.
2. Echocardiogram—can diagnose a variety of mechanical complications of MI, identify valve disease, estimate EF, look for pericardial effusion, etc.
3. Hemodynamic monitoring with a Swan-Ganz catheter may be indicated: PCWP, pulmonary artery pressure, cardiac output, cardiac index, SVR—keep cardiac output >4 L/min, cardiac index >2.2, PCWP <18 mm Hg.

E. Treatment

1. ABCs
2. Identify and treat underlying cause
 - a. Acute MI
 - Standard treatment with aspirin, heparin (see MI section)
 - Aggressive management, that is, emergent revascularization with PCI (or CABG), has been shown to improve survival
 - b. If cardiac tamponade, pericardiocentesis/surgery
 - c. Surgical correction of valvular abnormalities
 - d. Treatment of arrhythmias
3. Vasopressors or inotropes
 - a. Dopamine is often the initial vasopressor used. Norepinephrine is another consideration
4. Dobutamine (inotrope) may be used in combination with dopamine to further increase cardiac output
5. Afterload-reducing agents such as nitroglycerin or nitroprusside are typically not used initially because they aggravate hypotension. They may be used later with vasopressors
5. **IV fluids are likely to be harmful if left ventricular pressures are elevated. Patients may in fact need diuretics.**
6. While still controversial, IABPs are often used for hemodynamic support (see Clinical Pearl 1-15). Effects include:
 - a. Decreased afterload
 - b. Increased cardiac output
 - c. Decreased myocardial oxygen demand

58. Complications of myocardial infarction: acute left ventricular failure.

Diagnostics. Treatment.

Acute Left Ventricular Failure Definition: Acute left ventricular failure is defined as sudden onset of dyspnea at rest or worsening dyspnoea of pre-existing chronic congestive **cardiac failure** occurring in patients with a **cardiac** condition. It is not a disease but a syndrome and complication of heart disease.

Left ventricular failure occurs when there is **dysfunction** of the **left ventricle** causing insufficient delivery of blood to vital body organs.

This occurs when your left ventricle isn't pumping efficiently. Instead of pumping blood out to your body, the blood backs up into your lungs. You may become short of breath as a result.

There are two types of left-sided heart failure:

Systolic heart failure is the **most common** cause of heart failure. It happens when your heart is weak or enlarged. During systolic heart failure, the muscle in your left ventricle is unable to contract or shorten. This prevents blood from being pumped effectively out to your body.

Diastolic heart failure happens when blood isn't able to properly fill your left ventricle. Because of this, your heart pumps less blood to your body than normal. This low blood flow is likely caused by the ventricle stiffening.

Symptoms of diastolic heart failure are indistinguishable from those of systolic heart failure. Because of this, diagnosis can only be performed using Doppler echocardiography.

Your doctor will assess your medical history and perform a physical exam. They'll listen to your heart and lungs with a stethoscope to detect any congestion or abnormal heart rhythms. Your doctor may also check for fluid buildup in your abdomen, legs, and the veins in your neck.

In addition, your doctor might order some combination of the following tests:

- Chest X-ray. This **imaging test** allows your doctor to better examine your heart and lungs.
- Blood tests. These check your thyroid and kidney function.
- Stress test. This type of test measures your heart activity during physical exercise.
- Electrocardiogram. During this **test**, your doctor will attach electrodes to your skin and record your heart's electrical activity.
- Echocardiogram. This **test** uses sound waves to form an image of your heart that shows how much blood your heart is pumping.
- Angiogram. During this test, your doctor will insert a thin tube into your groin or arm and into your coronary arteries. After injecting dye through a catheter, your doctor can see an image of your arteries.
- CT scan. This **test** helps diagnose heart problems by showing your doctor detailed images of your organs. It involves lying inside a machine while the images are taken using X-rays.
- MRI scan. This scan produces detailed images of your organs using magnets and radio waves instead of X-rays. [Learn more about heart MRIs.](#)

Treatment:

- Angiotensin-converting enzyme (ACE) inhibitors. ...
- Angiotensin II receptor blockers. ...
- Beta blockers. ...
- Diuretics. ...
- Aldosterone antagonists. ...
- Inotropes. ...
- Digoxin (Lanoxin).

- Nitrate and aspirin
- Need hospitalization and oxygen therapy

59. Complications of myocardial infarction: acute and chronic aneurysm.

Diagnostics. Treatment.

An aneurysm is the enlargement of an artery caused by weakness in the arterial wall. Often there are no symptoms, but a ruptured aneurysm can lead to fatal complications.

An aneurysm refers to a weakening of an artery wall that creates a bulge, or distention, of the artery.

The bulge can take two main shapes:

- Fusiform aneurysms bulge all sides of a blood vessel
- Saccular aneurysms bulge only on one side

Abdominal aortic aneurysm

Thoracic aortic aneurysm

Diagnosis:

Ultrasound

MRI for not ruptured aneurysm

CT for ruptured aneurysm

Treatment. The **treatment** of your **aneurysm** depends on how big it is. If it's less than 5 centimeters, or 2 inches, your doctor might try to **treat** it with **medication** first. He might prescribe drugs, such as beta blockers and calcium channel blockers to lower your blood pressure and relax your blood vessels.

- open surgery to fit a synthetic or stent graft
- endovascular stent-graft surgery.

In endovascular surgery, the surgeon accesses the blood vessels through a small incision near the hip. Stent-graft surgery inserts an endovascular graft through this incision using a catheter. The graft is then positioned in the aorta to seal off the aneurysm.

Clipping or coiling also

60. chronic gastritis: Definition. Classification. Clinic. Diagnostics.

61. Chronic gastritis: treatment depending on the etiology.

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Chronic Gastritis

- **Definition**
- CG – is a chronic inflammation of the gastric mucosa with the restructuring of its structure and progressive atrophy, disorders of secretory, motor and endocrine functions, with different clinical manifestations .
- CG is the most common diseases among diseases of the digestive system. Its prevalence among adult population is 50-80%.
- **Etiology**

The most common cause of chronic gastritis is infection with the *bacillus Helicobacter pylori* - 90%.

Other causative factors:

- heavy use of NSAIDs, especially aspirin;
- excessive alcohol consumption;
- heavy smoking;
- severe stress, that is trauma, burns, surgery;
- Ischemia;
- systemic infection;

Imbalance between the **protection** factor and aggression factor 5%

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- #### Classification Chronic gastritis
- Type A (autoimmune) characterized by the presence of antibodies to parietal cells, a high level of gastrin in the blood and a predominant lesion of the body of the stomach;
 - Type B develops as a result of infection of the gastric mucosa of HP and bacterial inflammation, mainly the antrum of the stomach, a normal or reduced level of gastrin in the blood and the absence of immune disorders;
 - Type C develops as a result duodenal gastric reflux or influence on mucosa of some medical product, more often non-steroid anti inflammatory agents or chemical substances;
 - Pangastrite (mixed type A and B).

Clinical manifestation:-

The symptoms are not specific.

With chronic gastritis and duodenitis the following syndromes are revealed:

- Pain syndrome (a dull, aching pain in the epigastric region);
- Dyspeptic syndrome (heartburn, belching, eructation, sometimes nausea and vomiting, which usually occurs when the errors in the diet, bloating, flatulence);
- Asthenovagetative syndrome (general weakness, fatigue).

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Classification Chronic gastritis

- Type A (autoimmune) characterized by the presence of antibodies to parietal cells, a high level of gastrin in the blood and a predominant lesion of the body of the stomach;
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- Asthenovagetative syndrome (general weakness, fatigue).

Methods of investigation of CG and CD

- During inspection we can not find specific signs of CG and CD
- At palpation can detect pain and tenderness in epigastric region
- Since clinical studies do not reveal any specific changes in the diagnosis of CG and CD, great importance is played by additional methods of investigation:

Diagnosis of HP
X-ray
Upper-endoscopy

Modern methods of diagnosing HP

- Bacteriological method – is a specific method of directly determining the sensibility of HP to antibacterial drugs. Limitations: the need for special laboratory equipment, adherence to fens rules transportation, selection of special media.
- Histological method – reveals the degree of dissemination of HP.
- Cytological method – simple, fast and sensitive way of diagnosis; parietal mucosa is obtained with a brush included in the endoscope.
- Maastricht IV (2012) recommends non invasive methods for diagnosis of HP – urease respiratory test, study feces for the presence of antigens, with the use monoclonal antibodies.

Urease respiratory test (URT)

- Urease respiratory test (URT) based on the definition of ^{13}C urea, is the best of all HP diagnostic tests, as it is a fast and highly accurate method. URT can be used for both - primary diagnosis of HP and for evaluation eradication of HP.



X-ray

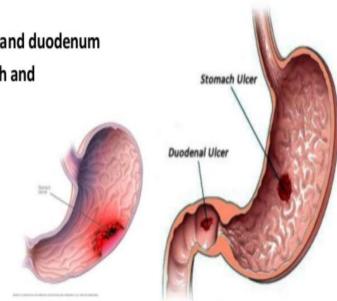
At the X-ray examination of stomach and duodenum, the following structural changes can be detected:

- broad and exaggerated folds of gastric mucosa,
- or the small, inconspicuous creases,
- or absence of gastric mucosa.



Complications of CG and CD

- Ulcer of stomach and duodenum
- Cancer of stomach and duodenum
- Types of anemia



Treatment of CG and CD

- Treatment includes non-pharmacological and drug therapy.
- Non-pharmacology therapy includes diet-therapy:
- Food should be full, varied and corresponds the conditions of chemical, thermal and mechanical sparing of the mucous membrane of the stomach and duodenum;
- It is advisable to exclude from the diet only food that this patient causes discomfort, for example fried dishes, fruit juice, coffee, spices, alcohol;
- Eating should be regular with a frequency of at least four times a day, dinner should not be later than two hours before bedtime;
- Contraindicated large breaks between meals, overeating and dry eating;
- Studies have shown that a strict diet not significantly affect the outcome of the disease;
- Cessation of smoking – increases the effectiveness of eradication therapy.

HP eradication therapy regimens recommended by the Maastricht Consensus V (Florence 2010)

- Clarithromycin (josamycin) 500 mg 2 times per day + amoxicillin 1000 mg 2 times per day. The duration of treatment is 10-14 days.
- Clarithromycin (josamycin) 500 mg 2 times per day + amoxicillin 1000 mg 2 times per day + bismuth tricalcium dictrite – 120 mg 4 times per day or 240 mg 2 times per day. This increase the efficiency of eradication by 15-20% and supplemented by the anti-inflammatory action of bismuth. The duration of treatment is 10-14days.
- PPI + bismuth tricalcium dictrite + metronidazole + tetracycline

Quadrotherapy based on bismuth preparations

PPI + metronidazole + tetracycline + bismuth tricalcium dictrite

Quadrotherapy without bismuth preparations

PPI + clarithromycin + amoxicillin + metronidazole

Sequential therapy

PPI + amoxicillin (first 5 days) + PPI + clarithromycin + metronidazole (the next 5 days)



Choice of therapy for some other conditions

Patients with chronic atrophic gastritis

Bismuth tricalcium dicitrate 240 mg 2 times per day or 120 mg 4 times per day + clarithromycin 500 mg 2 times per day + amoxicillin 1000 mg 2 times per day (duration 10-14 days)

Elderly patients with situation when high – great anti HP therapy impossible

Bismuth tricalcium dicitrate 240 mg 2 times per day or 120 mg 4 times per day +PPI (omeprazole or lansoprazole 2 times per day) + amoxicillin 1000 mg 2 times per day (duration 14 days) or bismuth tricalcium dicitrate 120 mg 4 times per day (duration 28 days)

In the presence of pain syndrome – a short course of PPI

The eradication of HP to pregnant women is not indicated

62. Functional dyspepsia: diagnostic criteria; clinical options, management.

Functional disorders

Functional dyspepsia

This is defined as chronic dyspepsia in the absence of organic disease. Other commonly reported symptoms include early satiety, fullness, bloating and nausea. 'Ulcer-like' and 'dysmotility-type' subgroups are often reported but there is overlap between these and with irritable bowel syndrome.

Pathophysiology

The cause is poorly understood but probably covers a spectrum of mucosal, motility and psychiatric disorders.

Clinical features

Patients are usually young (<40 years) and women are affected twice as commonly as men. Abdominal discomfort is associated with a combination of other 'dyspeptic' symptoms, the most common being nausea, satiety and bloating after meals. Morning symptoms are characteristic and pain or nausea may occur on waking. Direct enquiry may elicit symptoms suggestive of irritable bowel syndrome. Peptic ulcer disease must be considered, while in older people intra-abdominal malignancy is a prime concern. There are no diagnostic signs, apart from inappropriate tenderness on abdominal palpation, perhaps. Symptoms may appear disproportionate to clinical well-being and there is no weight loss. Patients often appear anxious. A drug history should be taken and the possibility of a depressive illness should be considered. Pregnancy should be ruled out in young women before radiological studies are undertaken. Alcohol misuse should be suspected when early-morning nausea and retching are prominent.

Investigations

The history will often suggest the diagnosis. All patients should be checked for *H. pylori* infection and patients over the age of 55 years should undergo endoscopy to exclude mucosal disease. While an ultrasound scan may detect gallstones, these are rarely responsible for dyspeptic symptoms.

Management

The most important elements are explanation and reassurance. Possible psychological factors should be explored and the concept of psychological influences on gut function should be explained. Idiosyncratic and restrictive diets are of little benefit but smaller portions and fat restriction may help.

Up to 10% of patients benefit from *H. pylori* eradication therapy and this should be offered to infected individuals. Eradication also removes a major risk factor for peptic ulcers and gastric cancer but at the cost of a small risk of side-effects and worsening symptoms of underlying gastro-oesophageal reflux disease. Drug treatment is not especially successful but merits trial. Antacids,

such as hydroxycarbonate, are sometimes helpful. Prokinetic drugs, such as metoclopramide (10 mg 3 times daily) or domperidone (10–20 mg 3 times daily), may be given before meals if nausea, vomiting or bloating is prominent. Metoclopramide may induce extrapyramidal side-effects, including tardive dyskinesia in young patients. H₂-receptor antagonist drugs may be tried if night pain or heartburn is troublesome. Low-dose tricyclic agents, such as amitriptyline, are of value in up to two-thirds.

Symptoms that can be associated with an identifiable cause of stress resolve with appropriate counselling. Some patients have major psychological disorders that result in persistent or recurrent symptoms and need behavioural or other formal psychotherapy (p. 1190).

Or



Gastrointestinal Diseases

Dyspepsia

A. General characteristics

1. "Dyspepsia" refers to a spectrum of epigastric symptoms, including heartburn, "indigestion," bloating, and epigastric pain/discomfort.
2. Dyspepsia is extremely common, and sometimes is confused with angina.
3. Etiology
 - a. GI causes—peptic ulcer disease (PUD), GERD, nonulcer dyspepsia (**functional dyspepsia**), gastritis, hepatobiliary disease (cholecystitis, biliary colic), malignancy (gastric, esophageal), pancreatic disease (pancreatitis, pseudocyst, cancer), esophageal spasm, hiatal hernia.
 - b. Other causes include lactose intolerance, malabsorption, DM (gastroparesis), and irritable bowel syndrome (IBS).

B. Diagnosis

1. Base the decision to perform tests on clinical presentation and response to empiric therapy.
2. **Endoscopy** is the test of choice for evaluation of dyspepsia.
 - a. It can identify an esophageal stricture or ulcer, cancer, and reflux esophagitis.
 - b. It should not be routinely performed in all patients with dyspepsia. Some general indications include:
 - Patients with alarming symptoms—weight loss, anemia, dysphagia, or obstructive symptoms.
 - Patients >55 years of age with new-onset dyspepsia.
 - Patients with recurrent vomiting or any evidence of upper GI bleeding.
 - Patients who do not respond to empiric therapy (see below).
 - Patients with signs of complications of PUD.
 - Patients with recurrent symptoms.
 - Patients with evidence of systemic illness.
3. Noninvasive testing for *Helicobacter pylori*: an option if the patient does not require an EGD.
 - a. Urea breath test: detects active infection.
 - b. Serology: cannot reliably determine active infection (antibodies may persist after *H. pylori* is cleared).
 - c. Stool antigen test: detects active infection.
 - d. Results
 - If positive, treat empirically for *H. pylori*.
 - If negative, PUD is unlikely and the patient likely has either GERD or nonulcer dyspepsia (treat empirically—see below).

C. Treatment

1. Treat the cause if known

Quick HIT

- Nonulcer dyspepsia
- A diagnosis of exclusion after appropriate tests (including endoscopy) does not reveal a specific cause.
 - Dyspepsia symptoms must be present for at least 4 weeks to make the diagnosis of nonulcer dyspepsia.

Ambulatory Medicine

CINE

2. Advise the patient to:
 - a. Avoid alcohol, caffeine, and other foods that irritate the stomach
 - b. Stop smoking
 - c. Raise the head of the bed when sleeping
 - d. Avoid eating before sleeping
3. Use a proton pump inhibitor (PPI) trial for 8 weeks. Endoscopy is indicated if this fails to relieve symptoms
4. Eradication of *H. pylori* infection—See Chapter 3

64.GERD: Pathogenesis. Classification of endoscopic changes. Clinic. Diagnostics. Differential diagnosis.

65 .GERD: Treatment (correction of lifestyle habits and pharmacotherapy).

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Quick HIT
If GERD is associated with dysphagia, this suggests the development of peptic stricture. Alternatively, a motility disorder or cancer may be present.

Quick HIT
Diagnostic tests are usually not necessary for typical, uncomplicated cases of GERD, and therapy can be initiated. Tests are indicated in individual patients and in persistent cases (despite treatment). Endoscopy should be performed if worrisome symptoms (anemia, weight loss, or dysphagia) are present.

Quick HIT
GERD is a chronic disorder. Regular follow-up is recommended to identify any complications (e.g., Barrett esophagus, stricture, esophagitis).

Ambulatory Medicine

2. Advise the patient to:

- Avoid alcohol, caffeine, and other foods that irritate the stomach
- Stop smoking
- Raise the head of the bed when sleeping
- Avoid eating before sleeping
- Take a proton pump inhibitor (PPI) trial for 8 weeks. Endoscopy is indicated if this fails to relieve symptoms
- Eradication of *H. pylori* infection—See Chapter 3

●●● Gastroesophageal Reflux Disease

A. General characteristics

1. GERD is a multifactorial problem. Inappropriate relaxation of the LES (decreased LES tone) is the primary mechanism, leading to retrograde flow of stomach contents into the esophagus. Other factors that may contribute include:

- Decreased esophageal motility to clear refluxed fluid
- A hiatal hernia (common finding in patients with GERD)
- Dietary factors (e.g., alcohol, tobacco, chocolate, high-fat foods, coffee)—may decrease LES pressure and exacerbate the condition

2. GERD is a very common condition. Its prevalence increases with age

B. Clinical features

1. Typical symptoms of dyspepsia

- Pseudoreflux burping shortly after eating (especially after large meals)
- Exacerbated by lying down after meals
- May mimic cardiac chest pain (which may lead to unnecessary workup for ischemic heart disease)
- Regurgitation
- Waterbrash—reflex salivary hypersecretion
- Cough—due to either aspiration of refluxed material or a reflex triggered by acid reflux into the lower esophagus
- Hoarseness, sore throat, feeling a lump in the throat
- Early satiety, postprandial nausea/vomiting

3. Diagnosis

- Endoscopy with biopsy—the test of choice but not necessary for typical uncomplicated cases
- Indicated if heartburn is refractory to treatment, or is accompanied by dysphagia, odynophagia, or GI bleeding
- A biopsy should also be performed to assess changes in esophageal mucosa.
- Upper GI series (barium contrast study)—this is only helpful in identifying complications of GERD (strictures/ulcerations), but cannot diagnose GERD itself.
- Twenty-four-hour pH monitoring in the lower esophagus—this is the most sensitive and specific test for GERD. It is the gold standard, but is usually unnecessary.
- Esophageal manometry—is used if a motility disorder is suspected.

4. Complications

- Erosive esophagitis—These patients are at high risk of developing complications such as stricture, ulcer, or Barrett esophagus. These patients are candidates for long-term PPI therapy (see below).
- Peptic stricture
- Consists of fibrotic rings that narrow the lumen and obstruct the passage of food
- Present in 10% of patients with chronic reflux
- EGD can confirm the diagnosis. Dilatation should be performed
- Esophageal ulcer—possible cause of upper GI bleeding
- Barrett esophagus—occurs in 10% of patients with chronic reflux
- The normal, stratified, squamous epithelium of the distal esophagus is replaced by columnar epithelium. Dysplastic changes may occur, with risk of adenocarcinoma

20:44 Gastrointestinal Diseases – 2 / 10 65%

- b. Patients who have had symptomatic GERD for at least 5 years (and can undergo surgery if cancer is found) should be screened for the possibility of Barrett esophagus
- c. Endoscopy with biopsy is required. If the patient has documented Barrett esophagus without any dysplastic changes, periodic surveillance is appropriate (every 3 years)
- d. Medical treatment—long-term PPIs
- 5. Recurrent pneumonia (due to recurrent pulmonary aspiration)—The cytologic aspirate finding on bronchoscopy that can diagnose aspiration of gastric contents is **lipid-laden macrophages** (from phagocytosis of fat)
- 6. Pitting of dental enamel (dental erosion); gingivitis
- 7. Laryngitis, pharyngitis

E. Treatment

- 1. Initial treatment:
 - a. Behavior modification—diet (avoid fatty foods, coffee, alcohol, orange juice, chocolate; avoid large meals before bedtime); sleep with trunk of body elevated; stop smoking
 - b. Antacids—after meals and at bedtime
- 2. Add an H₂ blocker—can be used instead of or in addition to antacids for mild and intermittent symptoms
- 3. If above treatment fails or patient has severe GERD (e.g., erosive esophagitis), switch to a PPI
- 4. Antireflux surgery for severe or resistant cases
 - a. Indications for surgery
 - Intractability (failure of medical treatment)
 - Respiratory problems due to reflux and aspiration of gastric contents
 - Severe esophageal injury (ulcer, hemorrhage, stricture, Barrett esophagus)
 - b. Types of surgery
 - Nissen fundoplication (may be done open or laparoscopically)—procedure of choice for a patient with normal esophageal motility
 - Partial fundoplication—when esophageal motility is poor
 - Outcome of surgery—excellent results have been reported

●●● Diarrhea

A. General characteristics

- 1. Most cases of diarrhea are acute, benign, and self-limited (see also Clinical Pearl 12-4). Some cases are chronic and may be associated with underlying disease.
- 2. Acute diarrhea is diarrhea that lasts less than 2 to 3 weeks; chronic diarrhea lasts more than 4 weeks.
- 3. Most common cause of acute diarrhea is viral infection (rotavirus and the Norwalk virus are the most common). Most severe forms of acute diarrhea are due to bacterial infections (*Shigella*, *Escherichia coli*, *Salmonella*, *Campylobacter*, *Clostridium*).

Degree	Finding
A	One or more erosions smaller than 5 mm
B	One or more erosions greater than 5 mm in its greater extension, non-continual between esophageal fold apices
C	Contiguous (or convergent) erosions between at least two esophageal fold apices, commitment of less than 75% of the esophagus
D	Erosion of at least 75% of the esophagus circumference

ResearchGate

Los Angeles endoscopic classification | Download Table

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65. Barrett's esophagus: morphological data; monitoring by endoscopy; treatment.

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INTRODUCTION:

- Barrett esophagus sometimes called Barrett syndrome or columnar epithelium lined lower oesophagus (CELO), refers to an abnormal change (metaplasia) in the cells of the lower portion of the esophagus.
- When the normal squamous epithelium lining of the esophagus is replaced by goblet cells (cells usually found lower in the gastrointestinal tract), Barrett's esophagus is diagnosed.
- The medical significance of Barrett esophagus is its strong association with esophageal adenocarcinoma, a particularly lethal cancer.

CAUSES:

- An adaptation to chronic acid exposure from reflux esophagitis
- Gastroesophageal reflux disease GERD

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SIGNS AND SYMPTOMS:

The change from normal to premalignant cells that indicate Barrett esophagus does not cause any particular symptoms. Barrett esophagus, however, is associated with the following symptoms:

- ✗ frequent and longstanding heartburn
- ✗ trouble swallowing (dysphagia)
- ✗ vomiting blood (hematemesis)
- ✗ pain under the breastbone where the esophagus meets the stomach
- ✗ unintentional weight loss because eating is painful

The risk of developing Barrett esophagus is increased by central obesity (vs. peripheral obesity).

MECHANISM

- ✗ Barrett esophagus occurs due to chronic inflammation.
- ✗ The principal cause of the chronic inflammation is GERD.
- ✗ In this disease, acidic stomach, bile, small intestine and pancreatic contents cause damage to the cells of the lower esophagus.
- ✗ Recently, it was shown that bile acids are able to induce intestinal differentiation, in gastroesophageal junction cells, through inhibition of the Epidermal growth factor receptor (EGFR) receptor and the protein kinase enzyme Akt.

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DIAGNOSIS:

- Diagnosis of Barrett esophagus requires endoscopy (more specifically esophagogastroduodenoscopy, a procedure in which a fibre optic cable is inserted through the mouth to examine the esophagus, stomach, and duodenum) and biopsy.
- Barrett esophagus is marked by the presence of columnar epithelium in the lower esophagus, replacing the normal squamous cell epithelium—an example of metaplasia.
- The cells of Barrett esophagus, after biopsy, are classified into four general categories:
 - non-dysplastic
 - low-grade dysplasia
 - high-grade dysplasia
 - frank carcinoma
- High-grade dysplasia

MANAGEMENT:

- Treatment options for high-grade dysplasia include:
 - surgical removal of the esophagus (esophagectomy)
 - endoscopic treatments such as endoscopic mucosal resection or radiofrequency ablation (destruction).
 - Proton pump inhibitor drugs have not yet been proven to prevent esophageal cancer.
 - Laser treatment is used in severe dysplasia, while overt malignancy may require surgery, radiation therapy, or systemic chemotherapy.
 - Endoscopic mucosal resection (EMR) has also been evaluated as a management technique. Additionally an operation known as a Nissen fundoplication can reduce the reflux of acid from the stomach into the esophagus.
 - In a variety of studies, non-steroidal anti-inflammatory drugs (NSAIDs), like aspirin, have shown evidence of preventing esophageal cancer in Barrett esophagus patients.

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66. Gastroduodenal ulcers: Etiological factors, Pathogenesis. Classification. Clinic. Peculiarities of ulcerative lesions of the stomach and duodenum. Differential diagnosis.

67 .Gastroduodenal ulcers: Diagnosis. Treatment of gastric and duodenal ulcers. Antisecretory therapy: drugs, the duration of the treatment. Indications for antihelicobacter therapy. Scheme of the 1st and 2nd lines. Approaches to antihelicobacter therapy in cases of clarithromycin resistance.

Quick HIT

Most cases of PUD are due to *H. pylori* infection and NSAID use. It can be difficult to determine the cause in a patient with *H. pylori* infection who also uses NSAIDs. Both may be responsible. Therefore, if in doubt, test for *H. pylori*.

- If patient is ill and the perforation is large (or if there is communication into pleural cavity), surgery should be performed within 24 hours of presentation (success rate is higher).

Diseases of the Stomach

Peptic Ulcer Disease

A. Causes

- Most common causes
 - Helicobacter pylori* infection
 - NSAIDs— inhibit prostaglandin production, which leads to impaired mucosal defenses
 - Acid hypersecretory states, such as Zollinger-Ellison syndrome
- Other causes
 - Smoking—ulcers twice as likely in cigarette smokers as in nonsmokers
 - Alcohol and coffee—may exacerbate symptoms, but causal relationship as yet unproven
 - Other potential but unproven causes include emotional stress, personality type (“type A”), and dietary factors

B. Clinical features

- Epigastric pain
 - Aching or gnawing in nature
 - Nocturnal symptoms and the effect of food on symptoms are variable (see Table 3-5)
- May be complicated by upper GI bleeding
- Other symptoms: nausea/vomiting, early satiety, and weight loss

C. Diagnosis

- Endoscopy
 - Most accurate test in diagnosing ulcers.
 - Essential in diagnosis of gastric ulcers because biopsy is necessary to rule out malignancy—duodenal ulcers do not require biopsy.

23:45

Diseases of the Stomach – 1 / 5

39%

Clarytromycine resistance therapy : ?(use of metronidazole instead)

TABLE 3-5 Duodenal Versus Gastric Ulcers

	Duodenal Ulcers	Gastric Ulcers
Pathogenesis	Caused by an increase in offensive factors (higher rates of basal and stimulated gastric acid secretion)	Caused by a decrease in defensive factors (gastric acid level is normal/low unless ulcer is pyloric or prepyloric)
<i>Helicobacter pylori</i> Infection	70%–90% of patients	60%–70% of patients
Malignant Potential	Low (malignancy is very rare) should undergo biopsy to rule out	High (5%–10% are malignant)—malignancy
Location	Majority are 1–2 cm distal to pylorus (usually on posterior wall)	Type I (most common, 70%) on lesser curvature of stomach Type II: gastric and duodenal ulcer Type III: prepyloric (within 2 cm of pylorus) Type IV: near esophagogastric junction
Age Distribution	Occurs in younger patients (<40)	Occurs in older patients (>40)
Associated Blood Type	Type O	Type A
Risk Factors	NSAIDs	Smoking
Other	Eating usually relieves pain Nocturnal pain is more common than in gastric ulcers	Eating does not usually relieve pain Complication rates are higher than those of duodenal ulcers. There is a higher recurrence rate with medical therapy alone

- c. Preferred when severe or acute bleeding is present (can perform electrocautery of bleeding ulcers).
d. Can obtain endoscopic biopsy for diagnosis of *H. pylori*.
2. Barium swallow
a. Sometimes used initially but is less reliable than endoscopy.
b. Double-contrast techniques preferred due to improved accuracy.
3. Laboratory test—for diagnosis of *H. pylori* infection
a. Biopsy: Histologic evaluation of endoscopic biopsy is the gold standard.
b. Urine detection via urea breath test is the most convenient test (sensitivity and specificity >95%). It documents active infection and helps to assess the results of antibiotic therapy.
c. Serology (lower specificity)—The presence of antibodies to *H. pylori* does not indicate current infection—Antibodies to *H. pylori* can remain elevated for months or even years after eradication of infection (90% positive).
• The following may lead to false-negative test results: proton pump inhibitors (PPIs), bismuth, many antibiotics and upper GI bleeding.
4. Serum gastrin measurement—if considering Zollinger-Ellison syndrome as a diagnosis

D. Treatment

1. Medical—Majority of patients with PUD can be successfully treated by curing *H. pylori* infection, avoidance of NSAIDs, and appropriate use of antisecretory drugs.
a. *H. pylori* infection
• Discontinue aspirin/NSAIDs.
• Restrict alcohol use but do not restrict any foods.
• Stop smoking, decrease emotional stress.
• Avoid eating before bedtime (eating stimulates nocturnal gastric acid levels); decrease coffee intake (although no strong link has been established with ulcer disease).

TABLE 3-6 *Helicobacter pylori* Eradication

	Regimen	Advantage	Disadvantage
Triple Therapy	PPI plus amoxicillin and clarithromycin	Twice daily dosing	More expensive than bismuth-based triple therapy
Quadruple Therapy	PPI, bismuth subsalicylate, metronidazole, and tetracycline	Half the time as triple therapy (a 1-week program as opposed to 2 weeks for triple therapy), yet has similar eradication results	Expense of PPI

Quick HIT

If a peptic ulcer is uncomplicated, a barium study or endoscopy is not needed initially. Initiate empiric antibiotic therapy, if you suspect any of the complications of PUD, order confirmatory studies.

Diseases of the Gastrointestinal System

Quick HIT

Acid Suppression Therapy

- H₂ blockers
- Ranitidine
- Famotidine
- Nizatidine
- Cimetidine
- PPIs
- Esomeprazole
- Omeprazole
- Pantoprazole
- Rabeprazole

- b. Acid suppression therapy
- H₂ receptor blockers—Cimetidine (Tagamet) and Ranitidine (Zantac). Block histamine-based parietal cell acid secretion. Accelerate healing of ulcers.
 - PPIs—omeprazole (Prilosec), lansoprazole (Prevacid). Block H+/K⁺ ATPase pump directly in parietal cell membrane. Most effective antisecretory agents (although expensive).
 - Antacids—somewhat outdated for primary therapy and more appropriately used for adjunctive therapy/symptomatic relief. Examples include aluminum hydroxide (Mylanta), calcium carbonate (Tums), Bismuth subsalicylate (Pepto-Bismol).

c. Eradication of *H. pylori* with triple or quadruple therapy (see Table 3-5). Once infection cleared, the rate of recurrence is very low.

• For initial therapy, triple therapy (PPI, amoxicillin and clarithromycin) for 10 days to 2 weeks.

• For retreatment, quadruple therapy (PPI, bismuth, metronidazole, and tetracycline).

d. Cytoprotection

- Sucralfate—facilitates ulcer healing, must be taken frequently, is costly, and can cause GI upset.
- Misoprostol—reduces risk for ulcer formation associated with NSAID therapy, is costly, and can cause GI upset (common side effect).
- e. Treatment regimens

• If *H. pylori* test is positive, begin eradication therapy with either triple or quadruple regimen (see Table 3-6). Also begin acid suppression with antacids, an H₂ blocker, or a PPI.

• If the patient has an active NSAID-induced ulcer, stop NSAID use (may switch to acetaminophen). Also begin with either a PPI or misoprostol.

Continue for 4 to 8 weeks, depending on severity. Treat the *H. pylori* infection as above if present.

• Antisecretory drugs can be discontinued after 4 to 6 weeks in patients with uncomplicated ulcers who are asymptomatic. Patients at increased risk of recurrence (especially if underlying cause of ulcer is not reversed) may benefit from maintenance therapy.

• *H. pylori*-negative ulcers that are NOT caused by NSAIDs can be treated with antisecretory drugs (either H₂ blockers or PPI).

2. Surgical

- a. Rarely needed electively
- b. Required for the complications of PUD (bleeding, perforation, gastric outlet obstruction) (see Table 3-7 and Figure 3-9).

••• Acute Gastritis

- Acute gastritis refers to inflammation of the gastric mucosa.
- There are multiple causes: NSAIDs/aspirin; *H. pylori* infection; alcohol, heavy cigarette smoking, or caffeine; extreme physiologic stress (e.g., shock, sepsis, burns).

**Classification of peptic ulcer**

- Peptic ulcers classified based on region or location of illness
 - Stomach (called gastric ulcer)
 - Duodenum (called duodenal ulcer)
 - Esophagus (called Esophageal ulcer)
 - Meckel's Diverticulum (called Meckel's Diverticulum ulcer)

Modified Johnson Classification of peptic ulcers

Type I: Ulcer along the lesser curve of stomach

Type II: Two ulcers present - one gastric, one duodenal/prepyloric

Type III: Prepyloric ulcer

Type IV: Proximal gastroesophageal ulcer

Type V: Anywhere (associated with chronic NSAID use)

68. Complications of gastroduodenal ulcers. Diagnosis, treatment.

TABLE 3-7 Complications of Peptic Ulcer Disease

	Clinical Findings	Diagnostic Studies	Management	Other
Perforation	Acute, severe abdominal pain, signs of peritonitis, hemodynamic instability	Upright CXR (free air under diaphragm), CT scan is the most sensitive test for perforation (detects free abdominal air)	Emergency surgery to close perforation and perform definitive ulcer operation (such as highly selective vagotomy or truncal vagotomy/pyloroplasty)	Can progress to sepsis and death if untreated
Gastric Outlet Obstruction	Nausea/vomiting (poorly digested food), epigastric fullness/early satiety, weight loss	Barium swallow and upper endoscopy; saline load test (empty stomach with a nasogastric tube, add 750 mL saline, aspirate after 30 min—test is positive if aspirate >400 mL)	Initially, nasogastric suction; replace electrolyte/volume deficits; supplement nutrition if obstruction is longstanding Surgery is eventually necessary in 75% of patients	Most common with duodenal ulcers and type III gastric ulcers
GI Bleeding	Bleeding may be slow (leading to anemic symptoms) or can be rapid and severe (leading to shock)	Stool guaiac, upper GI endoscopy (diagnostic and therapeutic)	Resuscitation; diagnose site of bleed via endoscopy and treat; perform surgery for acute bleeds that require transfusion of ≥6 units of blood	Peptic ulcer disease is the most common cause of upper GI bleeding

69 .Causes of intestinal dysfunction: enteropathy, colonopathy; fermentopathy; other reasons.

?????????

70 . Celiac disease. Classification, clinic of gastrointestinal and nongastrointestinal symptoms. Celiac disease associated conditions and complications. Diagnostics. Treatment.

Diseases of the small intestine

Disorders causing malabsorption

21

Celiac disease

Celiac disease is an inflammatory disorder of the small bowel occurring in genetically susceptible individuals, which results from intolerance to wheat gluten and similar proteins found in rye, barley and, to a lesser extent, oats. It can result in malabsorption and responds to a gluten-free diet. The condition occurs worldwide but is more common in northern Europe. The prevalence in the UK is approximately 1%, although 50% of these people are asymptomatic. These include both undiagnosed 'silent' cases of the disease and cases of 'latent' celiac disease – genetically susceptible people who may later develop clinical celiac disease.

Pathophysiology

The precise mechanism of mucosal damage is unclear but immunological responses to gluten play a key role (Fig. 21.41). There is a strong genetic component, with around 10% of first-degree relatives of an index case affected, and there is strong (approximately 75%) concordance in monozygotic twins. There is a strong association with human leukocyte antigen (HLA)-DQ2/DQ8. Dysbiosis of the intestinal microbiota has been identified but it is unclear if this is pathological or a response to the underlying mucosal changes.

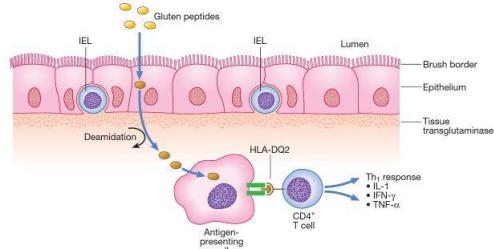


Fig. 21.41 Pathophysiology of celiac disease. After being taken up by epithelial cells, gluten peptides are deaminated by the enzyme tissue transglutaminase in the subepithelial layer. They are then able to fit the antigen-binding motif on human leukocyte antigen (HLA)-DQ2-positive antigen-presenting cells. Recognition by CD4⁺ T cells triggers a Th1 immune response with generation of pro-inflammatory cytokines: interleukin-1 (IL-1), interferon gamma (IFN- γ) and tumour necrosis factor alpha (TNF- α). Lymphocytes infiltrate the lamina propria and an increase in intra-epithelial lymphocytes (IELs), crypt hyperplasia and villous atrophy ensue.

Clinical features

Celiac disease can present at any age. In infancy, it occurs after weaning on to cereals and typically presents with diarrhoea, malabsorption and failure to thrive. In older children, it may present with non-specific features, such as delayed growth. Features of malnutrition are found on examination and mild abdominal distension may be present. Children have retarded growth and pubertal delay, leading to short stature in adulthood.

In adults, the disease usually presents during the third or fourth decade and females are affected twice as often as males. The presentation is highly variable, depending on the severity and extent of small bowel involvement. Some have florid malabsorption, while others develop non-specific symptoms, such as fatigue, weight loss, iron deficiency or iron deficiency anaemia. Other presentations include oral ulceration, dyspepsia and bloating. Unrecognised celiac disease is associated with mild under-nutrition and osteoporosis.

Celiac disease is associated with other HLA-linked autoimmune disorders and with certain other diseases (Box 21.42). In some centres, people at higher risk of developing celiac disease, such as those with type 1 diabetes, may undergo periodic antibody screening. Such screening may identify people with asymptomatic or minimally symptomatic disease; there is controversy about the optimum management strategy for such individuals.

Investigations

These are performed to confirm the diagnosis and to look for consequences of malabsorption.

Duodenal biopsy

Endoscopic small bowel biopsy is the gold standard. Endoscopic appearances should not preclude biopsy, as the mucosa usually looks normal. As the histological changes can be patchy, an adequate number of biopsies – currently, more than four biopsies from the second part of the duodenum plus one from the duodenal bulb – should be retrieved. The histological features are

21.42 Disease associations of celiac disease

- Type 1 diabetes mellitus (2–5%)
- Thyroid disease (5%)
- Primary biliary cirrhosis (3%)
- Sjögren's syndrome (3%)
- Immunodeficiency A deficiency (2%)
- Peripheral anaemia
- Cerebral atrophy
- Neurological complications:
 - Encephalopathy
 - Cerebellar atrophy
 - Peripheral neuropathy
 - Epilepsy
- Gastroenteritis
- Dermatitis herpetiformis
- Down's syndrome
- Enteropathy-associated T-cell lymphoma
- Small bowel carcinoma
- Squamous carcinoma of oesophagus
- Ulcerative colitis
- Pernicious anaemia
- Microscopic colitis
- Splenic atrophy

21.43 Important causes of subtotal villous atrophy

- | | |
|---|--|
| <ul style="list-style-type: none"> • Celiac disease • Tropical sprue • Dermatitis herpetiformis • Lymphoma • HIV-related enteropathy | <ul style="list-style-type: none"> • Giardiasis • Hypogammaglobulinaemia • Radiation • Whipple's disease • Zollinger-Ellison syndrome |
|---|--|

usually characteristic but other causes of villous atrophy should be considered (Box 21.43 and Fig. 21.42). Sometimes the villi appear normal but there are excess numbers of intra-epithelial lymphocytes (lymphocytic duodenitis).

Antibodies

Antibody tests constitute a valuable screening tool in patients with diarrhoea or other suggestive symptoms but are not a diagnostic substitute for small bowel biopsy at present. Tissue transglutaminase (tTG) is now recognised as the autoantigen. I

82



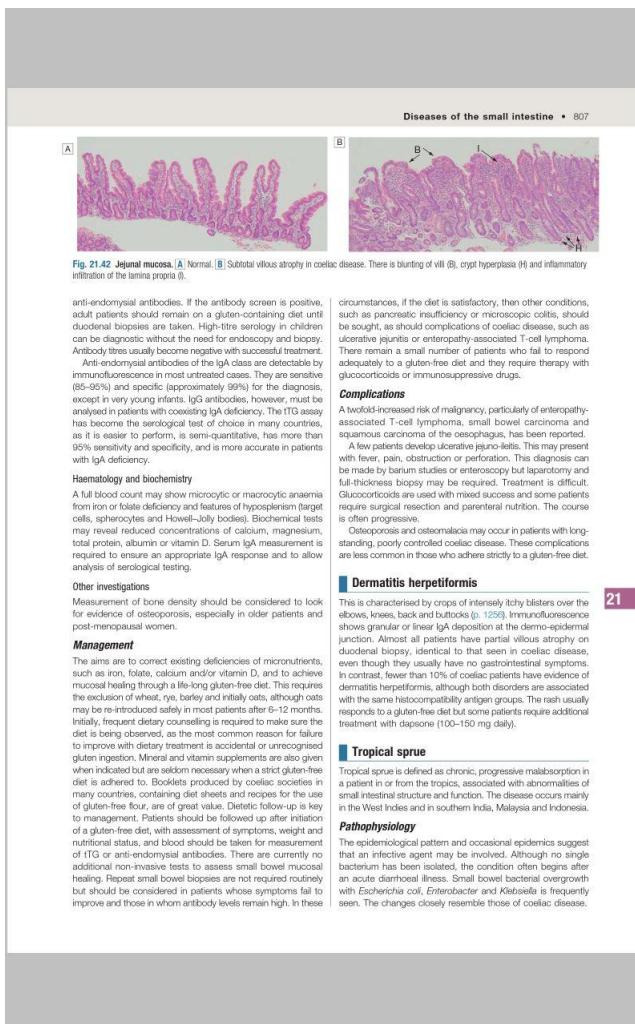


Fig. 21.42 Jejunal mucosa. [A] Normal. [B] Subtotal villous atrophy in coeliac disease. There is blunting of villi (B), crypt hyperplasia (I) and inflammatory infiltration of the lamina propria (I).

anti-endomysial antibodies. If the antibody screen is positive, adult patients should remain on a gluten-containing diet until duodenal biopsies are taken. High-titre serology in children can be detected by the small bowel endoscopy biopsy. Antibody titres usually become negative when the diet is followed.

Anti-endomysial antibodies of the IgG class are detectable by immunofluorescence in most untreated cases. They are sensitive (85–95%) and specific (approximately 99%) for the diagnosis, except in very young infants. IgG antibodies, however, must be analysed in patients with coexisting IgA deficiency. The IgG assay has become the serological test of choice in many countries, as it is easier to perform, is semi-quantitative, has more sensitivity and specificity, and is more accurate in patients with IgA deficiency.

Haematology and biochemistry

A full blood count may show anaemia or macrocytic anaemia from iron or folate deficiency and features of hypocomplement target cells, spherulocytes and Howell-Jolly bodies. Biochemical tests may reveal reduced concentrations of calcium, magnesium, total protein, albumin or vitamin D. Serum IgA measurement is required to ensure an appropriate IgA response and to allow analysis of serological testing.

Other investigations

Measurement of bone density should be considered to look for evidence of osteoporosis, especially in older patients and post-menopausal women.

Management

The main goal is to correct existing deficiencies of micronutrients, such as iron, folate, calcium and/or vitamin D, and to achieve mucosal healing through a life-long gluten-free diet. This requires the exclusion of wheat, rye, barley and oats; although oats may be re-introduced safely in most patients after 6–12 months. Initially, frequent dietary counselling is required to make sure the diet is being observed, as the most common reason for failure to improve with dietary treatment is accidental or unrecognized gluten intake. It is important to exclude other causes of malabsorption when indicated but are seldom necessary when a strict gluten-free diet is adhered to. Bodkin's produced by coeliac societies in many countries, containing diet sheets and recipes for the use of gluten-free flour, are of great value. Dietetic follow-up is key to management. Patients should be followed up after initiation of a gluten-free diet, with regard to symptoms, weight and nutritional intake. Blood should be tested for IgA, IgG, IgM, IgA or IgG anti-endomysial antibodies. There are currently no additional non-invasive tests to assess small bowel mucosal healing. Repeat small bowel biopsies are not required routinely but should be considered in patients whose symptoms fail to improve and those in whom antibody levels remain high. In these

circumstances, if the diet is satisfactory, then other conditions, such as pancreatic insufficiency or microscopic colitis, should be sought, as should complications of coeliac disease, such as ulcerative jejunitis or enteropathy-associated T-cell lymphoma. There remains a small number of patients who fail to respond adequately to a gluten-free diet and they require therapy with glucocorticoids or immunosuppressive drugs.

Complications

A twofold-increased risk of malignancy, particularly of enteropathy-associated tumour, has been reported.

A few patients develop ulcerative jejuno-ileitis. This may present with fever, pain, obstruction or perforation. This diagnosis can be made by barium studies or enteroscopy but laparotomy and full-thickness biopsy may be required. Treatment is difficult. Glucocorticoids are used with mixed success and some patients require surgical resection and parenteral nutrition. The course is often progressive.

Osteoporosis and osteomalacia may occur in patients with long-standing, poorly controlled coeliac disease. These complications are less common in those who adhere strictly to a gluten-free diet.

Dermatitis herpetiformis

This is characterised by crops of intensely itchy blisters over the elbows, knees, back and buttocks (p. 1259). Immunofluorescence shows granular or linear IgA deposition at the dermo-epidermal junction. Almost all patients have partial villous atrophy on duodenal biopsy, identical to that seen in coeliac disease, even though they usually have no gastrointestinal symptoms. In contrast, fewer than 10% of coeliac patients have evidence of dermatitis herpetiformis, and both disorders are associated with the same histocompatibility antigen groups. The rash usually responds to a gluten-free diet but some patients require additional treatment with dapsone (100–150 mg daily).

Tropical sprue

Tropical sprue is defined as chronic, progressive malabsorption in a patient in or from the tropics, associated with abnormalities of small intestinal structure and function. The disease occurs mainly in the West Indies and in southern India, Malaysia and Indonesia. **Pathophysiology**

The epidemiological pattern and occasional epidemics suggest that an infective agent may be involved. Although no single bacterium has been isolated, the condition often begins after an acute diarrhoeal illness. Small bowel bacterial overgrowth with *Escherichia coli*, *Enterobacter* and *Klebsiella* is frequently seen. The changes closely resemble those of coeliac disease.

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MARSH – OBER HUBER CLASSIFICATION	
MARSH I	Increased Intraepithelial Lymphocytes
MARSH II	Increased Intraepithelial Lymphocytes and Crypt Hyperplasia
MARSH IIIA	Increased Intraepithelial Lymphocytes, Crypt Hyperplasia and Partial Villous Atrophy
MARSH IIIB	Increased Intraepithelial Lymphocytes, Crypt Hyperplasia and Subtotal Villous Atrophy
MARSH IIIC	Increased Intraepithelial Lymphocytes, Crypt Hyperplasia and Total Villous Atrophy

71. Crohn's disease. Pathogenesis. Classification. Clinic: intestinal, extraintestinal manifestations; coexisting diseases; complications

72. Crohn's disease. Diagnostics. Goals and stages of therapy.

- Unknown etiology believed to be caused by overgrowth of bacteria
- Similar symptoms to celiac sprue including weight loss, diarrhea, cramps, fatigue, malabsorption
- Abnormal flattening of villi can be observed during endoscopy
- Treat with antibiotics and folic acid for 6 months or longer

Inflammatory Bowel Disease

Crohn Disease ("Regional Enteritis")

A. General characteristics

1. Crohn disease is a chronic transmural inflammatory disease that can affect any part of the GI tract (mouth to anus) but most commonly involves the small bowel (terminal ileum).
2. Distribution: There are three major patterns of disease.
 - a. Forty percent of patients have disease in the terminal ileum and cecum.
 - b. Thirty percent of patients have disease confined to the small intestine.
 - c. Twenty-five percent of patients have disease confined to the colon.
 - d. Rarely, other parts of the GI tract may be involved (stomach, mouth, esophagus).
3. Pathology
 - a. Terminal ileum is the hallmark location, but other sites of GI tract may also be involved
 - b. Skip lesions—discontinuous involvement
 - c. Fistulae
 - d. Luminal strictures
 - e. Noncaseating granulomas
 - f. Transmural thickening and inflammation (full-thickness wall involvement)—results in narrowing of the lumen
 - g. Mesenteric "fat creeping" onto the antimesenteric border of small bowel

B. Clinical features

1. Diarrhea (usually without blood)
2. Malabsorption and weight loss (common)
3. Abdominal pain (usually RLQ), nausea, and vomiting
4. Fever, malaise
5. Extraintestinal manifestations in 15% to 20% of cases (uveitis, arthritis, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, aphthous oral ulcers, cholelithiasis, and nephrolithiasis) (see also Clinical Pearl 3-8)

C. Diagnosis

1. Endoscopy (sigmoidoscopy or colonoscopy) with biopsy—typical findings are aphthous ulcers, cobblestone appearance, pseudopolyps, patchy (skip) lesions
2. Barium enema
3. Upper GI with small bowel follow-through

D. Complications

1. Fistulas—between colon and other segments of intestine (enteroenteral), bladder (enterovesical), vagina (enterovaginal), and skin (enterocutaneous)
2. Anorectal disease (in 30% of patients)—fissures, abscesses, perianal fistulas
3. SBO (in 20% to 30% of patients) is the most common indication for surgery. Initially, it is due to edema and spasm of bowel with intermittent signs of obstruction; later, scarring and thickening of bowel cause chronic narrowing of lumen
4. Malignancy—increased risk of colonic and small bowel tumors (but less common than in UC)
5. Malabsorption of vitamin B₁₂ and bile acids (both occur in terminal ileum)
6. Cholelithiasis may occur secondary to decreased bile acid absorption

Quick HIT

- Epidemiology of IBD
- More common in Caucasians than other racial groups
 - Particularly common in Jewish populations
 - Mean age of onset is 15 to 35 years

Quick HIT

Crohn disease has a chronic course characterized by unpredictable flares and remissions. The effectiveness of medical treatment decreases with advancing disease, and complications eventually develop, requiring surgery. There is no cure, and recurrence is common even after surgery.

Quick HIT

Patients may have vague abdominal pain and diarrhea for years before a diagnosis of Crohn disease is considered.

CLINICAL PEARL 3-8

Extraintestinal Manifestations of IBD

- Eye lesions
 - Episcleritis—parallels bowel disease activity
 - Anterior uveitis—Independent course
- Skin lesions
 - Erythema nodosum—especially in Crohn disease; parallels bowel disease activity
 - Pyoderma gangrenosum—especially in UC; parallels bowel disease activity in 50% of cases
- Arthritis—most common extraintestinal manifestation of IBD
 - Migratory monoarticular arthritis—parallels bowel disease activity (coincides with exacerbation of colitis)
 - Ankylosing spondylitis—patients with UC have a 30 times greater incidence of ankylosing spondylitis than the general population; the course is independent of the colitis
 - Sacroiliitis—does not parallel bowel disease activity
- Thromboembolic/hypercoagulable state—can lead to deep venous thrombosis (DVT), pulmonary embolism (PE), or a cardiovascular accident (CVA)
- Idiopathic thrombocytopenic purpura
- Osteoporosis
- Gallstones in Crohn disease (ileal involvement)
- Sclerosing cholangitis in UC

7. Nephrolithiasis—increased colonic absorption of dietary oxalate can lead to calcium oxalate kidney stones
8. Aphthous ulcers of lips, gingiva, and buccal mucosa (common)
9. Toxic megacolon—less common in Crohn disease than in UC
10. Growth retardation
11. Narcotic abuse, psychosocial issues due to chronicity and often disabling nature of the disease

E. Treatment

1. Medical

- a. Sulfasalazine
 - This is useful if the colon is involved. 5-ASA (mesalamine) is the active compound and is released in the colon—it is more useful in UC than in Crohn disease.
 - 5-ASA compounds block prostaglandin release and serve to reduce inflammation.
 - There are preparations of 5-ASA that are more useful in distal small bowel disease.
 - b. Metronidazole—if no response to 5-ASA
 - c. Systemic corticosteroids (prednisone)—for acute exacerbations and if no response to metronidazole
 - d. Immunosuppressants (azathioprine, 6-mercaptopurine)—in conjunction with steroids if the patient does not respond to above agents
 - e. Bile acid sequestrants (cholestyramine or colestipol)—for patients with terminal ileal disease who cannot absorb bile acids
 - f. Antidiarrheal agents generally not a good choice (may cause ileus)
2. Surgical (eventually required in most patients)
 - a. Reserve for complications of Crohn disease
 - b. Involves segmental resection of involved bowel
 - c. Disease recurrence after surgery is high—up to 50% of patients experience disease recurrence at 10 years postoperatively
 - d. Indications for surgery include SBO, fistulas (especially between bowel and bladder, vagina), disabling disease, and perforation or abscess
 3. Nutritional supplementation and support—parenteral nutrition is sometimes necessary

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Pathogenesis

- An increased permeability of the mucous membrane.
- This may lead to increased passage of luminal antigens, which then induce a cell-mediated inflammatory response.
- This results in the release of proinflammatory cytokines, such as interleukin-2 and tumour necrosis factor,
- which coordinate local and systemic inflammatory responses.
- potentially genetically determined increase in gut permeability, combined with an abnormal immune-mediated response to colonisation of the gut with subspecies of the normal enteric microflora, may initiate the disease.

Classification of CD

On the behavior of disease as it progresses:

- Stricturing disease causes narrowing of the bowel which may lead to bowel obstruction or changes in the caliber of the feces.


Stricturing

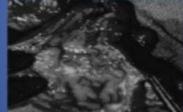
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Classification of CD

- Penetrating disease creates abnormal passage ways between the bowel and other structures such as the skin.
- Inflammatory disease causes inflammation without causing strictures or fistulae.


Inflammatory


Penetrating

73. Ulcerative colitis. Etiology. Pathogenesis. Classification. Clinic: intestinal, extra-intestinal manifestations; coexisting diseases; complications.

74. Drugs for an ulcerative colitis treatment, Goals and stages of therapy.

Ulcerative Colitis**A. General characteristics**

1. UC is a chronic inflammatory disease of the colon or rectal mucosa (see also Table 3-8).
2. It may occur at any age (usually begins in adolescence or young adulthood).
3. Distribution: UC involves the rectum in all cases and can involve the colon either partially or entirely.
 - a. Rectum alone (in 10% of cases)
 - b. Rectum and left colon (in 40% of cases)
 - c. Rectum, left colon, and right colon (in 30% of cases)
 - d. Pancolitis (in 30% of cases)
4. The course is unpredictable and variable and is characterized by periodic exacerbations and periods of complete remission. Less than 5% of patients have an initial attack without any recurrence.
5. Pathology
 - a. Uninterrupted involvement of rectum and/or colon—no skip lesions
 - b. Inflammation is not transmural (as it is in Crohn disease). It is limited to the mucosa and submucosa.
 - c. PMNs accumulate in the crypts of the colon (crypt abscesses).

Quick HIT

Patients with UC may have nonbloody diarrhea at first, with eventual progression to bloody diarrhea.

B. Clinical features (wide range of presentation)

1. Hematochezia (bloody diarrhea)
2. Abdominal pain
3. Bowel movements are frequent but small
4. Fever, anorexia, and weight loss (severe cases)
5. Tenesmus (fecal dry heaves)
6. Extraintestinal symptoms (e.g., jaundice, uveitis, arthritis, skin lesions)—see Clinical Pearl 3-8

C. Diagnosis: perform the following initial studies

1. Stool cultures for *C. difficile*, ova, and parasites—to rule out infectious diarrhea
2. Fecal leukocytes
3. WBCs can appear in UC, ischemic colitis, or infectious diarrhea
4. Colonoscopy—to assess the extent of disease and the presence of any complications

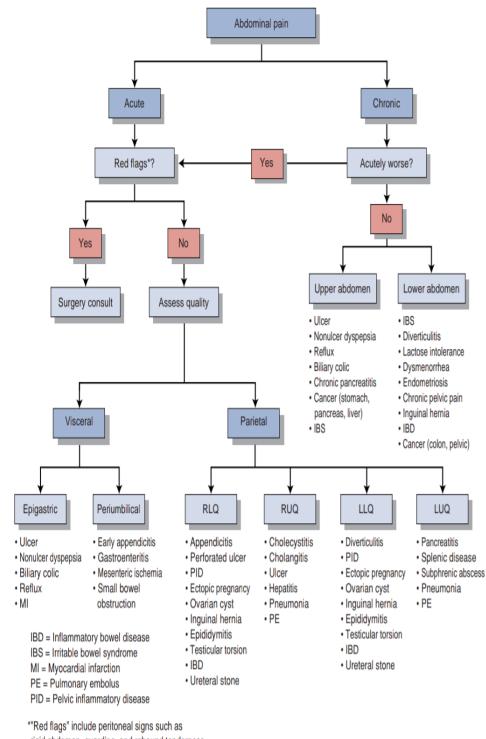
D. Complications

1. Iron deficiency anemia
2. Hemorrhage

TABLE 3-8 Crohn Disease Versus Ulcerative Colitis

Crohn Disease	Ulcerative Colitis	
Involvement	Transmural—intestinal wall from mucosa to serosa Discontinuous involvement (skip lesions)	Mucosa and submucosa Continuous involvement (no skip lesions)
Location	Terminal ileum (most common) Can involve any part of the GI tract (recurrence—recurrences occur)	Confined to colon and rectum Colectomy is curative
Complications	Fistulae and abscesses are more common than in UC because the entire wall is involved	SC and colorectal cancer are more common than in Crohn disease

3. Electrolyte disturbances and dehydration secondary to diarrhea
4. Strictures, benign and malignant (usually malignant)
5. Colon cancer—The risk correlates with extent and duration of colitis. In distal proctitis there is an increased risk of CRC.
6. Sclerosing cholangitis (SC)—The course not parallel with bowel disease and is not prevented by colectomy
7. Cholangiocarcinoma—Half of bile duct cancers are associated with UC
8. Toxic megacolon is the leading cause of death in UC and affects <5% of patients. It is associated with the risk of colonic perforation
9. Growth retardation
10. Narcotic abuse
11. Psychosocial issues (e.g., depression) due to chronicity and often disabling nature of the disease

**FIGURE 3-12** Approach to the diagnosis of nontraumatic abdominal pain in adults.

(Adapted from Steane PO, Siart LM, Esell MH, et al. *Essentials of Family Medicine*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:246, Figure 16.2.)

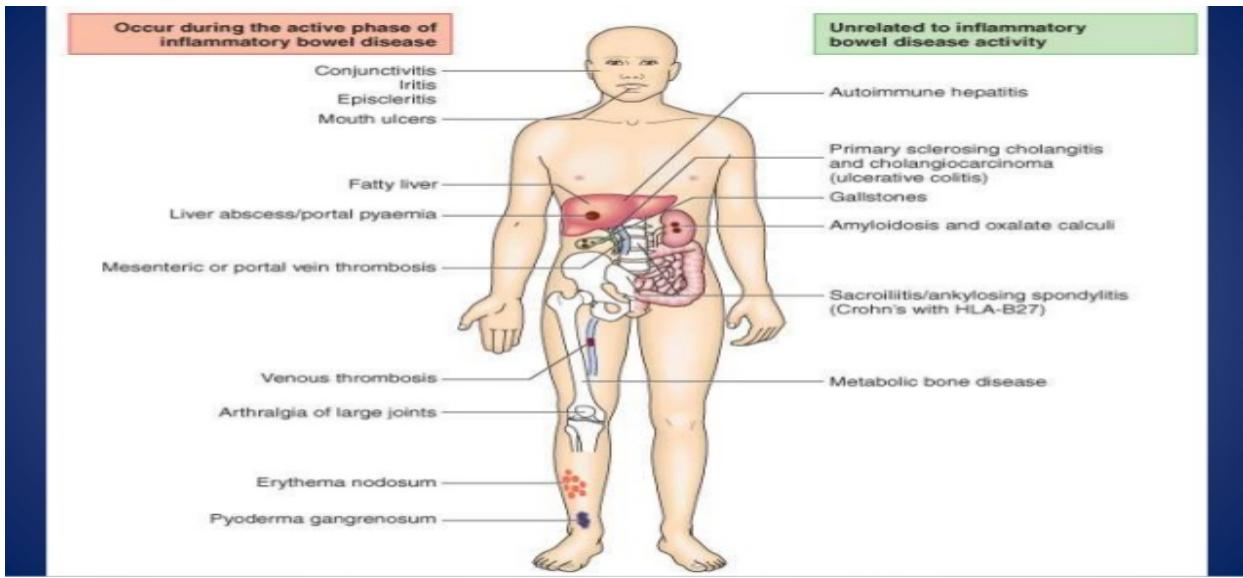
E. Treatment

1. Medical (Figure 3-12)
 - a. Systemic corticosteroids are used for acute exacerbations.
 - b. Sulfasalazine (topical application as a suppository) is the mainstay of treatment. Preferred over topical steroids because they are effective as maintenance therapy. Remission rates as high as 93% have been reported.
 - It is effective in maintaining remissions. 5-ASA (mesalamine) is the active component.
 - 5-ASA enemas can be used for proctitis and distal colitis.
 - c. Immunosuppressive agents in patients with refractory disease may prevent relapses but are not effective for acute attacks.
2. Surgical—often curative (unlike Crohn disease) and involves total colectomy.
Indications for surgery include:
 - a. Severe disease that is debilitating, refractory, and unresponsive to medical therapy
 - b. Toxic megacolon (risk of perforation), obstruction (due to stricture), severe hemorrhage, perforation
 - c. Fulminant exacerbation that does not respond to steroids
 - d. Evidence of colon cancer or increased risk of colon cancer
 - e. Growth failure or failure to thrive in children
 - f. Systemic complications

The screenshot shows a presentation slide titled "Etiology" in yellow font. The slide content is as follows:

- The cause of UC remains unclear, although interplay of genetic, microbial, and immunologic factors clearly exists.
- A limited number of environmental factors have clearly been proven to either modify the disease or regulate the lifetime risk of developing it.
- These include:
 - Tobacco use.
 - Antibiotic use.
 - Appendectomy.
 - Oral contraceptive pills.

On the right side of the slide, there are social sharing icons for "Share", "Like", and "Save". At the bottom right, it says "5 / 68". The browser toolbar at the top includes tabs for "Glokovoy nerve - Google", "Corticospinal tract", "Course: General Surgery", "Home - YouTube", "General_med_Area", and "Ulcerative colitis", along with a search bar and other navigation icons.



1.7K/s iQi 45% 1:19 AM

G loktvoi nerve - Goo X W Corticospinal tract X Course: General SU X Home - YouTube X General_med_Anes X Ulcerative colitis X +

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Extra-intestinal Complications of UC

System or Site	Manifestation
Hepatobiliary	Primary sclerosing cholangitis Cholangiocarcinoma Gallstones
Dermatologic	Erythema nodosum Pyoderma gangrenosum Sweet syndrome
Oral	Aphthous ulceration
Ocular	Episcleritis Uveitis/iritis
Musculoskeletal	Enteropathic arthropathy Sacroiliitis Ankylosing spondylitis Osteopenia/osteoporosis
Hematologic	Thromboembolic disease

75 .Irritable bowel syndrome. Definition. Diagnostic criteria. Symptoms of anxiety. Clinic. The purpose and directions of therapy. Prognosis.

•• Irritable Bowel Syndrome**A. General characteristics**

- IBS refers to an idiopathic disorder associated with an intrinsic bowel motility dysfunction (abnormal resting activity of GI tract) that affects 10% to 15% of all adults.
- Common associated findings include depression, anxiety, and somatization. Psychiatric symptoms often precede bowel symptoms. Symptoms are exacerbated by stress and irritants in the intestinal lumen.
- All laboratory test results are normal, and no mucosal lesions are found on sigmoidoscopy. IBS is a benign condition and has a favorable long-term prognosis.
- Symptoms should be present for at least 3 months to diagnose IBS.

Quick HIT**Differential Diagnosis of IBS**

Colon cancer; IBD; drugs, mesenteric ischemia, celiac disease, ischemic colitis, ganglionic, pseudo-obstruction, depression, somatization, intermittent sigmoid volvulus, megacolon, bacterial overgrowth syndrome, endometriosis.

00:53

B. Clinical features

- Change in frequency/consistency of stool—diarrhea, constipation (or alternating diarrhea and constipation)
- Cramping abdominal pain (relieved by defecation)—location varies widely, but sigmoid colon is the common location of pain
- Bloating or feeling of abdominal distension

C. Diagnosis

- This is a clinical diagnosis, and a diagnosis of exclusion.
- Rome III diagnostic criteria: recurrent abdominal pain/discomfort ≥ 3 days per month in the last 3 months, and 2 of the following:
 - Pain/discomfort improves with defecation.
 - Symptom onset is associated with a change in the frequency of the stool.
 - Symptom onset is associated with a change in the form of the stool.

Gastrointestinal Diseases - 8 / 10

21%

- Initial tests that may help exclude other causes include CBC, renal panel, fecal occult blood test, stool examination for ova and parasites, erythrocyte sedimentation rate, and possibly a flexible sigmoidoscopy. Order these tests only if there is suspicion of other causes for the symptoms.

D. Treatment

- For mild symptoms, diet and lifestyle changes (e.g., avoiding dairy products, excess caffeine). Manage the symptoms below as indicated:
 - Diarrhea—diphenoxylate, loperamide.
 - Constipation—colace, psyllium, cisapride.
 - Abdominal pain—antispasmodics (e.g., pinaverium, trimebutine, peppermint oil, cimetropium/dicyclomine), antidiarrheals, rifaximin.

Quick HIT

The following must be frequently excluded in diagnosing IBS:

- Obstruction (plain abdominal film)
- IBD
- Lactose or sorbitol intolerance
- Malignancy (in older patients or those with family history—colonoscopy, occult blood in stool)

**21.64 Supporting diagnostic features and alarm features in irritable bowel syndrome****Features supporting a diagnosis of IBS**

- Presence of symptoms for more than 6 months
- Frequent consultations for non-gastrointestinal problems
- Previous medically unexplained symptoms
- Worsening of symptoms by stress

Alarm features

- | | |
|-------------------------------|----------------------------------|
| • Age > 50 years; male gender | • Family history of colon cancer |
| • Weight loss | • Anaemia |
| • Nocturnal symptoms | • Rectal bleeding |

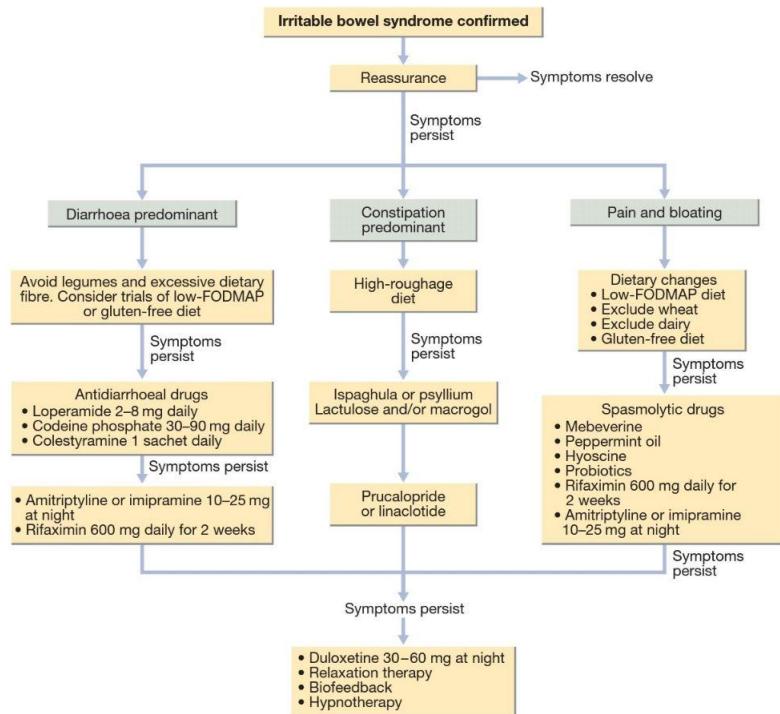
i 21.65 Dietary management of irritable bowel syndrome

- Eat regularly and avoid missing meals
- Take time to eat
- Ensure adequate hydration and avoid carbonated and caffeinated drinks
- Reduce alcohol intake
- Reduce intake of 'resistant' starch and insoluble fibre
- Avoid foods with artificial sweeteners
- Consider a wheat-free diet
- Consider a lactose exclusion diet
- Consider a diet low in FODMAPs

(FODMAPs = fermentable oligo-, di- and monosaccharides, and polyols)

Behavioural and psychosocial factors

Most patients seen in general practice do not have psychological problems but about 50% of patients referred to hospital have a psychiatric illness, such as anxiety, depression, somatisation and neurosis. Panic attacks are also common. Acute psychological stress and overt psychiatric disease are known to alter visceral perception and gastrointestinal motility. There is an increased prevalence of abnormal illness behaviour, with frequent consultations for minor symptoms and reduced coping ability (p. 1202). These factors contribute to but do not cause IBS.



76 .Diverticular bowel disease. Prevalence. Clinical forms. Diagnostics. Complications.

77 .Diverticular bowel disease. Treatment of individual forms. Forecast.

most common symptom.

Diverticulosis**A. General characteristics**

1. Caused by increased intraluminal pressure—inner layer of colon bulges through focal area of weakness in colon wall (usually an area of blood vessel penetration).
2. Risk factors
 - a. Low-fiber diets: Constipation causes intraluminal pressures to increase.
 - b. Positive family history.
 - c. Prevalence increases with age.
4. The most common location is the sigmoid colon. However, diverticula may occur anywhere in the colon.

B. Clinical features

1. Usually asymptomatic and discovered incidentally on barium enema or colonoscopy done for another reason.
2. Vague left lower quadrant (LLQ) discomfort, bloating, constipation/diarrhea may be present.
3. Only 10% to 20% become symptomatic (i.e., develop complications—see below).

C. Diagnosis

1. Barium enema is the test of choice.
2. Abdominal x-rays are usually normal and are not diagnostic for diverticulosis.

D. Treatment

1. High-fiber foods (such as bran) to increase stool bulk
2. Psyllium (if the patient cannot tolerate bran)

E. Complications

1. Painless rectal bleeding (up to 40% of patients)
 - a. Bleeding is usually clinically insignificant and stops spontaneously. No further treatment is necessary in these patients.
 - b. Bleeding can be severe in about 5% of patients. In many cases, the bleeding stops spontaneously. Colonoscopy may be performed to locate site of bleeding (mesenteric angiography in certain cases). If bleeding is persistent and/or recurrent, surgery may be needed (segmental colectomy).
2. Diverticulitis (15% to 25% of patients)
 - a. Occurs when feces become impacted in the diverticulum, leading to erosion and microperforation.
 - b. Can be complicated (see also Clinical Pearl 3-1) or uncomplicated. Uncomplicated diverticulitis accounts for most cases and refers to diverticulitis without the complications listed in Clinical Pearl 3-1.

CLINICAL PEARL 3-1**Complications of Diverticulitis**

- Abscess formation (can be drained either percutaneously under CT guidance or surgically)
- Colovesical fistula—accounts for 50% of fistulas secondary to diverticulitis; 50% close spontaneously
- Obstruction—due to chronic inflammation and thickening of bowel wall
- Free colonic perforation—uncommon but catastrophic (leads to peritonitis)

<http://internalmedicinebook.com>**Quick HIT**

Diverticulosis (pouches in the colon wall) should be distinguished from diverticulitis, which refers to inflammation or infection of the diverticula and is a complication of diverticulosis.

Quick HIT

- Complications of diverticulosis include painless rectal bleeding and diverticulitis.
- Complications of diverticulitis include bowel obstruction, abscess, and fistulas.

Quick HIT

- Diverticulitis recurs in about 30% of patients treated medically, usually within the first 5 years.
- Lower GI bleeding is very rare in diverticulitis, but common in diverticulosis.

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0.00K/s

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DISEASES OF THE GASTROINTESTINAL SYSTEM • 117

c. Clinical features: fever, LLQ pain, leukocytosis.

- Other possible features: alteration in bowel habits (constipation or diarrhea), vomiting, and sometimes a painful mass on rectal examination if inflammation is near the rectum.
- Diagnostic tests
 - CT scan (abdomen and pelvis) with oral and IV contrast is the test of choice; it may reveal a swollen, edematous bowel wall or an abscess.
 - Abdominal radiographs help in excluding other potential causes of LLQ pain, and can rule out ileus or obstruction (indicated by air-fluid levels, distension), and perforation (indicated by free air).
 - Barium enema and colonoscopy are contraindicated in acute diverticulitis due to the risk of perforation.

d. Treatment

- Uncomplicated diverticulitis is managed with IV antibiotics, bowel rest (NPO), IV fluids. Mild episodes can be treated on outpatient basis if patient is reliable and has few or no comorbid conditions. If symptoms persist after 3 to 4 days, surgery may be necessary. Antibiotics continued for 7 to 10 days. After successful treatment, about one-third have recurrence. Surgery recommended for recurrent episodes (resection of involved segment).
- Complicated diverticulitis—surgery indicated.

Quick HIT

- Diverticulosis—barium enema is test of choice
- Diverticulitis—CT scan is test of choice (barium enema and colonoscopy contraindicated)

Quick HIT

- As many as 25% of patients with bleeding arteriovenous malformations have aortic stenosis. However, no

Diverticulosis

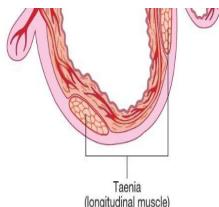
Diverticula are acquired and are most common in the sigmoid and descending colon of middle-aged people. Asymptomatic diverticula (diverticulosis) are present in over 50% of people above the age of 70 years. Symptomatic diverticular disease supervenes in 10–25% of cases, while complicated diverticulitis (acute diverticulitis, pericolic abscess, bleeding, perforation or stricture) is uncommon.

Pathophysiology

A life-long refined diet with a relative deficiency of fibre is widely thought to be responsible and the condition is rare in populations with a high dietary fibre intake, such as in Asia, where it more often affects the right side of the colon. It is postulated that small-volume stools require high intracolonic pressures for propulsion and this leads to herniation of mucosa between the taeniae coli (Fig. 21.62). Diverticula consist of protrusions of mucosa covered by peritoneum. There is commonly hypertrophy of the circular muscle coat. Inflammation is thought to result from impaction of diverticula with faecoliths. This may resolve spontaneously or progress to cause haemorrhage, perforation, local abscess formation, fistula and peritonitis. Repeated attacks of inflammation lead to thickening of the bowel wall, narrowing of the lumen and eventual obstruction.

Clinical features

Symptoms are usually the result of associated constipation or spasm. Colicky pain is suprapubic or felt in the left iliac fossa. The sigmoid colon may be palpable and, in attacks of diverticulitis, there is local tenderness, guarding, rigidity ('left-sided appendicitis') and sometimes a palpable mass. During these episodes, there may be diarrhoea, rectal bleeding or fever. The differential diagnosis includes colorectal cancer, ischaemic colitis,



21

Fig. 21.62 The human colon in diverticulosis. The colonic wall is weak between the taeniae. The blood vessels that supply the colon pierce the circular muscle and weaken it further by forming tunnels. Diverticula usually emerge through these points of least resistance.

IBD and infection. Diverticular disease may be complicated by perforation, pericolic abscess, fistula formation (usually colovesical) or acute rectal bleeding. These complications are more common in patients who take NSAIDs or aspirin. After one attack of diverticulitis, the recurrence rate is around 3% per year. Over 10–30 years, perforation, obstruction or bleeding may occur, each affecting 5% of patients.

Investigations

Investigations are usually performed to exclude colorectal neoplasia. Diverticula can be seen during colonoscopy or on imaging modalities such as CT scan, CT colonography or barium enema (see Fig. 21.12C, p. 773). In severe diverticulitis, colonoscopy requires expertise and carries a risk of perforation. CT is used to assess complications, such as perforation or pericolic abscess.

Management

Diverticular disease that is asymptomatic and discovered coincidentally requires no treatment. Constipation can be relieved by a high-fibre diet, with or without a bulking laxative (ispaghula husk, 1–2 sachets daily), taken with plenty of fluids. Stimulant laxatives (see Box 21.73 below) should be avoided. Antispasmodics may sometimes help. Acute attacks of diverticulitis can be treated with antibiotics active against Gram-negative and anaerobic organisms. Severe cases require intravenous fluids, intravenous antibiotics, analgesia and nasogastric suction, but randomised trials show no benefit from acute resection compared to conservative management. Emergency surgery is reserved for severe haemorrhage or perforation. Percutaneous drainage of acute paracolic abscesses can be effective and avoids the need for emergency surgery. Patients who have repeated attacks of obstruction should undergo elective surgery once the acute episode has settled, in order to resect the affected segment of bowel with restoration of continuity by primary anastomosis.

5
15
30



78 .Chronic hepatitis. Classification: etiology, levels of activity. Clinical and laboratory syndromes (mesenchymal — inflammatory, cytolysis, cholestasis, hepatocellular insufficiency). Criteria for the activity of chronic hepatitis: clinical, biochemical, morphological

A screenshot of a mobile presentation slide. The top navigation bar shows various tabs like 'Home - YouTube', 'General_med_Ane', 'chronic hepatitis', 'Система дистанц.', 'Chronic Hepatitis', 'morphology of ch.', and others. The slide has a dark background with two main sections: 'Definition' on the left and 'Etiology' on the right.

Definition

- Chronic Hepatitis is hepatic inflammation of at least 6 months' duration, differently aetiology, morphologically by the presence signs of hepatic inflammatory, dystrophy and fibrosis with or without cirrhosis.
- Clinically the main symptoms of this disease are jaundice, pain in the right hypochondrium, dyspepsia, skin itch (pruritus), hepatomegaly, low-grade fever.

Etiology

- Viruses** Hepatitis B,C,D,E,F and their combination (90%), rarely virus Epstein-Barr, virus yellow fever, cytomegalovirus
- Bacteria** (tuberculosis)
- Autoimmune diseases**
- Alcohol** intoxication
- Toxic-allergic agent** (medicinal drugs: tetracycline, NSAID, narcotic drugs, isoniazid, methyldopa, nitrofurans, other)

A screenshot of a mobile presentation slide. The top navigation bar shows tabs like 'Home - YouTube', 'General_med_Ane', 'chronic hepatitis', 'Система дистанц.', 'Chronic Hepatitis', 'morphology of ch.', and others. The slide has a dark background with two main sections: 'Etiology' on the left and 'Pathogenesis' on the right.

Etiology

- Protozoa** associated with hepatitis (amebiasis, malaria, toxoplasmosis, Kala-Azar)
- Helminths**: schistosomiasis, ascariasis, echinococcus, toxocariasis, other
- Spirochetes**
- Non-specific reactive hepatitis**
- Unknown** (sarcoidosis, idiopathic granulomatous hepatitis)

Pathogenesis

- After acute hepatitis viruses or other etiology, pathological agent (if the patient does not receive etiological treatment) is persistent into hepatocytes and brings an inflammatory reaction (fission, edema, necrosis, dystrophy, hepatocyte's cholestasis and mononuclear infiltration, edema intraportal tracts) hepatomegaly and disorder all functions (dysfunction) of the liver. Immunoinflammatory reactions may be autoimmune genesis.
- Hepatomegaly is the cause of pain and discomfort in the right hypochondrium. Hepatocyte's dysfunction is the cause of jaundice (icterus), dysproteinemia, elevated bilirubin and enzyme levels (ALT, AST, LDH, GGT, Alkaline phosphatase, others), prothrombin level decreases, others.

Morphology

▪ Histopathology

- Histology for chronic hepatitis is varied
- Mildest: significant inflammation in portal tracts only, with lots of macrophages, lymphocytes (i.e. immune cells of a chronic nature) with well preserved liver architecture.
- Severe: bridging necrosis, i.e. portal tracts "bridged" by necrotic bands. deposition of fibrous tissue first only near portal tracts and then eventually periportal fibrosis with bridging

Chronic Hepatitis, morphology

- Hepatocyte injury, necrosis, and regeneration
- Sinusoidal cell reactive changes
- Portal tract Inflammation:
 - Confined to portal tracts, or
 - Spillover into adjacent parenchyma, with necrosis of hepatocytes ("interface hepatitis"), or
 - Bridging inflammation and necrosis
- Fibrosis:
 - continued loss of hepatocytes results in fibrous septa formation which ultimately leads to cirrhosis
- HBV: "ground-glass" hepatocytes, "sanded" nuclei
- HCV: bile duct damage, lymphoid aggregate formation
- **Cirrhosis: The end-stage outcome**

Clinical features

▪ Complains:

- Discomfort or pain over right hypochondrium,
- anorexia,
- nausea, vomiting,
- mild fever,
- Skin itch
- malaise, fatigue, weight loss
- Dyspeptic syndrome
- Arthralgia, arthritis may be in severe cases

Clinical features

▪ Inspectio:

- Skin has subicteric tint
- Sclera subicteric
- Gingival hemorrhage
- Petechial skin rash
- Teleangiectasias

▪ Palpatio:

- Hepat enlargement (large liver mass), soft and painful
- Splenomegaly, oedema, ascites may be due to severe cases

CHRONIC HEPATITIS DIAGNOSIS

LABORATORY SYNDROMES:

- **Cytolytic** syndrome (\uparrow AST, \uparrow ALT, \uparrow GGT, \uparrow Bilirubin)
- **Cholestatic** syndrome (\uparrow conjugated Bilirubin, \uparrow Alkaline phosphatase, \uparrow GGT, \uparrow cholesterol)
- **Liver cellular insufficiency** syndrome (\downarrow Albumine, \downarrow prothrombin, \downarrow cholesterol, \downarrow fibrinogen)
- **Mesenchyme-inflammatory** syndrome (\uparrow ESR, \uparrow γ -globulins, \uparrow timol test \uparrow Le, \uparrow C-react. protein)
- **Hypersplenism** (anemia, thrombocytopenia, leukocytopenia)

79. Chronic viral hepatitis: clinical presentation, verification of viral hepatitis, complications, prognosis, primary prevention, vaccination.

80. Treatment of hepatitis: diet, indications for use of antiviral drugs, corticosteroids and immunosuppressive drugs.

Hepatitis B virus (HBV) (a DNA virus.) *Spread:* Blood products, IV drug abusers (IVDU), sexual, direct contact. *Deaths:* 1 million/yr. *Risk groups:* IV drug users and their sexual partners/carers; health workers; haemophiliacs; men who have sex with men; haemodialysis (and chronic renal failure); sexually promiscuous; foster carers; close family members of a carrier or case; staff or residents of institutions/prisons; babies of HBsAg +ve mothers; adopted child from endemic area.

Endemic in: Far East, Africa, Mediterranean. *Incubation:* 1-6 months.

Signs: Resemble hepatitis A but arthralgia and urticaria are commoner.

Tests: HBsAg (surface antigen) is present 1-6 months after exposure. HBeAg (e antigen) is present for 1½-3 months after acute illness and implies high infectivity. HBsAg persisting for >6 months defines carrier status and occurs in 5-10% of infections; biopsy may be indicated unless ALT ↘ and HBV DNA <2000IU/mL. Antibodies to HBcAg (anti-HBc) imply past infection; antibodies to HBsAg (anti-HBs) alone imply vaccination. HBV PCR allows monitoring of response to therapy. See fig 6.29 and table 6.11. *Vaccination:* See p287. Passive immunization (specific anti-HBV immunoglobulin) may be given to non-immune contacts after high-risk exposure.

Complications: Fulminant hepatic failure, cirrhosis, HCC, cholangiocarcinoma, cryoglobulinaemia, membranous nephropathy, polyarteritis nodosa (p556).

R: Avoid alcohol. Immunize sexual contacts. Refer all with chronic liver inflammation (eg ALT ≥30IU/L), cirrhosis, or HBV DNA >2000IU/mL for antivirals (choice is 48 wks pegylated (PEG) interferon alfa-2a vs long-term but better tolerated nucleos(t)ide analogues, eg tenofovir, entecavir). The aim is to clear HBsAg and prevent cirrhosis and HCC (risk is ↑↑ if HBsAg and HBeAg +ve).

Hepatitis C virus (HCV) RNA flavivirus. *Spread:* Blood: transfusion, IV drug abuse, sexual contact. UK prevalence: >200 000. Early infection is often mild/asymptomatic. ~85% develop silent chronic infection; ~25% get cirrhosis in 20yrs—of these, ≤4% get hepatocellular cancer (HCC)/yr. *Risk factors for progression:* Male, older, higher viral load, use of alcohol, HIV, HBV. *Tests:* LFT (AST:ALT <1:1 until cirrhosis develops, p276), anti-HCV antibodies confirms exposure; HCV-PCR confirms ongoing infection/chronicity; liver biopsy or non-invasive elastography if HCV-PCR +ve to assess liver damage and need for treatment. Determine HCV genotype (1-6).

R: box; quit alcohol. *Other complications:* Glomerulonephritis; cryoglobulinaemia; thyroiditis; autoimmune hepatitis; PAN; polymyositis; porphyria cutanea tarda.

Chronic Hepatitis C

Definition

Chronic hepatitis C is a chronic infection caused by HCV which develops after 6 months from acute phase of infection.

Chronic hepatitis C is the main form of HCV infection. It is chronic in 70-85% of infected individuals.

usually progresses slowly and is characterised with non-specific clinical symptoms.

The slide is titled 'HEPATITIS C' in large red capital letters. Below the title, under the heading 'Symptoms', it states: 'The incubation period for hepatitis C is 2 weeks to 6 months. Following initial infection, approximately 80% of people do not exhibit any symptoms. Those who are acutely symptomatic may exhibit fever, fatigue, decreased appetite, nausea, vomiting, abdominal pain, dark urine, grey-coloured faeces, joint pain and jaundice (yellowing of skin and the whites of the eyes).'

Clinical Presentation

- Most patients with chronic hepatitis have asymptomatic elevations of serum aminotransferase levels and do not have physical signs of liver disease.
- 6% have symptomatic liver disease.
- Fatigue is the most common symptom.
- Dull right upper quadrant pain.
- Less common-anorexia, nausea, pruritis, arthralgia, myalgia

Figure 1 hbv

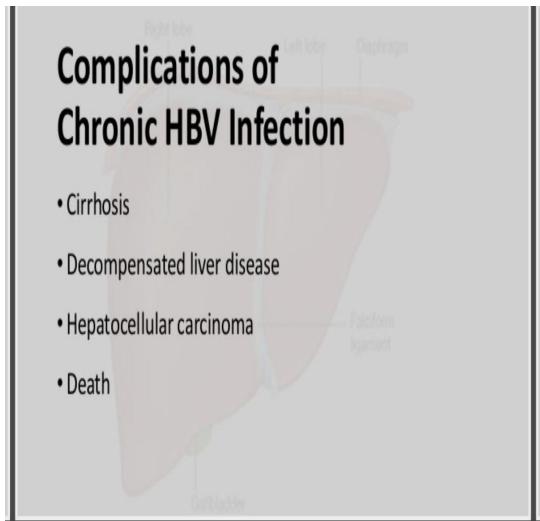
Chronic HBV	HBs Ag	HBeAg	IgM anti-HBc	IgG anti-HBc	Anti HBs	Anti Hbe	HBV DNA	Interpretation
Infection	+	+	-	+	-	-	+++	HBeAg+ chronic hepatitis
	+	-	-	+	-	+	±	Inactive carrier state
	+	-	-	+	-	+	++	HBeAg- chronic hepatitis
	+	±	±	+	-	±	++	Exacerbations of chronic hepatitis

LABORATORY DIAGNOSIS

- Serologic tests to detect HCV antibodies:
 - enzyme immunoassay (EIA). False negative in pts on HD, immunodeficiency; false positive in autoimmune disorder.
 - recombinant immunoblot assay (RIBA)
- Target amplification technique to detect HCV RNA (molecular assay)
 - polymerase chain reaction (PCR). A positive test confirms HCV infection.

DR.T.V.RAO MD

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СДО БГМУ Пурия Шерафат

HEPATITIS C

Prevention

Primary prevention

There is no vaccine for hepatitis C; therefore prevention of HCV infection depends upon reducing the risk of exposure to the virus in health-care settings, in higher risk populations, for example, people who inject drugs, and through sexual contact.

The following list provides a limited example of primary prevention interventions recommended by WHO:

- hand hygiene: including surgical hand preparation, hand washing and use of gloves;
- safe handling and disposal of sharps and waste;
- safe cleaning of equipment;
- testing of donated blood;
- improved access to safe blood;
- training of health personnel.

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Prevention



Vaccination

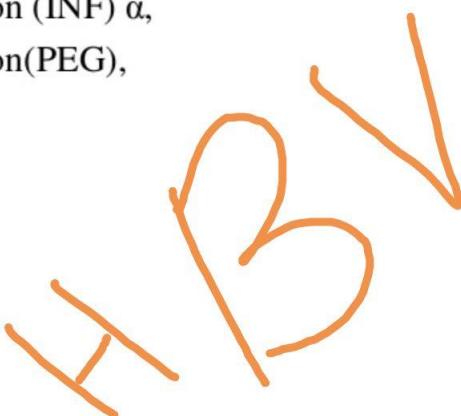
- Health care workers/EPI/Neonates of HBsAg positive mother.
- Hepatitis B Immunoglobulin
 - HBIG may be used to protect persons who are exposed to hepatitis B.
 - ♦ *It is particular efficacious within 48 hours of the incident.*
- Other measures
 - Screening of blood donors, blood and body fluid precautions.

Prognosis and survival

- ✓ The estimated five year rates of progression (Fattovich 2008):
 - ✓ Chronic hepatitis to cirrhosis - **10-20%**
 - ✓ Compensated cirrhosis to hepatic decompensation - **20-30%**
 - ✓ Compensated cirrhosis to hepatocellular carcinoma - **5-15%**
- ✓ Accordingly, the survival rates are:
 - ✓ Compensated cirrhosis - **85% at five years**
 - ✓ Decompensated cirrhosis - 55-70% at one year and **15-35% at five years**

Treatment Options

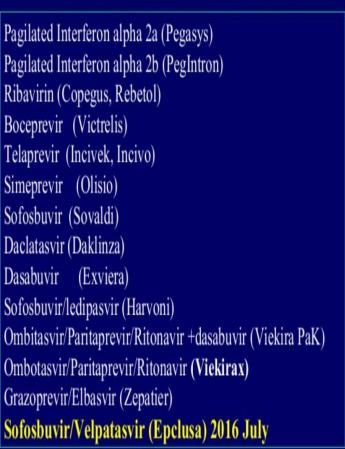
- 7 drugs have been approved to date
- Injectable Interferon (INF) α ,
- PEGylated Interferon(PEG),
- Lamivudine,
- Adefovir,
- Entecavir,
- Telbivudine,
- Tenofovir.



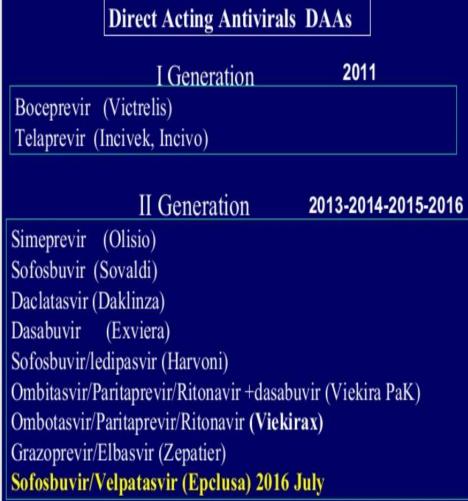
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slideshare.net/mobile/BasheerOudah/hepatitis-c-69695441 slideshare.net/mobile/BasheerOudah/hepatitis-c-69695441


Drugs for HCV (FDA approved)

- Paginated Interferon alpha 2a (Pegasys)
- Paginated Interferon alpha 2b (PegIntron)
- Ribavirin (Copegus, Rebetol)
- Boceprevir (Vicrelis)
- Telaprevir (Incivek, Incivo)
- Simeprevir (Olysio)
- Sofosbuvir (Sovaldi)
- Daclatasvir (Daklinza)
- Dasabuvir (Exviera)
- Sofosbuvir/Ledipasvir (Harvoni)
- Ombitasvir/Paritaprevir/Ritonavir +dasabuvir (Viekira PaK)
- Ombitasvir/Paritaprevir/Ritonavir (Viekirax)
- Grazoprevir/Elbasvir (Zepatier)
- Sofosbuvir/Velpatasvir (Epclusa) 2016 July**

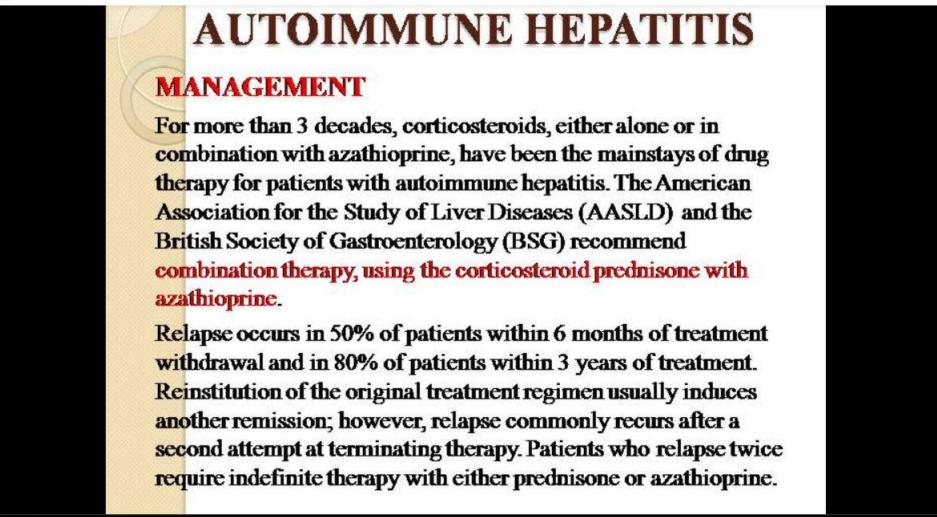

Direct Acting Antivirals DAAs

I Generation	2011
Boceprevir (Vicrelis)	
Telaprevir (Incivek, Incivo)	

II Generation	2013-2014-2015-2016
Simeprevir (Olysio)	
Sofosbuvir (Sovaldi)	
Daclatasvir (Daklinza)	
Dasabuvir (Exviera)	
Sofosbuvir/Ledipasvir (Harvoni)	
Ombitasvir/Paritaprevir/Ritonavir +dasabuvir (Viekira PaK)	
Ombitasvir/Paritaprevir/Ritonavir (Viekirax)	
Grazoprevir/Elbasvir (Zepatier)	
Sofosbuvir/Velpatasvir (Epclusa) 2016 July	

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СДО БГМУ Пурия Шерафат



AUTOIMMUNE HEPATITIS

MANAGEMENT

For more than 3 decades, corticosteroids, either alone or in combination with azathioprine, have been the mainstays of drug therapy for patients with autoimmune hepatitis. The American Association for the Study of Liver Diseases (AASLD) and the British Society of Gastroenterology (BSG) recommend combination therapy, using the corticosteroid prednisone with azathioprine.

Relapse occurs in 50% of patients within 6 months of treatment withdrawal and in 80% of patients within 3 years of treatment. Reinstitution of the original treatment regimen usually induces another remission; however, relapse commonly recurs after a second attempt at terminating therapy. Patients who relapse twice require indefinite therapy with either prednisone or azathioprine.

81 .Alcohol liver disease. Risk factors. Toxic doses of ethanol. Clinical forms.

82. Acute alcoholic hepatitis. Clinical and laboratory features. Assessment of the severity of acute alcoholic hepatitis. Treatment. Forecast.

83 .Chronic alcoholic hepatitis. Diagnostics. Indications for puncture biopsy.

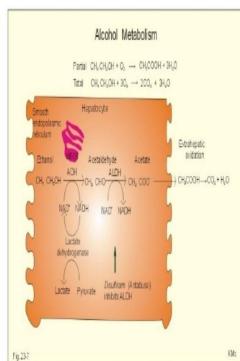
84 .Treatment of alcoholic liver disease.

Note?????? : I didn't find distinct feature between acute and chronic alcoholic hepatitis

Metabolism of Alcohol

- Alcohol metabolism by the liver result in increase in the NADH/NAD ratio & change in the oxidation-reduction status with reduced intracellular state. This leads to:

- 1-Increase hepatic fatty acid production
 - 2-Impaired carbohydrate and protein metabolism
 - 3-Centrilobular necrosis of the hepatic acinus
- The exact mechanism of alcohol hepatitis and cirrhosis is unknown.



Spectrum of alcoholic liver disease

- The three most widely recognized forms of ALD are :

- **alcoholic fatty liver (steatosis).**
- **acute alcoholic hepatitis.**
- **alcoholic cirrhosis.**

alcoholic fatty liver (steatosis)

- appears to be the initial change and is the most common response to alcohol ingestion
- The increased liver fat is derived from the diet, from free fatty acids mobilized from adipose tissue, and from lipid synthesized in the liver and inadequately degraded or excreted
- may cause mild abnormalities of liver function tests, including elevated ALT
- patients have an excellent prognosis if they abstain from alcohol.

alcoholic hepatitis

- It is characterized by necrosis of hepatocytes, and deposition of Mallory hyaline bodies.
- A polymorphonuclear reaction develops locally in response to the Mallory-containing and necrotic liver cells.
- typically presents with jaundice, low grade fever, and tender hepatomegaly
- Alcoholic hepatitis is often viewed as the intermediary step between fatty liver and cirrhosis

alcoholic cirrhosis

- represents end-stage disease
- Classically of micronodular type
- develop in 10 to 20% of those who are chronically heavy drinkers.
- Although irreversible, patients may live many years with few obvious effects particularly with cessation of drinking
- Decompensation of cirrhosis triggered by sepsis, bleeding, continued excessive drinking

Mechanisms of liver injury in Alcoholic hepatitis

- Genetic factors
- Malnutrition
- Toxic effects on cell membranes
- Hypermetabolic state of the hepatocyte
- Generation of free radicals and oxidative injury
- Formation of acetaldehyde adducts
- Role of the immune system
- Cytokines
- Role of concomitant viral disease

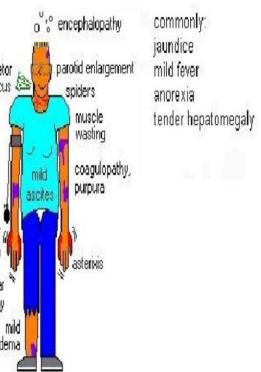
presentation

Alcoholic Hepatitis

physical exam must be in context of history and lab findings.

may be asymptomatic especially if stop drinking

may present with features of decompensation depending on degree of liver damage



INVESTIGATIONS

- Laboratory findings
- Ultrasonography
- Liver biopsy

laboratory findings in alcoholic hepatitis

Liver Function tests

- Increased AST to ALT ratio (2 to 1) (below 400IU/L)
- ALT usually < 100 IU/L
- Increased Gamma-GT (variable)
- Increased alkaline phosphatase (variable)
- Note: AST has 50% sensitivity, 82% specificity for alcohol-induced liver injury. ALT has 35% sensitivity, 86% specificity for alcohol-induced liver injury.

Liver synthetic function (decrease after significant liver injury)

- INR
- Albumin

laboratory findings in alcoholic hepatitis

Renal function (impaired in advanced ALD)

- Urea/ creatinine

Haematological

- Mild anaemia (usually macrocytic)
- Thrombocytopenia

Other abnormalities

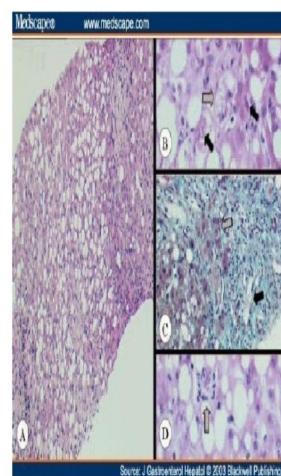
- Hyperuricaemia
- Hypertriglyceridaemia
- Raised IgA
- Hyperglycaemia

Ultrasonography

- Preferred study as inexpensive ,noninvasive and widely available
- The liver appears enlarged and diffusely hyperechoic.
- Helpful in excluding gallstones ,bile duct obstruction and hepatic or biliary neoplasm.

Liver biopsy

- Accurate assessment of severity of liver damage
 - Consider in patients in whom diagnosis is uncertain
- A steatosis
• B black arrows
Mallory bodies
• C pericellular fibrosis
• D satellitosis
Degeneration of hepatocytes



PROGNOSIS

- Alcoholic hepatitis carries a significant mortality
- The most established tool for predicting survival in alcoholic hepatitis is Maddrey's discriminant function (MDF)
- An MDF ≥ 32 indicates a poor prognosis with a risk of mortality around 35%.

Calculating Maddrey's discriminant function

$$MDF = \frac{\text{bilirubin } (\mu\text{mol/l})}{17} + (\text{PT - control (secs)} \times 4.6)$$

PROGNOSIS

Other factors that correlate with poor prognosis include :

- older age,
- impaired renal function,
- encephalopathy,
- rise in the white blood cell count in the first 2 weeks of hospitalization

Nearly 2/3 of patients with severe alcoholic hepatitis will die in the hospital

THERAPY

- Therapeutic agents for alcoholic hepatitis:

Evidence support use of:
1-corticosteroids
2-pentoxifylline
3-nutritional support

Insufficient evidence:
1-Anabolic steroids
2-Malotilate
3-Etanercept
4-Infliximab

Evidence not supporting use:
1-Propylthiouracil
2-Insulin and glucagon
3-Colchicine

Corticosteroids

- Steroid effects are mediated through a decrease in immune mediated injury, inhibition of cytokine production and activation, as well as suppression of extracellular matrix protein expression.
- should not be started until a sepsis screen has excluded infection
- Meta-analysis of three randomised trials showed an improvement in 28 day survival, but benefit was not seen at later time points
- The side effects of corticosteroids are justified only in patients with severe alcoholic hepatitis (MDF > 32).

Pentoxifylline

- Pentoxifylline inhibits tumor necrosis factor (TNF)-production.
- showed promise in one randomised controlled trial of patients with an MDF ≥ 32 who were not treated by steroids
- associated with a marked reduction in the incidence of hepatorenal syndrome and improved 28 day mortality with no significant side effects
- No trial has assessed combination therapy with steroids and pentoxifylline

Nutritional support

- Energy expenditure increased up to 60% in AH
- Severe negative nitrogen balance occurs in AH
- Nutritional status correlates with survival in moderate and severe AH
- 1-1.5g/Kg/day protein is required to achieve neutral balance in cirrhotics. This requirement increases significantly in AH
- Total enteral nutrition is recommended in patients admitted with AH. Studies have shown a decreased mortality rate in patients receiving enteral feeding.
- Oral supplementation is ineffective due to anorexia and poor compliance due to encephalopathy and insufficient protein-calorie content to meet metabolic demands

85 .Non-alcoholic steatohepatitis. Pathogenesis. Natural course. Clinic. Diagnostics. Indications for puncture biopsy of the liver.

86 .Non-alcoholic steatohepatitis. Directions of therapy. Indications for medical correction of body weight. Criteria for the effectiveness of therapy.

● ● ● Nonalcoholic Steatohepatitis

- Histology of the liver is identical to that in patients with alcoholic liver disease, but these patients do not have a history of alcohol use!
- Associated with obesity, hyperlipidemia, diabetes mellitus (some patients have none of these).
- Usually asymptomatic and a benign course (but cirrhosis develops in 10% to 15%).
- Typically discovered on routine laboratory tests (mild elevation in alanine aminotransferase [ALT] and aspartate aminotransferase [AST]).
- Treatment is not clearly established.

Non-alcoholic fatty liver disease (NAFLD)

The commonest liver disorder in Western industrialized countries (prevalence $\approx 20\%$), NAFLD¹² represents ↑fat in hepatocytes (steatosis) visualized, eg on ultrasound *that cannot be attributed to other causes* (most commonly alcohol so consider NAFLD if drink ♂<18u/wk, ♀<9u). If inflammation is also present (↑LFT, typically ↑ALT) = non-alcoholic steatohepatitis (NASH). Rule out other causes of liver disease (p284) and check for associated metabolic disorders (obesity, dyslipidaemia, diabetes, hypertension). Progression to cirrhosis may occur—biopsy or elastography may be needed (p248). **Risk factors for progression** Older age; obesity; DM; NASH. **Treatment** Control risk factors, including obesity (bariatric surgery helps). Address cardiovascular risk (commonest cause of death, see p93). Avoid alcohol consumption. No drug is of proven benefit, though vitamin E may improve histology in fibrosis (eg 400iu/d—higher doses associated with excess mortality). **Follow-up** Monitor for complications (NASH, cirrhosis, DM). If cirrhotic, screen for HCC with ultrasound ± AFP twice-yearly.

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Gastroenterology

DEFINITION

Nonalcoholic Fatty Liver Disease (NAFLD)

- (a) there is evidence of hepatic steatosis, either by imaging or by histology and
- (b) there are no causes for secondary hepatic fat accumulation such as significant alcohol consumption, use of steatogenic medication or hereditary disorders

Histologically further categorized into

- Nonalcoholic Fatty Liver (NAFL)
- Nonalcoholic Steatohepatitis (NASH)

Nonalcoholic Fatty Liver (NAFL)

Evidence of Hepatic steatosis either by imaging or Histology ($> 5\%$ of hepatocytes histologically) without any other Cause for secondary Fat Accumulation with no evidence of hepatocellular injury in the form of ballooning of the hepatocytes or no evidence of fibrosis.

The risk of progression to cirrhosis and liver failure is minimal.

Nonalcoholic steatohepatitis (NASH)

Presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without fibrosis.

This can progress to cirrhosis, liver failure and rarely liver cancer

PATHOGENESIS AND RISK FACTORS

Insulin resistance is related to obesity and is central to the pathogenesis of NAFLD.

In addition, oxidative stress and cytokines are important contributing factors, together resulting in steatosis and progressive liver damage in genetically susceptible individuals.

Key histologic components of NASH are steatosis, hepatocellular ballooning, and lobular inflammation

RISK FACTORS AND ASSOCIATED CONDITIONS

Risk factors	Disease progression	Associated conditions
• Insulin resistance/metabolic syndrome	• Obesity, Increased BMI and waist circumference	• Hyperlipidemia
• Jejunoileal bypass surgery	• Uncontrolled diabetes, hyperglycemia, hypertriglyceridemia	• Insulin resistance/metabolic syndrome
• Age—highest risk in 40–65-year-olds, but it does occur in children < 10 y old	• Sedentary lifestyle, lack of exercise	• Type 2 diabetes
• Ethnicity—higher risk in Hispanics and Asians, lower risk in African-Americans	• Insulin resistance	• Hepatitis C
• Positive family history—genetic predisposition	• Metabolic syndrome	• Rapid weight loss
• Drugs and toxins—e.g., amiodarone, coralgil, tamoxifen, perhexiline maleate, corticosteroids, synthetic estrogens, methotrexate, IV tetracycline, highly active antiretroviral drugs (HAART)	• Age	• Total parenteral nutrition
	• Genetic factors	• Wilson's disease, Weber-Christian disease, a beta lipoproteinemia, diverticulosis, polycystic ovary syndrome, obstructive sleep apnea

PROGNOSIS AND COMPLICATIONS

Disease progression from NAFLD to NASH to cirrhosis/liver failure and HCC.

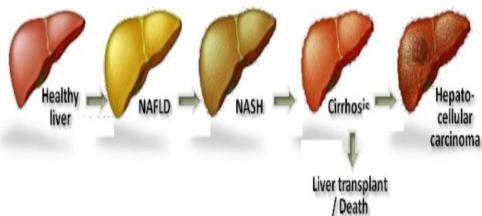
Concurrence of NAFLD with hepatitis C or human immunodeficiency virus (HIV) worsens their prognoses and decreases their responses to therapy.

Liver biopsy may indicate the severity of disease, but only fibrosis, and not inflammation or necrosis, has been confirmed to predict the disease prognosis.

End-stage NASH is an often under-recognized cause of cryptogenic cirrhosis

NASH-related (cryptogenic) cirrhosis increases the risk of hepatocellular carcinoma (HCC).

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)



Physical exam

- ✓ Abdominal obesity
- ✓ Enlarged liver
- ✓ RUQ tenderness on palpation

Central obesity correlates with severity of inflammation on biopsy, and dorsocervical lipohypertrophy (buffalo hump) correlates with hepatocyte injury.

In case of progression/advanced liver disease: spider angiomas, ascites, hepatomegaly, splenomegaly, palmar erythema, jaundice, hepatic encephalopathy.

WHEN TO OBTAIN A LIVER BIOPSY IN PATIENTS WITH NAFLD?

Liver biopsy should be considered in patients with NAFLD who are at increased risk to have steatohepatitis and advanced fibrosis. (Strength - 1, Evidence - B)

The presence of metabolic syndrome and the NAFLD Fibrosis Score may be used for identifying patients who are at risk for steatohepatitis and advanced fibrosis. (Strength - 1, Evidence - B)

Liver biopsy should be considered in patients with suspected NAFLD in whom competing etiologies for hepatic steatosis and co-existing chronic liver diseases cannot be excluded without a liver biopsy. (Strength - 1, Evidence - B)

DIAGNOSTIC TESTS FOR FATTY LIVER

Test	Sensitivity	Specificity	Remarks
Histology, liver biopsy	The gold standard	Cannot reliably distinguish between ASH and NASH	Significant variability between pathologists' reading of the same sample; a highly experienced hepatopathologist is best
Liver enzymes	Low	Low	AST/ALT usually < 1.0; values may be normal
Imaging			
Ultrasound	Limited	Limited	Insensitive unless steatosis > 33%; operator-dependent
MRI, MRS, CT scan ± contrast enhancement	Results are variable and not well verified		Test are costly, less available, cannot distinguish steatosis and fibrosis or NASH/ASH or stage disease, and are insensitive if there is < 33% steatosis; see reference list and extended reference list

MANAGEMENT

Therapeutic rationale

Targets for therapy : insulin resistance and oxidative stress

Goals of treatment: reduce the histologic features and improve insulin resistance and liver enzyme levels.

LIFESTYLE INTERVENTION

Weight loss generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity.

Loss of at least 3–5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation.

Exercise alone in adults with NAFLD may reduce hepatic steatosis but its ability to improve other aspects of liver histology remains unknown.



AVOID FRUCTOSE

Fructose (++++) in corn syrup)

Soda, canned industrial dishes

Experimental Data



Mice fed with fructose developed more severe inflammatory injuries compare to High fat diet Mice

-kholi, Hepatology 2010-

Human Data

In patients with NASH fructose consumption is associated with liver fibrosis

-Abdel malek Hepatology 2010-



INSULIN SENSITIZING AGENTS

METFORMIN

A recent meta analysis concluded that 6–12 months of metformin plus lifestyle intervention did not improve aminotransferases or liver histology, compared with lifestyle intervention alone, independently of metformin dose or the presence of diabetes.

June 2012 AGA 1597

Metformin has no significant effect on liver histology and is not recommended as a specific treatment for liver disease in adults with NASH. (Strength – 1, Evidence - A)

INSULIN SENSITIZING AGENTS

THIAZOLIDINEDIONES

- Rosiglitazone^{**}: improved enzymes and steatosis, but not inflammation
- Pioglitazone:^{***}+weight gain, but significantly improved aminotransferases, steatosis, ballooning, and inflammation

*Uygun, et al *Aliment Pharm Ther* 2004

*Nair, et al *Aliment Pharm Ther* 2004

**Ratziu, et al *Gastroenterology* 2008

***Sanyal, et al *NE J Med* 2010

Vit E>>

87 .Deficiency of alpha 1 antitrypsin: pathogenesis. Screening. Clinic. Stages of diagnosis. Treatment in the pre-cirrhotic stages. Indications for liver transplantation

α_1 -antitrypsin (A1AT) deficiency

A1AT deficiency is an inherited disorder affecting lung (emphysema) and liver (cirrhosis and HCC). A1AT is a glycoprotein and one of a family of serine protease inhibitors made in the liver that control inflammatory cascades. Deficiency is called a **serpinopathy**. It makes up 90% of serum α_1 -globulin on electrophoresis (p687). A1AT deficiency is the chief genetic cause of liver disease in children. In adults, its lack is more likely to cause emphysema. Lung A1AT protects against tissue damage from neutrophil elastase—a process that is also induced by cigarette smoking (p184). **Prevalence** ~1:4000 (higher in Caucasians).

Genetics Genetic variants of A1AT are typed by electrophoretic mobility as *medium* (M), *slow* (S), or *very slow* (Z). S and Z types are due to single amino acid substitutions at positions 264 and 342, respectively. These result in ↓production of α_1 -antitrypsin (S=60%, Z=15%). The normal genotype is PiMM, the high risk homozygote is PiZZ; heterozygotes are PiMZ and PiSZ (at low risk of developing liver disease).

The patient Symptomatic patients usually have the PiZZ genotype: dyspnoea from emphysema; cirrhosis; cholestatic jaundice. Cholestasis often remits in adolescence.

Tests Serum α_1 -antitrypsin (A1AT) levels ↓, usually (eg <11 μmol/L or <75% of lower limit of normal, which is ~0.9 g/L; labs vary). Note the 'usually'. Because A1AT is part of the acute-phase response, inflammation may hide a low level. Unless you do genotyping, you will inevitably mis-label some cirrhosis as cryptogenic. **Lung function testing:** Shows reductions in FEV₁ with obstructive pattern (p162). There may be some bronchodilator reversibility. **Liver biopsy:** (See p248.) Periodic acid Schiff (PAS) +ve; diastase-resistant globules. **Phenotyping:** By isoelectric focusing requires expertise to distinguish SZ and ZZ phenotypes. Phenotyping can miss null phenotypes. **Prenatal diagnosis:** Possible by DNA analysis of chorionic villus samples obtained at 11–13 wks' gestation.

Management Smoking cessation. Prompt treatment/preventative vaccination for lung infections. Giving IV A1AT pooled from human plasma is expensive but COPD exacerbations *may* be prevented (no good randomized trials). **Liver transplantation:** Needed in decompensated cirrhosis. **Lung transplantation:** Improves survival and has a comparable survival to transplantation in non-A1AT-deficient COPD. **Inhaled A1AT:** Has been tried in lung disease.

Prognosis Some patients have life-threatening symptoms in childhood, whereas others remain asymptomatic and healthy into old age. Worse prognosis if male, a smoker, or obese. Emphysema is the cause of death in most, liver disease in ~5%. In adults, cirrhosis ± HCC affect 25% of A1AT-deficient adults >50 yrs.

Alpha₁-antitrypsin deficiency

Alpha₁-antitrypsin (α_1 -AT) is a serine protease inhibitor (Pi) produced by the liver. One of its main anti-protease functions is the breakdown of neutrophil elastase. The mutated form of α_1 -AT (PiZ) cannot be secreted into the blood by liver cells because it is retained within the endoplasmic reticulum of the hepatocyte. Homozygous individuals (PiZZ) have low plasma α_1 -AT concentrations, although globules containing α_1 -AT are found in the liver, and these people may develop hepatic and pulmonary disease. Liver manifestations include cholestatic jaundice in the neonatal period (neonatal hepatitis), which can resolve spontaneously; chronic hepatitis and cirrhosis in adults; and, in the long term, HCC. Alpha₁-AT deficiency is a not uncommon exacerbating factor for liver disease of other aetiologies, and the possibility of dual pathology should be considered when severity of disease, such as ALD, appears disproportionate to the level of underlying insult.

There are no clinical features that distinguish liver disease due to α_1 -AT deficiency from liver disease due to other causes, and the diagnosis is made from the low plasma α_1 -AT concentration and genotyping for the presence of the mutation. Alpha₁-AT-containing globules can be demonstrated in the liver (Fig. 22.41)

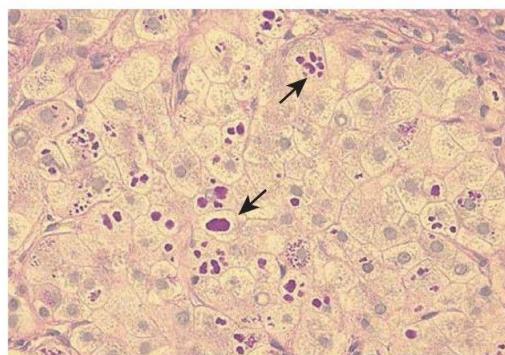


Fig. 22.41 Liver histology in α_1 -antitrypsin deficiency. Accumulation of periodic acid-Schiff-positive granules (arrows) within individual hepatocytes is shown in this section from a patient with α_1 -AT deficiency.

but this is not necessary to make the diagnosis. Occasionally, patients with liver disease and minor reductions of plasma α_1 -AT concentrations have α_1 -AT variants other than PiZZ, but the relationship of these to liver disease is uncertain.

There is no specific treatment. The risk of severe and early-onset emphysema means that all patients should be advised to stop smoking.

88. Hereditary hemochromatosis: pathogenesis. Screening. Clinic. Stages of diagnosis. Treatment. Forecast

●●● Hemochromatosis

A. General characteristics

1. An autosomal recessive disease of iron absorption.
2. Excessive iron absorption in the intestine leads to increased accumulation of iron (as ferritin and hemosiderin) in various organs. Over many years, fibrosis in involved organs occurs secondary to hydroxyl free radicals that are generated by the excess iron.
3. Affected organs
 - a. Liver (primary organ)
 - b. Pancreas
 - c. Heart
 - d. Joints
 - e. Skin
 - f. Thyroid, gonads, hypothalamus
4. This is an inherited disease, so screen the patient's siblings. Early diagnosis and treatment before development of complications (primarily cirrhosis, but also heart disease and diabetes) improves survival.

B. Clinical features

1. Most patients are asymptomatic initially.
2. Findings may include signs of liver disease, fatigue, arthritis, impotence/amenorrhea, abdominal pain, and cardiac arrhythmias.

C. Complications

1. Cirrhosis
 - a. Cirrhosis increases the risk of HCC by 200-fold.
 - b. The presence of liver disease is a primary factor in determining the prognosis.
2. Cardiomyopathy—CHF, arrhythmias
3. Diabetes mellitus—due to iron deposition in the pancreas
4. Arthritis—most common sites are the second and third metacarpophalangeal joints, hips, and knees
5. Hypogonadism—impotence, amenorrhea, loss of libido
6. Hypothyroidism
7. Hyperpigmentation of skin (resembles suntan, "bronzelike")

D. Diagnosis

1. Markedly elevated serum iron and serum ferritin
2. Elevated iron saturation (transferrin saturation)
3. Decreased total iron-binding capacity (TIBC)
4. Liver biopsy (determines hepatic iron concentration) required for diagnosis
5. Genetic testing for chromosomal abnormalities

E. Treatment

1. Perform repeated phlebotomies—this is the treatment of choice and improves survival dramatically if initiated early in the course of the disease.
2. Treat any complications (e.g., CHF, diabetes, hypothyroidism, arthritis).
3. Consider liver transplantation in advanced cases.

●●● Hepatocellular Adenoma

- Benign liver tumor, most often seen in young women (15 to 40 years of age). Oral contraceptive use, female sex, and anabolic steroid use are the main risk factors.
- Patient may be asymptomatic; hepatocellular adenoma may be discovered incidentally on abdominal imaging studies. RUQ pain or fullness may be present.

<http://internalmedicinebook.com>

Quick HIT

Hemochromatosis: Early in the disease course, mild elevation of ALT and AST levels may be the only abnormalities that are noted because the patient is usually asymptomatic. Obtain iron studies. If the iron level is elevated, order a liver biopsy to confirm the diagnosis.

Hereditary haemochromatosis

In hereditary haemochromatosis (HHC), iron is deposited throughout the body and total body iron may reach 20–60 g (normally 4 g). The important organs involved are the liver, pancreatic islets, endocrine glands, joints and heart. In the liver, iron deposition occurs first in the periportal hepatocytes, extending later to all hepatocytes. The gradual development of fibrous septa leads to the formation of irregular nodules, and finally regeneration results in macronodular cirrhosis. An excess of liver iron can occur in alcoholic cirrhosis but this is mild in comparison with haemochromatosis.

Pathophysiology

The disease is caused by increased absorption of dietary iron and is inherited as an autosomal recessive trait. Approximately 90% of patients are homozygous for a single point mutation resulting in a cysteine to tyrosine substitution at position 282 (C282Y) in the HFE protein, which has structural and functional similarity to the HLA proteins. The mechanisms by which HFE regulates iron absorption are unclear. It is believed, however, that HFE normally interacts with the transferrin receptor in the basolateral membrane of intestinal epithelial cells. In HHC, it is thought that the lack of functional HFE causes a defect in uptake of transferrin-associated iron, leading to up-regulation of enterocyte iron-specific divalent metal transporters and excessive iron absorption. A histidine-to-aspartic acid mutation at position 63 (H63D) in HFE causes a less severe form of haemochromatosis that is most commonly found in patients who are compound heterozygotes also carrying a C282Y mutated allele. Fewer than 50% of C282Y homozygotes will develop clinical features of haemochromatosis; therefore other factors must also be important. HHC may promote accelerated liver disease in patients with alcohol excess or hepatitis C infection. Iron loss in menstruation and pregnancy can delay the onset of HHC in females.

Clinical features

Symptomatic disease usually presents in men over 40 years of age with features of liver disease (often with hepatomegaly), type 2 diabetes or heart failure. Fatigue and arthropathy are early symptoms but are frequently absent. Leaden-grey skin pigmentation due to excess melanin occurs, especially in exposed parts, axillae, groins and genitalia; hence the term 'bronzed diabetes'. Once again, absence of this feature does not preclude the diagnosis. Impotence, loss of libido and testicular atrophy are recognised complications, as are early-onset osteoarthritis targeting unusual sites such as the metacarpophalangeal joints, chondrocalcinosis and pseudogout. Cardiac failure or cardiac dysrhythmia may occur due to iron deposition in the heart.

Investigations

Serum iron studies show a greatly increased ferritin, a raised plasma iron and saturated plasma iron-binding capacity. Transferrin saturation of more than 45% is suggestive of iron overload. Significant liver disease is unusual in patients with ferritin lower than 1000 µg/L (100 µg/dL). The differential diagnoses for elevated ferritin are inflammatory disease or excess ethanol consumption for modest elevations (< 1000 µg/L (100 µg/dL)). Very significant ferritin elevation can be seen in adult Still's disease. In terms of imaging techniques, MRI has high specificity for iron overload but poor sensitivity. Liver biopsy allows assessment of fibrosis and distribution of iron (hepatocyte iron characteristic of haemochromatosis). The Hepatic Iron Index (HII) provides quantification of liver iron (µmol of iron per g dry weight of liver/age in years). An HII of more than 1.9 suggests genetic haemochromatosis (Fig. 22.40). Both the C282Y and the H63D mutations can be identified by genetic testing, which is now in routine clinical use.

Management

Treatment consists of weekly venesection of 500 mL blood (250 mg iron) until the serum iron is normal; this may take 2 years or more. The aim is to reduce ferritin to under 50 µg/L (5 µg/dL). Thereafter, venesection is continued as required to keep the serum ferritin normal. Liver and cardiac problems

improve after iron removal, but joint pain is less predictable and can improve or worsen after iron removal. Type 2 diabetes does not resolve after venesection. Other therapy includes that for cirrhosis and diabetes. First-degree family members should be investigated, preferably by genetic screening and also by checking the plasma ferritin and iron-binding saturation. Liver biopsy is indicated in asymptomatic relatives only if the LFTs are abnormal and/or the serum ferritin is greater than 1000 µg/L (100 µg/dL) because these features are associated with significant fibrosis or cirrhosis. Asymptomatic disease should also be treated by venesection until the serum ferritin is normal.

Pre-cirrhotic patients with HHC have a normal life expectancy, and even cirrhotic patients have a good prognosis compared with other forms of cirrhosis (three-quarters of patients are alive 5 years after diagnosis). This is probably because liver function is well preserved at diagnosis and improves with therapy. Screening for hepatocellular carcinoma (p. 890) is mandatory because this is the main cause of death, affecting one-third of patients with cirrhosis, irrespective of therapy. Venesection reduces but does not abolish the risk of hepatocellular carcinoma in the presence of cirrhosis.

89 . Wilson's disease: pathogenesis. Clinic. Stages of diagnosis. Treatment. Indications for liver transplantation.

••• Wilson Disease

A. General characteristics

1. An autosomal recessive disease of copper metabolism.
2. Mutations in the ATP7B gene lead to impairment of copper excretion into bile, and incorporation of copper into ceruloplasmin, a copper-binding protein that is necessary for copper excretion.
3. Therefore, copper accumulates in liver cells. As hepatocytes die, copper leaks into plasma and accumulates in various organs, including kidney, cornea, and brain.
4. The disease is most often apparent during childhood/adolescence (after age 5), and the majority of cases present between ages 5 and 35.

B. Clinical features

1. Clinical features are due to copper deposition in various organs.
2. Liver disease (most common initial manifestation): Manifestations vary and may include acute hepatitis, cirrhosis, and fulminant hepatic failure.
3. **Kayser–Fleischer rings** (yellowish rings in cornea) are caused by copper deposition in cornea; they do not interfere with vision (Figure 3-1).
4. CNS findings are due to copper deposition in the CNS.
 - a. Extrapiramidal signs—parkinsonian symptoms (resting tremor, rigidity, bradykinesia), chorea, drooling, incoordination due to copper deposition in basal ganglia.
 - b. Psychiatric disturbances—depression, neuroses, personality changes, psychosis.
5. Renal involvement—aminoaciduria, nephrocalcinosis.

C. Diagnosis

1. Diagnosis is made by determining the following (patients may have many or only a few of these findings):
 - a. Hepatic disease—elevated aminotransferases; impaired synthesis of coagulation factors and albumin.
 - b. Decreased serum ceruloplasmin levels (seen in 90% of patients), although ranges within normal do not exclude the diagnosis.
 - c. Liver biopsy—significantly elevated copper concentration.
2. If diagnosed, first-degree relatives must be screened as well.

D. Treatment

1. Chelating agents—for example, d-penicillamine, which removes and detoxifies the excess copper deposits
2. Zinc
 - a. Prevents uptake of dietary copper
 - b. Given alone (presymptomatic or pregnant patients) or in conjunction with chelating agents (to symptomatic patients)

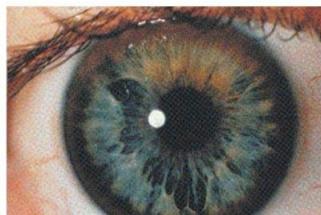


FIGURE 3-1 **Kayser–Fleischer ring.**

(From Humes DH, DuPont HL, Gardner LB, et al. *Kelley's Textbook of Internal Medicine*, 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; Figure 105.4.)

Wilson's disease/hepatolenticular degeneration

Wilson's disease is a rare (3/100 000) inherited disorder of copper excretion with excess deposition in liver and CNS (eg basal ganglia). It is treatable, so screen all with cirrhosis.

Genetics

An autosomal recessive disorder of a copper transporting ATPase, ATP7B. Physiology Total body copper content is ~25mg. Intake ~3mg/day (absorbed in proximal small intestine). In the liver, copper is incorporated into ceruloplasmin. In Wilson's disease, copper incorporation into ceruloplasmin in hepatocytes and excretion into bile are impaired. Copper accumulates in liver, and later in other organs.

Signs Children present with *liver disease* (hepatitis, cirrhosis, fulminant liver failure); young adults often start with *CNS signs*: tremor; dysarthria, dysphagia; dyskinésias; dystonias; dementia; Parkinsonism; ataxia/clumsiness.

Mood: Depression/mania; labile emotions; libido; personality change. Ignoring these may cause years of needless misery; often the doctor who is good at combining the analytical and integrative aspects will be the first to make the diagnosis.

Cognition: ↓Memory; slow to solve problems; ↓IQ; delusions; mutism.

Kayser–Fleischer (KF) rings: Copper in iris (see 6 in following list); they are not invariable.

Also: Haemolysis; blue lunulae (nails); arthritis; hypermobile joints; grey skin.

Tests Equivocal copper studies need expert interpretation.

1. Urine: 24h copper excretion is *high*, eg >100mcg/24h (normal <40mcg).

2. tLFT: non-specific (but ALT >1500 is *not* part of the picture).

3. Serum copper: typically <11μmol/L.

4. Serum ceruloplasmin: <200mg/L (<140mg/L is pathognomonic)—beware incidental low values in protein-deficiency states (eg nephrotic syndrome, mal-absorption).

5. Molecular genetic testing can confirm the diagnosis.

6. Slit lamp exam: KF rings: in iris/Descemet's membrane (fig 5.42 OHCS p452).

7. Liver biopsy: ↑Hepatic copper (copper >250mcg/g dry weight); hepatitis; cirrhosis.

8. MRI: degeneration in basal ganglia, fronto-temporal, cerebellar, and brainstem.

Management Diet: Avoid foods with high copper content (eg liver, chocolate, nuts, mushrooms, legumes, and shellfish). Check water sources (eg wells, pipes) for copper. **Drugs:** Lifelong penicillamine (500mg/6-8h po for 1yr, maintenance 0.75-1g/d). **SES:** nausea, rash, WCC, ↓Hb, ↑platelets, haematuria, nephrosis, lupus. Monitor FBC and urinary copper and protein excretion. **Liver transplantation:** (See p277.) If severe liver disease. **Screen siblings:** Asymptomatic homozygotes need treating.

Prognosis Pre-cirrhotic liver disease is reversible; CNS damage less so. There are no clear clinical prognostic indicators. Fatal events: liver failure, bleeding, infection.

90. Autoimmune liver disease. Autoimmune hepatitis: clinic, diagnosis. Pharmacotherapy of autoimmune hepatitis. Indications for liver transplantation

Autoimmune hepatitis (AIH)

An inflammatory liver disease of unknown cause³³ characterized by abnormal T-cell function and autoantibodies directed against hepatocyte surface antigens. Classification is by autoantibodies (see table 6.12). AIH predominantly affects young or middle-aged women (bimodal, ie 10–30yrs—or >40yrs old). Up to 40% present with acute hepatitis and signs of autoimmune disease, eg fever, malaise, urticarial rash, polyarthritis, pleurisy, pulmonary infiltration, or glomerulonephritis. The remainder present with gradual jaundice or are asymptomatic and diagnosed incidentally with signs of chronic liver disease. Amenorrhoea is common and disease tends to attenuate during pregnancy. **Complications** Those associated with cirrhosis (p276) and drug therapy.

Tests Serum bilirubin, AST, ALT, and ALP all usually ↑, hypergammaglobulinaemia (esp. IgG), +ve autoantibodies (see table 6.12). Anaemia, ↓WCC, and ↓platelets indicate hypersplenism. **Liver biopsy:** (See p248.) Mononuclear infiltrate of portal and periportal areas and piecemeal necrosis ± fibrosis; cirrhosis → worse prognosis. **MRCP:** (See p742.) Helps exclude PSC if ALP ↑ disproportionately.

Diagnosis Depends on excluding other diseases (no lab test is pathognomonic). Diagnostic criteria based on IgG levels, autoantibodies, and histology in the absence of viral disease are helpful. Sometimes diagnosis is a challenge—there is overlap with other chronic liver disease: eg PBC (p282), PSC (p282) and chronic viral hepatitis.

Table 6.12 Classifying autoimmune hepatitis: types I-II

- | | |
|----|---|
| I | Seen in 80%. Typical patient: ♀ <40yrs. Antismooth muscle antibodies (ASMA) +ve in 80%. Antinuclear antibody (ANA) +ve in 10%. IgG in 97%. Good response to immunosuppression in 80%. 25% have cirrhosis at presentation. |
| II | Commoner in Europe than USA. More often seen in children, and more commonly progresses to cirrhosis and less treatable. Typically anti-liver/kidney microsomal type 1 (LKM) antibodies +ve. ASMA and ANA -ve. |

Management Immunosuppressant therapy: Prednisolone 30mg/d PO for 1 month; ↓ by 5mg a month to a maintenance dose of 5–10mg/d PO. Corticosteroids can sometimes be stopped after 2yrs but relapse occurs in 50–86%. Azathioprine (50–100mg/d PO) may be used as a steroid-sparing agent to maintain remission. Remission is achievable in 80% of patients within 3yrs. 10- and 20yr survival rates are >80%. SEs are a big problem (p376)—partly ameliorated by a switch to budesonide, eg in non-cirrhotic AIH.

Liver transplantation: (See p277.) Indicated for decompensated cirrhosis or if there is failure to respond to medical therapy, but recurrence may occur. It is effective (actuarial 10y survival is 75%).

Prognosis Appears not to matter whether symptomatic or asymptomatic at presentation (10yr survival ~80% for both). The presence of cirrhosis at presentation reduces 10yr survival from 94% to 62%. Overlap syndromes: AIH-PBC (primary biliary cholangitis) overlap is worse than AIH-AIC (autoimmune cholangitis).

Associations of autoimmune hepatitis

- | | |
|--------------------------|----------------------------------|
| • Pernicious anaemia | • Autoimmune haemolysis |
| • Ulcerative colitis | • Diabetes mellitus |
| • Glomerulonephritis | • PSC (p282) |
| • Autoimmune thyroiditis | • HLA A1, B8, and DR3 haplotype. |

Autoimmune hepatitis

Autoimmune hepatitis is a disease of immune-mediated liver injury characterised by the presence of serum antibodies and peripheral blood T lymphocytes reactive with self-proteins, a strong association with other autoimmune diseases (Box 22.49), and high levels of serum immunoglobulins – in particular, elevation of IgG. Although most commonly seen in women, particularly in the second and third decades of life, it can develop in either sex at any age. The reasons for the breakdown in immune tolerance in autoimmune hepatitis remain unclear, although cross-reactivity with viruses such as HAV and EBV in immunogenetically susceptible individuals (typically those with human leucocyte antigen (HLA)-DR3 and DR4, particularly HLA-DRB3*0101 and HLA-DRB1*0401) has been suggested as a mechanism.

Pathophysiology

Several subtypes of this disorder have been proposed that have differing immunological markers. Although the different patterns can be associated with variation in disease aspects, such as response to immunosuppressive therapy, histological patterns are similar in the different settings and the basic approach to treatment (complete control of liver injury using immunosuppressive drugs and maintained with appropriate therapy) is the same. The formal classification into disease types has fallen out of favour in recent years.

The most frequently seen autoantibody pattern is high titre of antinuclear and anti-smooth muscle antibodies, typically associated with IgG hypergammaglobulinaemia (type I autoimmune hepatitis in the old classification), frequently seen in young adult females. Disease characterised by the presence of anti-liver-kidney microsomal (LKM) antibodies, recognising cytochrome P450 IID6 expressed on the hepatocyte membrane, is typically seen in paediatric populations and can be more resistant to treatment than ANA-positive disease. Adult onset of anti-LKM can be seen in chronic HCV infection. This was classified as type II disease in the old system. More recently, a pattern of antibody reactivity with anti-soluble liver antigen (anti-SLA) has been described in

typically adult patients, often with aggressive disease and usually lacking autoantibodies of other specificities.

Clinical features

The onset is usually insidious, with fatigue, anorexia and eventually jaundice. The non-specific nature of the early features can lead to the diagnosis being missed in the early disease stages. In about one-quarter of patients the onset is acute, resembling viral hepatitis, but resolution does not occur. This acute presentation can lead to extensive liver necrosis and liver failure. Other features include fever, arthralgia, vitiligo and epistaxis. Amenorrhoea can occur. Jaundice is mild to moderate or occasionally absent, but signs of chronic liver disease, especially spider naevi and hepatosplenomegaly, can be present. Associated autoimmune disease, such as Hashimoto's thyroiditis or rheumatoid arthritis, is often present and can modulate the clinical presentation.

Investigations

Serological tests for autoantibodies are often positive (Box 22.50), but low titres of these antibodies occur in some healthy people and in patients with other inflammatory liver diseases. ANA also occur in connective tissue diseases and other autoimmune diseases (with an identical pattern of homogenous nuclear staining) while anti-smooth muscle antibody has been reported in infectious mononucleosis and a variety of malignant diseases. Anti-microsomal antibodies (anti-LKM) occur particularly in children and adolescents. Elevated serum IgG levels are an important diagnostic and treatment response feature if present, but the diagnosis is still possible in the presence of normal IgG levels. If the diagnosis of autoimmune hepatitis is suspected, liver biopsy should be performed. It typically shows interface hepatitis, with or without cirrhosis. Scoring systems, such as the International Autoimmune Hepatitis Group (AIHG) criteria, are useful for epidemiological study and for assessing trial eligibility but are complex for normal clinical practice.

Management

Treatment with glucocorticoids is life-saving in autoimmune hepatitis, particularly during exacerbations of active and symptomatic disease. Initially, prednisolone (40 mg/day) is given orally; the dose is then gradually reduced as the patient and LFTs improve. Maintenance therapy should only be instituted once LFTs are normal (as well as IgG if elevated). Approaches to maintenance include reduced-dose prednisolone (ideally, below 5–10 mg/day), usually in the context of azathioprine (1.0–1.5 mg/kg/day). Azathioprine can also be used as the sole maintenance immunosuppressive agent in patients with low-risk disease. Newer agents, such as mycophenolate mofetil (MMF), are increasingly being used but formal evidence to inform practice in this area is lacking. Patients should be monitored for acute exacerbations (LFT and IgG screening with patients alerted

i 22.49 Conditions associated with autoimmune hepatitis

- Migrating polyarthritis
- Urticaria/caseous lymphadenopathy
- Hashimoto's thyroiditis
- Thyrotoxicosis
- Myxoedema
- Pleurisy
- Coombs-positive haemolytic anaemia
- Transient pulmonary infiltrates
- Ulcerative colitis
- Glomerulonephritis
- Nephrotic syndrome

i 22.50 Frequency of autoantibodies in chronic non-viral liver diseases and in healthy people

Disease	Antinuclear antibody (%)	Anti-smooth muscle antibody (%)	Antimitochondrial antibody ^a
Healthy controls	5	1.5	0.01
Autoimmune hepatitis	80	70	15
Primary biliary cholangitis	25	35	95
Cryptogenic cirrhosis	40	30	15

^aPatients with antimitochondrial antibody frequently have cholestatic liver function tests and may have primary biliary cholangitis (see text).

91. Primary sclerosing cholangitis: prevalence, pathogenesis, clinic, diagnosis, complications, treatment. Indications for liver transplantation.

Primary Sclerosing Cholangitis

A. General characteristics

1. A chronic idiopathic progressive disease of intrahepatic and/or extrahepatic bile ducts characterized by thickening of bile duct walls and narrowing of their lumens; leads to cirrhosis, portal hypertension, and liver failure (Table 3-3).

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FIGURE 3-3 Porcelain gallbladder. Note the thin layer of mineralization surrounding the gallbladder wall.

(Courtesy of Dr Frank Gaillard, Radiopaedia.org.)

Quick HIT

Complications of PSC

- Cholangiocarcinoma (in up to 20% to 30% of patients)
- Recurrent bouts of cholangitis (in about 15% of patients)
- Can progress to secondary biliary cirrhosis, portal HTN, and liver failure

B. Clinical features

1. Signs and symptoms begin insidiously.
2. Chronic cholestasis findings, including jaundice and pruritus; all patients eventually present with chronic obstructive jaundice
3. Other symptoms: fatigue, malaise, weight loss

C. Diagnosis

1. ERCP and PTC are diagnostic studies of choice—see multiple areas of bead-like stricturing and bead-like dilatations of intrahepatic and extrahepatic ducts.
2. Laboratory tests show cholestatic LFTs.

D. Treatment

1. There is no curative treatment other than liver transplantation.

TABLE 3-3

Primary Biliary Cirrhosis Versus Primary Sclerosing Cholangitis

	Primary Biliary Cirrhosis	Primary Sclerosing Cholangitis
Pathology	Intrahepatic bile duct destruction	Intra- and extrahepatic bile duct thickening and luminal narrowing
Demographics	Female > Male 9:1	Male > Female
Association with Inflammatory Bowel Disease	None	Strong association with ulcerative colitis (UC) and also Crohn Disease
Diagnosis	+ antimitochondrial antibodies (AMAs) in 90%–95% of patients. Liver biopsy to confirm diagnosis	ERCP will show bead-like dilations in intra- and extrahepatic bile ducts
Treatment	Ursodeoxycholic acid slows progression, liver transplantation	Liver transplantation

<http://internalmedicinebook.com>

2. When a dominant stricture causes cholestasis, ERCP with stent placement for biliary drainage and bile duct dilatation may relieve symptoms.
3. Use cholestyramine for symptomatic relief (to decrease pruritus).

Quick HIT

92 . Primary biliary cholangitis (formerly known as primary biliary cirrhosis): pathogenesis, clinic, diagnosis, complications, treatment. Indications for liver transplantation.

2. When a dominant stricture causes cholestasis, ERCP with stent placement for biliary drainage and bile duct dilatation may relieve symptoms.
3. Use cholestyramine for symptomatic relief (to decrease pruritus).

●● Primary Biliary Cirrhosis

A. General characteristics

1. PBC is a chronic and progressive cholestatic liver disease characterized by destruction of intrahepatic bile ducts with portal inflammation and scarring (Table 3-3).
2. It is a slowly progressive disease with a variable course. It may progress to cirrhosis and end-stage liver failure.
3. It is an autoimmune disease that is often associated with other autoimmune disorders.
4. It is most common in middle-aged women.

B. Clinical features

1. Fatigue
2. Pruritus (early in course of disease)
3. Jaundice (late in course of disease)
4. RUQ discomfort
5. Xanthomata and xanthelasmata
6. Osteoporosis
7. Portal HTN (with resultant sequelae)

C. Diagnosis

1. Laboratory findings
 - a. Cholestatic LFTs (elevated ALK-P)
 - b. Positive antimitochondrial antibodies (AMAs) found in 90% to 95% of patients. This is the hallmark of the disease (specificity of 98%). If serum is positive for AMAs, perform a liver biopsy to confirm diagnosis
 - c. Elevated cholesterol, HDL
 - d. Elevated immunoglobulin M
2. Liver biopsy (percutaneous or laparoscopic) to confirm the diagnosis
3. Abdominal ultrasound or CT scan to rule out biliary obstruction

D. Treatment

1. Treatment is symptomatic for pruritus (cholestyramine) and osteoporosis (calcium, bisphosphonates, vitamin D).
2. Ursodeoxycholic acid (a hydrophilic bile acid) has been shown to slow progression of the disease.
3. Liver transplantation is the only curative treatment available.

Quick HIT

Etiology of Secondary Biliary Cirrhosis

This disease occurs in response to chronic biliary obstruction from the following:

- Long-standing mechanical obstruction
- Sclerosing cholangitis
- Cystic fibrosis
- Biliary atresia

PBC and PSC

Primary Biliary Cirrhosis

- misnomer – actually a nonsuppurative autoimmune cholangitis
- autoimmune disease of the liver
- predominantly affects middle-aged women
- results in destruction of interlobular bile ducts
- causes cholestasis and, eventually, cirrhosis
- no cure

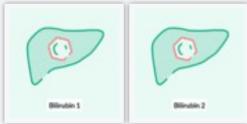
PBC Complications

- Chronic cholestasis
 - Loss of bone density
 - Malabsorption
 - Steatorrhea
 - Bile salt deficiency
 - Pancreatic disease
 - Coeliac disease
 - Vitamin A, D, E, K deficiency
- Portal hypertension
 - Oesophageal and gastric varices
 - Ascites
 - Encephalopathy
 - SBP
 - HRS or HPS
 - Hepatocellular carcinoma

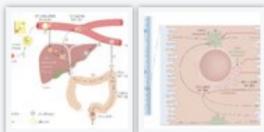
.93 Inherited hyperbilirubinemia. Classification, clinic, course, diagnosis and prognosis of Gilbert, Rotor and Dabin-Johnson syndromes

Inherited hyperbilirubinemia**Summary**

Hyperbilirubinemia describes serum bilirubin levels ≥ 1.1 mg/dL. In contrast to acute or chronic cholestatic liver disorders, which may also lead to increased serum bilirubin levels, syndromes associated with hyperbilirubinemia lead to isolated hyperbilirubinemia and hence do not affect liver enzymes. These syndromes cause a rise in either unconjugated or conjugated bilirubin. The clinical manifestation of hyperbilirubinemia is relatively mild, with the main symptom being transient jaundice. Aside from Crigler-Najjar syndrome type I, there is no need for management of inherited hyperbilirubinemia syndromes. Therefore, patients with hyperbilirubinemia generally have a good prognosis.

**Classification****Isolated hyperbilirubinemia**

\uparrow Unconjugated (indirect) bilirubin	Excess release	Hemolytic anemia
	Defective conjugation	Gilbert syndrome Crigler-Najjar syndrome
\uparrow Conjugated (direct) bilirubin	Defective excretion	Dubin-Johnson syndrome Rotor syndrome



References:[1][2]

Crigler-Najjar syndrome type II (Arias syndrome)

- **Etiology:** reduced levels of UDP-glucuronosyltransferase
- **Inheritance:** autosomal recessive
- **Clinical features**
 - Often asymptomatic
 - No neonatal jaundice, although jaundice may occur during the patient's first year of life
 - No neurological symptoms
- **Diagnosis**
 - ↑ Indirect bilirubin (< 20 mg/dL)
 - Normal liver function tests
 - No evidence of hemolysis
 - Responds to phenobarbital \rightarrow ↓ serum bilirubin levels
- **Treatment:** Patients are less likely to develop kernicterus. Specific treatment may therefore not be required. The following treatment options are, however, available if patients become icteric.
 - Phototherapy (as in type I)
 - Phenobarbital
 - Avoid hormonal contraception and hepatic enzyme inhibitors
- **Prognosis:** usually favorable; management of jaundice allows for normal quality of life

References:[4][6]

Crigler-Najjar syndrome

Crigler-Najjar syndrome type I

- **Etiology:** UDP-glucuronosyltransferase is (almost) absent.
- **Inheritance:** autosomal recessive
- **Clinical features**
 - Excessive, persistent neonatal jaundice
 - Neurological symptoms caused by kernicterus
- **Diagnosis**
 - ↑ Indirect bilirubin (20–50 mg/dL)
 - Normal liver function tests
 - No evidence of hemolysis
- **Management**
 - Phototherapy
 - Plasmapheresis during acute rises in serum bilirubin levels
 - Tin protoporphyrin
 - Calcium carbonate
 - Liver transplantation is the only curative treatment.
- **Prognosis**
 - Without treatment, Crigler-Najjar syndrome type I is incompatible with life because it causes kernicterus
 - If treated, patients may survive past puberty, but most will eventually develop kernicterus.

Rotor syndrome

- **Etiology:** Defective organic anion transport proteins (OATP) 1B1 and 1B3 in hepatocytes → impaired transport and reduced storage capacity of conjugated (direct) bilirubin
- **Inheritance:** autosomal recessive
- **Clinical features:** usually asymptomatic
- **Diagnosis**
 - Moderate, direct hyperbilirubinemia and mild, indirect hyperbilirubinemia
 - Normal liver function test
 - ↑ Urinary coproporphyrins I and III (fraction of isomer I < 70% of total)
 - Liver biopsy: normal, no pigmentation
- **Treatment:** not required
- **Special considerations**
 - Be careful when administering medication that is toxic to the liver → may worsen jaundice!
 - Contraindication for oral contraception

References: [7][9][10]

Sources

last updated 04/22/2020

Dubin-Johnson syndrome

- **Etiology:** defective multidrug resistance-associated protein 2 (MRP2) → impaired movement of conjugated (direct) bilirubin from the hepatocyte to the bile canaliculi
- **Inheritance:** autosomal recessive
- **Clinical features**
 - Mild to moderate jaundice
 - Onset often occurs during adolescence
 - May worsen because of medication (particularly contraceptives) or pregnancy
 - Splenomegaly may occur in rare cases.
- **Diagnosis**
 - Direct hyperbilirubinemia (direct bilirubin/total bilirubin up to 50%)
 - Liver biopsy: darker granular pigmentation
- **Treatment:** not required
- **Special considerations**
 - Be careful when administering medication that is toxic to the liver → may worsen jaundice!
 - Contraindication for oral contraception

References: [7][8]

Airplane mode 0K/s 55% 6:46 PM

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Gilbert syndrome (Gilbert-Meulengracht syndrome; Meulengracht disease)

- **Epidemiology**
 - Most common inherited hyperbilirubinemia: The prevalence is 3–7% in the US.
 - ♂ > ♀
 - Age of onset: adolescence
- **Etiology**
 - Mutation in the promoter region of *UGT1A1* gene → ↓ activity of UDP-glucuronosyltransferase → decreased conjugation of bilirubin → ↑ indirect bilirubin
 - Autosomal recessive inheritance
- **Clinical features**
 - Asymptomatic or unspecific symptoms such as fatigue and loss of appetite
 - Transient jaundice (varying from mild scleral jaundice to general jaundice) [3]
- **Trigger factors of transient jaundice**
 - Physical stress (trauma, disease, exhaustion)
 - Fasting periods
 - Alcohol consumption
- **Diagnosis**
 - ↑ Indirect bilirubin but < 3 mg/dL (higher levels are possible during episodes of increased bilirubin breakdown)
 - Normal liver function
 - No evidence of hemolysis
 - Detection of mutation using PCR
- **Treatment:** no management required

References: [4][5][3]

Cri-du-chat syndrome

94. Glomerulonephritis. Modern concepts of etiology and pathogenesis. Classification. Clinical picture.

Classification:

1. Can be primary (intrinsic renal pathology) or secondary (to a systemic disease). Two important categories of glomerular pathology are diseases that present with nephrotic syndrome and those that present with nephritic syndrome. Many conditions have features of both.
2. There is a wide range in the rate of disease progression, varying from days to weeks in the acute glomerular diseases, to years in the chronic disorders.

Causes:

1. GN is usually caused by immune-mediated mechanisms.
2. Other mechanisms include metabolic and hemodynamic disturbances.

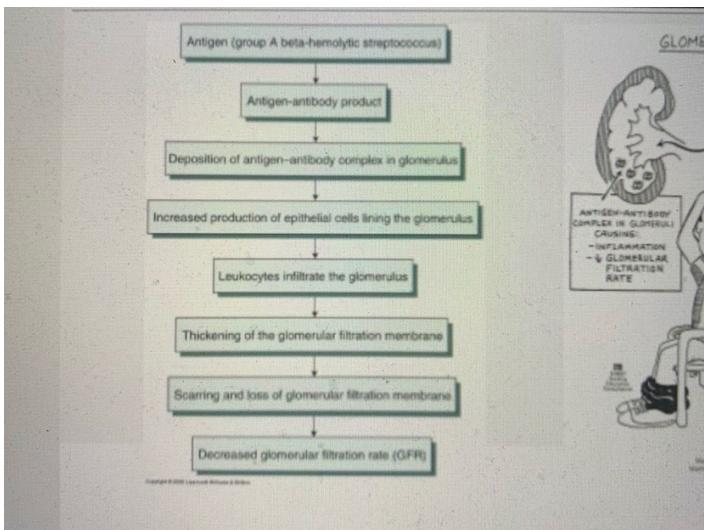
Clinical features:

1. Glomerular disorders are characterized by impairment in selective filtration of blood, resulting in excretion of larger substances such as plasma proteins and blood cells. As disease advances, GFR decreases proportionately, leading to renal failure and the possible need for dialysis and/or transplantation.
2. The classic features are proteinuria, hematuria, or both. Nephrotic range proteinuria is pathognomonic for glomerular disease.

TABLE 7-5 Nephritic Versus Nephrotic Syndrome		
	Nephritic Syndrome	Nephrotic Syndrome
Pathogenesis	Inflammation of glomeruli due to any of the causes of glomerulonephritis	Abnormal glomerular permeability due to a number of conditions
Causes	Poststreptococcal glomerulonephritis is the most common cause, but may be due to any of the causes of glomerulonephritis	Many conditions: Membranous glomerulonephritis is the most common cause in adults. Other causes include diabetes, SLE, drugs, infection, glomerulonephritis (focal segmental and others)
Laboratory Findings	Hematuria AKI—azotemia, oliguria Proteinuria, if present, is mild and not in nephrotic range	Urine protein excretion rate >3.5 g/24 hr Hypoalbuminemia Hyperlipidemia, fatty casts in urine
Clinical Findings	HTN Edema	Edema Hypercoagulable state Increased risk of infection

Possible Clinical Manifestations

- Proteinuria – asymptomatic
- Haematuria – asymptomatic
- Hypertension
- Nephrotic syndrome
- Nephritic syndrome
- Acute renal failure
- Rapidly progressive renal failure
- End stage renal failure



95. The main clinical syndromes in acute nephritis. Complications of acute nephritis. Laboratory and instrumental indicators of renal function.

Clinical syndromes:

Interstitial nephritis

In interstitial nephritis, the spaces between the kidney tubules become inflamed. This inflammation causes the kidneys to swell.

Pyelonephritis

Pyelonephritis is an inflammation of the kidney, usually due to a bacterial infection. In the majority of cases, the infection starts within the bladder and then migrates up the ureters and into the kidneys. Ureters are two tubes that transport urine from each kidney to the bladder.

Glomerulonephritis

This type of acute nephritis produces inflammation in the glomeruli. There are millions of capillaries within each kidney. Glomeruli are the tiny clusters of capillaries that transport blood and behave as filtering units. Damaged and inflamed glomeruli may not filter the blood properly. Learn more about glomerulonephritis.

Complications:

1. Acute kidney failure. Loss of function in the filtering part of the nephron can result in rapid accumulation of waste products.
2. Chronic kidney disease. Your kidneys gradually lose their filtering ability. ...
3. High blood pressure.
4. Nephrotic syndrome.

Diag:

1. Urinalysis (hematuria, proteinuria, RBC casts)
2. Blood tests (renal function tests) increased BUN and Cr levels
3. Needle biopsy of the kidney

96. The course of chronic glomerulonephritis. Outcomes. Forecast. Treatment of acute glomerulonephritis: regimen, diet, etiological treatment, glucocorticoids, immunosuppressants, antiplatelet agents, symptomatic therapy, treatment of complications. Prevention.

Nearly all forms of acute glomerulonephritis have a tendency to progress to chronic glomerulonephritis. The condition is characterized by irreversible and progressive glomerular and tubulointerstitial fibrosis, ultimately leading to a reduction in the glomerular filtration rate (GFR) and retention of uremic toxins. If disease progression is not halted with therapy, the net results are chronic kidney disease (CKD), end-stage renal disease (ESRD), and cardiovascular disease. Chronic glomerulonephritis is the third leading cause of CKD, and accounting for about 10% of all patients on dialysis.

The exact cause of CKD in patients with chronic glomerulonephritis may never be known in some patients. Therefore, it has generally been accepted that the diagnosis of CKD can be made without knowledge of the specific cause. [1]

The National Kidney Foundation (NKF) defines CKD on the basis of either of the following:

Evidence of kidney damage based on abnormal urinalysis results (eg, proteinuria or hematuria) or structural abnormalities observed on ultrasound images

A GFR of less than 60 mL/min for 3 or more months

In accordance with this definition, the NKF developed guidelines that classify the progression of renal disease into five stages, from kidney disease with a preserved GFR to end-stage kidney failure. This classification includes treatment strategies for each progressive level, as follows:

Stage 1 – This stage is characterized by kidney damage with a normal GFR (≥ 90 mL/min); the action plan consists of diagnosis and treatment, treatment of comorbid conditions, slowing of the progressing of kidney disease, and reduction of cardiovascular disease risks

Stage 2 – This stage is characterized by kidney damage with a mild decrease in the GFR (60-90 mL/min); the action plan is estimation of the progression of kidney disease

Stage 3 – This stage is characterized by a moderately decreased GFR (to 30-59 mL/min); the action plan consists of evaluation and treatment of complications

Stage 4 – This stage is characterized by a severe decrease in the GFR (to 15-29 mL/min); the action plan is preparation for renal replacement therapy

Stage 5 – This stage is characterized by kidney failure; the action plan is kidney replacement if the patient is uremic

At the later stages of glomerular injury, the kidneys are small and contracted and biopsy results cannot help distinguish the primary disease. Histology and clues to the etiology are often derived from other systemic diseases (if present). Considerable cause-specific variability is observed in the rate at which acute glomerulonephritis progresses to chronic glomerulonephritis.

The prognosis depends on the type of chronic glomerulonephritis (see Etiology). ESRD and death are common outcomes unless renal replacement therapy is instituted.

Chronic Glomerulonephritis

- Incidental discovery of occult proteinuria or HTN
- Usually presents as chronic renal failure or occult proteinuria
- Glomerulus has scar tissue
- Dialysis & transplant

Treatment:

Antibiotics

Antibiotics (eg, penicillin) are used to control local symptoms and to prevent spread of infection to close contacts. Antimicrobial therapy does not appear to prevent the development of GN, except if given within the first 36 hours. Antibiotic treatment of close contacts of the index case may help prevent development of PSGN.

Other agents

Loop diuretics may be required in patients who are edematous and hypertensive, in order to remove excess fluid and to correct hypertension.

Vasodilator drugs (eg, nitroprusside, nifedipine, hydralazine, diazoxide) may be used if severe hypertension or encephalopathy is present.

Glucocorticoids and cytotoxic agents are of no value, except in severe cases of PSGN.

Regime:

Antimicrobials (Antibiotics):

1. Penicillin V is more resistant than penicillin G to hydrolysis by acidic gastric secretions and is absorbed rapidly after oral administration. 250 mg of penicillin V = 400,000 U of penicillin.

2. Cephalexin is a first-generation cephalosporin that inhibits bacterial replication by inhibiting bacterial cell wall synthesis. It is bactericidal and effective against rapidly growing organisms forming cell walls.

Resistance occurs by alteration of penicillin-binding proteins. It is effective for the treatment of infections caused by streptococci or staphylococci, including penicillinase-producing staphylococci. It may be used to initiate therapy when streptococcal or staphylococcal infection is suspected.

Cephalexin is used orally when outpatient management is indicated. It is at least as effective as erythromycin in eradicating GABHS infection.

Loop Diuretics:

Furosemide increases excretion of water by interfering with the chloride-binding cotransport system, inhibiting sodium and chloride reabsorption in the ascending loop of Henle and the distal renal tubule.

Furosemide is rapidly absorbed from the gastrointestinal (GI) tract. The diuretic effect is apparent within 1 hour of oral (PO) administration, peaks by the second hour, and lasts for 4-6 hours. After intravenous (IV) administration, diuresis occurs within 30 minutes; the duration of action is about 2 hours; 66% of the dose is excreted in the urine.

Vasodilators:

Sodium nitroprusside

is a potent, rapidly acting IV antihypertensive agent. Its effect is immediate and usually ends as soon as infusion is stopped because of its rapid biotransformation. Sodium nitroprusside produces vasodilation and increases inotropic activity of the heart. At higher dosages, it may exacerbate myocardial ischemia by increasing heart rate. Use this agent only for treatment of acute severe hypertension or malignant hypertension that is refractory to standard therapy.

Hydralazine

Hydralazine lowers blood pressure by exerting a peripheral vasodilating effect through direct relaxation of vascular smooth muscle. Sodium retention and excessive sympathetic stimulation of the heart may be precluded by coadministration of a thiazide diuretic and a beta-blocker.

Calcium Channel Blockers:

Nifedipine

is a dihydropyridine calcium channel blocker. The specific mechanisms by which nifedipine reduces blood pressure have not been fully determined but are believed to be brought about largely by its vasodilatory action on peripheral blood vessels. Nifedipine relaxes coronary smooth muscle and produces coronary vasodilation, which, in turn, improves myocardial oxygen delivery.

Diet:

Sodium and fluid restriction should be advised for treatment of signs and symptoms of fluid retention (eg, edema, pulmonary edema). Protein restriction for patients with azotemia should be advised if there is no evidence of malnutrition.

Long-Term Monitoring:

Long-term studies on children with PSGN have revealed few chronic sequelae. Results of such studies are controversial because homogenous populations suitable for proper epidemiologic analysis have not been assembled.

Long-term studies show higher mortality rates in elderly patients, particularly those on dialysis. Patients may be predisposed to crescent formation.

97. Chronic glomerulonephritis. Etiology, pathogenesis.

Laboratory and instrumental methods of investigation in chronic glomerulonephritis. The course, the outcome of the disease.

Etiology:

The progression from acute glomerulonephritis to chronic glomerulonephritis is variable, depending to a considerable extent on the cause of the condition. Whereas complete recovery of renal function is the rule for patients with poststreptococcal glomerulonephritis, several other glomerulonephritides, such as immunoglobulin A (IgA) nephropathy, often have a relatively benign course, and many do not progress to ESRD. Progression patterns may be summarized as follows:

Rapidly progressive glomerulonephritis or crescentic glomerulonephritis – About 90% of patients progress to ESRD within weeks or months.

Focal segmental glomerulosclerosis – About 80% of patients progress to ESRD in 10 years; patients with the collapsing variant (malignant focal segmental glomerulosclerosis) have a more rapid progression; this form may be idiopathic or related to HIV infection

Membranous nephropathy – About 20-30% of patients with membranous nephropathy progress to chronic renal failure (CRF) and ESRD in 10 years

Membranoproliferative glomerulonephritis – About 40% of patients with membranoproliferative glomerulonephritis progress to CRF and ESRD in 10 years

IgA nephropathy – About 10% of patients with IgA nephropathy progress to CRF and ESRD in 10 years

Poststreptococcal glomerulonephritis – About 1-2% of patients with poststreptococcal glomerulonephritis progress to CRF and ESRD; older children who present with crescentic glomerulonephritis are at greatest risk

Lupus nephritis – Overall, about 20% of patients with lupus nephritis progress to CRF and ESRD in 10 years; however, patients with certain histologic variants (eg, class IV) may have a more rapid decline. [5] The presence of antineutrophil cytoplasmic antibody (ANCA) is also an independent risk factor for poor renal outcomes.

Pathophysiology:

Reduction in nephron mass from the initial injury reduces the GFR. This reduction leads to hypertrophy and hyperfiltration of the remaining nephrons and to the initiation of intraglomerular hypertension. These changes occur in order to increase the GFR of the remaining nephrons, thus minimizing the functional consequences of nephron loss. The changes, however, are ultimately detrimental because they lead to glomerulosclerosis and further nephron loss.

In early renal disease (stages 1-3), a substantial decline in the GFR may lead to only slight increases in serum creatinine levels. Azotemia (ie, a rise in blood urea nitrogen [BUN] and serum creatinine levels) is apparent when the GFR decreases to less than 60-70 mL/min. In addition to a rise in BUN and creatinine levels, the substantial reduction in the GFR results in the following:

Decreased production of erythropoietin, thus resulting in anemia

Decreased production of vitamin D, resulting in hypocalcemia, secondary hyperparathyroidism, hyperphosphatemia, and renal osteodystrophy

Reduction in acid, potassium, salt, and water excretion, resulting in acidosis, hyperkalemia, hypertension, and edema

Platelet dysfunction, leading to increased bleeding tendencies

Accumulation of toxic waste products (uremic toxins) affects virtually all organ systems. Azotemia occurring with the signs and symptoms listed above is known as uremia. Uremia occurs at a GFR of approximately 10 mL/min. Some of these toxins (eg, BUN, creatinine, phenols, and guanidines) have been identified, but none has been found to be responsible for all the symptoms.

Work up:

Laboratory Studies

Urinalysis

The presence of dysmorphic red blood cells (RBCs), albumin, or RBC casts suggests glomerulonephritis as the cause of renal failure. Waxy or broad casts are observed in all forms of chronic kidney disease (CKD), including chronic glomerulonephritis. Low urine specific gravity indicates loss of tubular concentrating ability, an early finding in persons with CKD. See Urinalysis.

Urinary protein excretion

Urinary protein excretion can be estimated by calculating the protein-to-creatinine ratio on a spot morning urine sample. The ratio of urinary protein concentration (in mg/dL) to urinary creatinine (in mg/dL) reflects 24-hour protein excretion in grams. For instance, if the spot urine protein value is 300 mg/dL and the creatinine value is 150 mg/dL, the protein-to-creatinine ratio is 2. Thus, in this example, the 24-hour urine protein excretion is 2 g. [11]

The estimated creatinine clearance rate is used to assess and monitor the glomerular filtration rate (GFR). The following 3 formulas are available for calculation of the GFR:

Cockcroft-Gault formula

Modification of Diet in Renal Disease (MDRD) Study formula

Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation

The Cockcroft-Gault formula is simple to use but overestimates the GFR by 10-15% because creatinine is both filtered and secreted. The MDRD formula is much more complex and has been found to underestimate GFR by 6.2% in patients with CKD and by 29% in healthy persons. [28] The CKD-EPI is based on the same four variables as the MDRD Study formula but uses a 2-slope “spline” to model the relationship between estimated GFR and serum creatinine, and a different relationship for age, sex, and race. The National Kidney Foundation (NKF) recommends using the CKD-EPI Creatinine Equation to estimate GFR; a CKD-EPI calculator is available on the NKF Web site.

The estimated creatinine clearance rate is also used to monitor response to therapy and to initiate an early transition to renal replacement therapy (eg, dialysis access placement and transplantation evaluation). The degree of proteinuria, especially albuminuria, helps predict the renal prognosis in patients with chronic glomerulonephritis. Patients with proteinuria exceeding 1 g/day have an increased risk of progression to end-stage renal failure.

Complete blood count

Anemia is a significant finding in patients with some decline in the GFR. Physicians must be aware that anemia can occur even in patients with serum creatinine levels lower than 2 mg/dL. Even severe anemia can occur at low serum creatinine levels. Anemia is the result of marked impairment of erythropoietin production.

Serum chemistry

Serum creatinine and urea nitrogen levels are elevated. Impaired excretion of potassium, free water, and acid results in hyperkalemia, hyponatremia, and low serum bicarbonate levels, respectively. Impaired vitamin D-3 production results in hypocalcemia, hyperphosphatemia, and high levels of parathyroid hormone. Low serum albumin levels may be present if uremia interferes with nutrition or if the patient is nephrotic.

Levels of fibroblast growth factor 21 (FGF21) have been found to be significantly elevated in patients with CKD and the high levels of FGF21 may explain the excess overall and cardiovascular mortality in patients with CKD. These adverse effects of elevated FGF21 are not clearly understood but research is under way to elucidate its biologic effects.

Renal ultrasonography

Obtain a renal ultrasonogram to determine renal size, to assess for the presence of both kidneys, and to exclude structural lesions that may be responsible for azotemia. Small kidneys often indicate an irreversible process.

Kidney biopsy

If the kidney is small, kidney biopsy is usually unnecessary; no specific pattern of disease can be discerned at this point. A kidney biopsy may be considered in the minority of patients who exhibit an acute exacerbation of their chronic disease. This may be particularly pertinent to patients with preserved kidney size and in those with lupus nephritis.

In early stages, the glomeruli may still show some histologic evidence of the primary disease. In advanced stages, the glomeruli are hyalinized and obsolescent. The tubules are disrupted and atrophic, and marked interstitial fibrosis and arterial and arteriolar sclerosis occur.

A study by Murray et al of 75 patients with suspected familial kidney disease who underwent genetic sequencing after kidney biopsy found that accurate genetic diagnosis can result in changes in clinical diagnosis, understanding of pathological mechanism, and treatment. These authors

recommended considering next-generation sequencing as a complement to kidney biopsy in the evaluation of patients with kidney disease.

98. Treatment of chronic glomerulonephritis: regimen, diet, drug therapy. Secondary prophylaxis.

Patients with chronic kidney disease (CKD) who are admitted to the hospital should receive careful monitoring of weight, intake, output, and renal function so that acute kidney injury (AKI) can be diagnosed and treated early if it occurs. All potentially nephrotoxic agents must be adjusted for the degree of CKD. Furthermore, agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, and intravenous (IV) contrast media must be avoided unless the benefits clearly outweigh the risks; they are strongly associated with AKI.

Progression from CKD to end-stage renal disease (ESRD) can be slowed by a variety of measures, including aggressive control of diabetes, hypertension, and proteinuria. Dietary protein restriction, phosphate restriction, and hyperlipidemia control may have significant impact on retarding disease progression. In obese patients, weight reduction and bariatric surgery may have beneficial effects on CKD. [13]

Specific therapies for some glomerular diseases (eg, lupus) should be implemented in appropriate settings. Aggressively manage anemia and renal osteodystrophy (eg, hyperphosphatemia, hypocalcemia, or hyperparathyroidism) before initiating renal replacement therapy. Also, aggressively manage comorbid conditions, such as heart disease and diabetes.

Nephrotic patients (urinary protein excretion >3.5 g/day) may have hyperlipidemia. As a part of cardiovascular health care, the lipid profile should be checked, and lipid-lowering therapy should be started for patients with hyperlipidemia.

Steroid therapy may induce or exacerbate diabetes, hypertension, weight gain, fat redistribution in the trunk (buffalo hump) and face (moon facies), cosmetic problems (eg, hirsutism and acne), and osteoporosis.

Monitor fasting blood glucose levels and blood pressure. Obtain baseline bone densitometry values. Repeat bone densitometry for bone pain. Oral calcium supplements (1 g/day) and vitamin D (400-800 IU/day) are recommended for prophylaxis against osteoporosis.

Medication:

The goals of pharmacotherapy are to reduce morbidity and to prevent complications. Medications used to treat chronic glomerulonephritis include angiotensin-converting enzyme (ACE) inhibitors (ACEIs), diuretics, calcium channel blockers, beta-adrenergic blockers, and alpha-adrenergic agonists.

ACE Inhibitors

Class Summary

ACEIs are renoprotective agents. They decrease intraglomerular pressure and, consequently, glomerular protein filtration by decreasing efferent arteriolar constriction.

Enalapril (Vasotec)

Enalapril is a competitive inhibitor of ACE. It reduces angiotensin II levels, thus decreasing aldosterone secretion. It decreases intraglomerular pressure and glomerular protein filtration by decreasing efferent arteriolar constriction.

Captopril

Captopril prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, resulting in lower aldosterone secretion. It is rapidly absorbed, but bioavailability is significantly reduced with food intake. Captopril achieves a peak concentration in 1 hour and has a short half-life. It is cleared by the kidney; impaired renal function requires reduction of the dosage. The drug is absorbed well orally.

It decreases intraglomerular pressure and glomerular protein filtration by decreasing efferent arteriolar constriction. Give captopril at least 1 hour before meals. If it is added to water, use it within 15 minutes. The dose can be low initially, then titrated upward as needed and as tolerated by the patient.

Lisinopril (Prinivil, Zestril)

Lisinopril prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, resulting in increased levels of plasma renin and a reduction in aldosterone secretion. It decreases intraglomerular pressure and glomerular protein filtration by decreasing efferent arteriolar constriction.

Benazepril (Lotensin)

Benazepril prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, resulting in increased levels of plasma renin and a reduction in aldosterone secretion.

It decreases intraglomerular pressure and glomerular protein filtration by decreasing efferent arteriolar constriction.

Fosinopril

Fosinopril is a competitive ACE inhibitor. It prevents conversion of angiotensin I to angiotensin II, a potent vasoconstrictor, resulting in increased levels of plasma renin and a reduction in aldosterone secretion. It decreases intraglomerular pressure and glomerular protein filtration by decreasing efferent arteriolar constriction.

Quinapril (Accupril)

Quinapril is a competitive ACE inhibitor. It reduces angiotensin II levels, decreasing aldosterone secretion. It decreases intraglomerular pressure and glomerular protein filtration by decreasing efferent arteriolar constriction.

Diuretics, Loop Class Summary

Diuretics are used to treat edema and hypertension. They increase urine excretion by inhibiting sodium and chloride transporters.

Furosemide (Lasix)

Furosemide is the diuretic of choice. It increases excretion of water by interfering with the chloride-binding cotransport system, which, in turn, inhibits sodium and chloride reabsorption in the ascending loop of Henle and the distal renal tubule.

Bumetanide (Bumex)

Bumetanide increases the excretion of water by interfering with the chloride-binding cotransport system, which, in turn, inhibits sodium, potassium, and chloride reabsorption in the ascending loop of Henle. These effects increase the urinary excretion of sodium, chloride, and water, resulting in profound diuresis. Renal vasodilation occurs after administration, renal vascular resistance decreases, and renal blood flow is enhanced. In terms of effect, 1 mg of bumetanide is equivalent to approximately 40 mg of furosemide.

Ethacrynic acid (Edecrin)

Ethacrynic acid increases the excretion of water by interfering with the chloride-binding cotransport system, which, in turn, inhibits sodium and chloride reabsorption in the ascending loop of Henle and distal renal tubule. This agent is used only in refractory cases. Continuous IV infusion is preferable in many cases. It is indicated for temporary treatment of edema associated with heart failure when greater diuretic potential is needed.

Diuretics, Thiazide Class Summary

Diuretics are used to treat edema and hypertension. They increase urine excretion by inhibiting sodium and chloride transporters.

Metolazone (Zaroxolyn)

Metolazone treats edema in congestive heart failure. It increases excretion of sodium, water, potassium, and hydrogen ions by inhibiting reabsorption of sodium in distal tubules. It may be more effective in cases of impaired renal function.

Hydrochlorothiazide (Microzide)

Hydrochlorothiazide inhibits reabsorption of sodium in distal tubules, causing increased excretion of sodium and water as well as potassium and hydrogen ions.

Calcium Channel Blockers

Class Summary

Calcium channel blockers are used to treat hypertension, angina, and atrial fibrillation.

Amlodipine (Norvasc)

Amlodipine blocks slow calcium channels, causing relaxation of vascular smooth muscles.

Nifedipine (Procardia)

Nifedipine relaxes coronary smooth muscle and produces coronary vasodilation, which, in turn, improves myocardial oxygen delivery. Sublingual administration is generally safe, theoretical concerns notwithstanding.

Felodipine

Felodipine relaxes coronary smooth muscle and produces coronary vasodilation, which, in turn, improves myocardial oxygen delivery. It benefits nonpregnant patients with systolic dysfunction, hypertension, or arrhythmias. It can be used during pregnancy if clinically indicated.

Calcium-channel blockers potentiate ACE inhibitor effects. Renal protection is not proven, but these agents reduce morbidity and mortality rates in congestive heart failure. Calcium channel blockers are indicated in patients with diastolic dysfunction. They are effective as monotherapy in black patients and elderly patients.

Isradipine (DynaCirc)

Isradipine is a dihydropyridine calcium channel blocker. It inhibits calcium from entering select voltage-sensitive areas of vascular smooth muscle and myocardium during depolarization. This causes relaxation of coronary vascular smooth muscle, which results in coronary vasodilation. Vasodilation reduces systemic resistance and blood pressure, with a small increase in resting heart rate. Isradipine also has negative inotropic effects.

Verapamil (Calan, Isoptin, Verelan)

During depolarization, verapamil inhibits calcium ions from entering slow channels and voltage-sensitive areas of vascular smooth muscle and myocardium. It can diminish premature ventricular contractions (PVCs) associated with perfusion therapy and decrease risk of ventricular fibrillation and ventricular tachycardia. By interrupting re-entry at the AV node, it can restore normal sinus rhythm (NSR) in patients with paroxysmal supraventricular tachycardias.

Diltiazem (Cardizem, Dilacor XR, Diltzac, Matzim LA)

During depolarization, diltiazem inhibits calcium ions from entering slow channels and voltage-sensitive areas of vascular smooth muscle and myocardium.

Beta-Blockers, Beta-1 Selective Alpha-Blockers, Antihypertensives Vasodilators

99. Secondary nephropathy. Differential diagnosis. Principles of treatment.

Secondary membranous nephropathy

- Infection-associated (*e.g.* hepatitis B virus, hepatitis C virus, syphilis, malaria)
- Disease-associated (*e.g.* rheumatoid arthritis, Sjögren's syndrome, bullous pemphigoid)
- Drug/toxin-induced (*e.g.* nonsteroidal anti-inflammatory drugs, gold, mercury, penicillamine)
- Malignancy-associated (carcinomas and non-carcinomas)

Miscellaneous (*e.g.* sickle cell disease, Guillain-Barre syndrome)

Differential Diagnosis

- Minimal change disease.
- Membranoproliferative glomerulonephritis.
- Focal segmental glomerulosclerosis.

Medscap

Symptomatic treatment includes the following:

A low-salt diet is key to reducing anasarca. Protein restrictions may or may not be useful in reducing the rate of progression of chronic renal failure.

Diuretics help control edema. Loop diuretics are used most often.

Treat hypertension aggressively.

Statins help treat hypercholesterolemia.

Nonsteroidal anti-inflammatory drugs (NSAIDs) can help to decrease the proteinuria; however, NSAIDs have been largely supplanted by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). ACE inhibitors decrease proteinuria and control hypertension; use ARBs for patients intolerant of ACE inhibitors.

Routine anticoagulation is controversial. However, the risk of renal vein thrombosis and other deep vein thromboses is significant, and the clinician must be vigilant in monitoring for signs of venous thromboembolism (VTE). Once VTE is found, anticoagulation is generally continued indefinitely. In a study of membranous nephropathy, the risk of developing VTE increased 3.9-fold with a reduction in serum albumin below the threshold of 2.8g/dL and 5.8-fold with a serum albumin of less than 2.2 g/dL. [14]

Do not treat patients with asymptomatic nonnephrotic proteinuria with immunosuppressives. Patients who are asymptomatic and nephrotic may undergo remission, particularly if they have normal renal function and an early lesion. They may also be observed.

Therapy with immunosuppressive agents (see Medication) is indicated in those patients who have the following:

Increased creatinine level at presentation

Progressive disease

Severe symptomatic nephrotic syndrome

Persistent nephrotic syndrome

Thromboembolism

Persistent nephrotic syndrome, male sex, and age older than 50 years

Increased IgG excretion, HLA-DR3 +/B8 +, white race, and elevation of urinary excretion of complement activation products

Tubulointerstitial changes or focal sclerosis

Surgical Care:

Kidney transplantation is indicated if the patient progresses to end-stage renal disease. Some risk of recurrence in the allograft is recognized.

Diet and Activity:

Institute a low-salt diet. Protein restrictions may or may not be useful.

Medications:

Corticosteroids alone are ineffective in the treatment of membranous nephropathy. Alternating months of corticosteroid therapy and oral cytotoxic therapy with cyclophosphamide or chlorambucil has shown efficacy, but should be reserved for patients who exhibit clinical features such as severe or prolonged nephrosis, renal insufficiency, infections, thromboembolic events, or hypertension.

Alternating monthly treatment with a combination of chlorambucil and steroids for 6 months has been tried with some success, especially in patients with a creatinine level of less than 1.7 mg/dL. A 20-year follow-up of such cases showed complete remission in 9 of 15 patients and partial remission in 4 of 15 patients; 2 of 15 patients did not respond. The 10-year survival rate of the treated patients was 100%, whereas that of the untreated patients was 40%. [15]

Cyclophosphamide may be safer than chlorambucil in this setting, although data on this comparison are limited. [16] The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest using cyclophosphamide rather than chlorambucil for initial therapy. As with chlorambucil, cyclophosphamide is given in alternating months with corticosteroids over 6 months, with adjustment of the cyclophosphamide dose according to the patient's age and estimated glomerular filtration rate. The goals are to achieve both total remission and preservation of renal function. [17]

Cyclical corticosteroid/alkylating agent therapy for idiopathic membranous nephropathy (IMN) (the Ponticelli regimen) is as follows:

Month 1: IV methylprednisolone (1 g) daily for 3 doses, then oral methylprednisolone (0.5 mg/kg/d) for 27 days

Month 2: Oral chlorambucil (0.15–0.2 mg/kg/d) or oral cyclophosphamide (2 mg/kg/d) for 30 days

Month 3: Repeat month 1

Month 4: Repeat month 2

Month 5: Repeat month 1

Month 6: Repeat month 2

Monitor every 2 weeks for 2 months, then every month for 6 months, with serum creatinine, urinary protein excretion, serum albumin, and white blood cell count. If the total leukocyte count falls to less than 3500/ μ L, hold chlorambucil or cyclophosphamide until recovery to 44000/ μ L.

KDIGO guidelines suggest conservative management for at least 6 months following the completion of this regimen before labelling the case as a treatment failure. [17]

Mycophenolate mofetil has been used with some success. A comparison of mycophenolate mofetil with cyclophosphamide showed decreased proteinuria and improved renal function in most patients, but mycophenolate mofetil did not appear as effective as or better tolerated than cyclophosphamide. [18] Although not recommended as initial therapy, it can be used in those patients who wish to avoid the toxicity of alkylating agents and for whom there is concern about the renal toxicity of calcineurin inhibitors.

Cyclosporine is indicated in those patients in whom the above cannot be used or in patients with a high risk of progression. In controlled trials, calcineurin inhibitors (CNIs), cyclosporine, and tacrolimus have also yielded increased remission rates of nephrotic syndrome and improved renal survival. These drugs can be used for at least 6 months in patients who meet the criteria for initial therapy but who choose not to or have contraindications to cyclical corticosteroid/alkylating agent regimen.

CNIs should be discontinued in patients who do not achieve complete or partial remission after 6 months of treatment. The dosage should be reduced at intervals of 4-8 weeks to a level of about 50% of the starting dosage once remission is maintained and continued for at least 12 months. Regimens are as follows:

Cyclosporine: 3.5–5.0 mg/kg/d given orally in 2 equally divided doses 12 hours apart, with prednisone 0.15 mg/kg/d, for 6 months

Tacrolimus: 0.05–0.075 mg/kg/d given orally in 2 divided doses 12 hours apart, without prednisone, for 6–12 months; levels should be monitored

It has been suggested that patients with IMN resistant to alkylating agent/steroid-based initial therapy be treated with a CNI and that patients with IMN resistant to CNI-based initial therapy be

treated with an alkylating agent/steroid-based therapy. Relapses of nephrotic syndrome in IMN should be treated by reinstitution of the same therapy that resulted in the initial remission and should be repeated only once if a 6-month cyclical corticosteroid/alkylating agent regimen was used for initial therapy.

Despite these multiple therapeutic options, some patients with compelling indications for therapy fail to respond and need alternative therapy. Rituximab (a monoclonal antibody against CD20 antigen of B lymphocytes) and corticotropin have both been used in this situation, in the hope of improving the outcome of IMN and avoiding the adverse effects of steroids and immunosuppressants. [19]

Titration of rituximab to circulating CD20 B cell counts may improve safety by avoiding hypersensitivity; it also may limit the costs of treatment while achieving similar results. [20] However, it has not been possible to precisely predict which patients will respond to rituximab. [21] In a 2012 study, monthly rituximab was used in 100 patients, with varying results. In patients with long-standing membranous nephropathy resistant to immunosuppressants, rituximab did not produce sustained complete or partial remission. Thus, treating resistant membranous nephropathy may continue to be challenging. Using rituximab as first-line therapy may not be cost effective and may expose the patient to the risk of potential adverse effects. [22]

Some rituximab-treated patients show complete or partial remission of proteinuria and reduced levels of phospholipase A(2) receptor autoantibodies. In successful cases, rituximab therapy induces prolonged remission and enables discontinuation of other medications without substantially increasing the risk of infections and other serious adverse events. [23]

In the Membranous Nephropathy Trial of Rituximab (MENTOR) study, rituximab was noninferior to cyclosporine in inducing complete or partial remission of proteinuria at 12 months and was superior in maintaining proteinuria remission up to 24 months. [24] In MENTOR, 130 patients with proteinuria of more than 5 g, creatinine clearance of more than 40 ml/min, and renin-angiotensin system (RAS) blocker use for at least 3 months were randomized to rituximab or cyclosporine. At 12 months, rates of complete or partial remission were 60% in the rituximab group, compared with 52% in the cyclosporine group. The difference became more pronounced at 24 months, with 60% of patients treated with rituximab reaching the primary composite endpoint compared with 20% of those who received cyclosporine.

Corticotropin requires further study, as its mechanism of action remains unclear. It has some place in the treatment of those patients that have severe and resistant membranous nephropathy. [25]

In secondary membranous nephropathy associated with hepatitis B, in addition to interferon, lamivudine monotherapy may induce and maintain complete remission. [26]

In patients with IMN, histology findings including interstitial fibrosis, tubular atrophy, and vascular sclerosis have been associated with the risk of renal failure, but it remains uncertain whether they

are independent of the clinical variables at the time of biopsy, predict rate of progression, or should guide therapy. Although these histologic features were associated with a reduced renal survival rate, they did not predict this outcome independently of the baseline clinical variables, nor did they correlate with the rate of decline in function.

Diuretics

Class Summary

Used to control volume overload.

Furosemide (Lasix)

Has a potent diuretic effect because it blocks sodium reabsorption in the thick ascending loop of Henle.

Corticosteroids

Induce remission of proteinuria.

Prednisone (Deltasone, Meticorten, Orasone, Sterapred)

Exerts an anti-inflammatory effect via the inhibition of inflammatory mediator gene transcription.

Methylprednisolone (Adalone, Medrol, Solu-Medrol)

Exerts an anti-inflammatory effect via inhibition of inflammatory mediator gene transcription.

Cyclophosphamide (Cytoxan, Neosar)

Used for remission of nephrotic syndrome. Interferes with normal function of DNA by alkylation and cross-linking the strands of DNA and by possible protein modification.

Chlorambucil (Leukeran)

For remission of proteinuria; given with prednisone (0.5 mg/kg/d) every other month. Steroids are given as 1 g methylprednisolone IV for 3 d. Interferes with

DNA replication and RNA transcription by alkylation and cross-linking the strands of DNA

Immunosuppressant agents

For remission of nephrotic syndrome.

Cyclosporine A (Sandimmune)

Inhibits production and release of IL-2, leading to inhibition of IL-2-mediated activation of T lymphocytes.

Angiotensin-converting enzyme inhibitors

Control blood pressure and proteinuria.

Lisinopril (Zestril, Prinivil)

Inhibition of ACE leads to decreased plasma angiotensin II, which, in turn, leads to decreased vasopressor activity and decreased aldosterone secretion. ACE inhibitors minimize secondary intraglomerular hypertension and hypertrophy, leading to decreased proteinuria in idiopathic membranous nephropathy.

Enalapril (Vasotec)

Competitive inhibitor of ACE. Reduces angiotensin II levels, decreasing aldosterone secretion.

100. Tubulo-interstitial nephritis: causes of development, diagnosis, treatment. Features of drug-induced interstitial nephritis.

Tubulointerstitial diseases of the kidney encompass diverse etiologies and pathophysiologic processes, and the patient can present with acute or chronic conditions. Many forms of tubulointerstitial injury involve exposure to drugs or other nephrotoxic agents such as heavy metals and, rarely, infection. By far the most common form of tubulointerstitial inflammation is hypersensitivity reaction to medications, termed allergic interstitial nephritis.

The following are causes of acute tubulointerstitial nephritis:

Hypersensitivity reactions: Any drug can cause an acute allergic reaction involving the kidneys (eg, penicillins, sulfa drugs, nonsteroidal anti-inflammatory drugs [NSAIDs] most common) (See Presentation.)

Immunologic diseases (eg, associated with lupus, Goodpasture syndrome)

Acute transplant rejection

Infections, including bacterial (must be accompanied by obstruction or reflux), viral (eg, cytomegalovirus [CMV], hantavirus, human immunodeficiency virus [HIV], hepatitis B [HBV]), fungal (eg, histoplasmosis), and parasitic (eg, Leishmania, Toxoplasma)

The following are causes of chronic tubulointerstitial nephritis:

Drugs (eg, analgesics, lithium, cyclosporine, tacrolimus)

Heavy metals (eg, lead, cadmium, mercury)

Obstructive uropathy, nephrolithiasis, reflux disease

Immunologic diseases (eg, lupus, Sjögren syndrome, primary glomerulopathies, sarcoidosis, vasculitis, antineutrophil cytoplasmic antibody [ANCA]–associated vasculitides, granulomatosis with polyangiitis, and chronic transplant nephropathy)

Neoplasia (eg, myeloma, leukemia, amyloidosis)

Atherosclerotic kidney disease (ischemic) - Underlying atherosclerotic disease, dyslipidemia, and smoking are conditions commonly associated with cholesterol microembolism; catheter manipulations above the level of the renal arteries or anticoagulation in a patient with atherosclerosis can trigger cholesterol microembolic disease

Metabolic diseases (eg, hypercalcemia, cystinosis, potassium depletion, hyperoxaluria)

Genetics (eg, Alport syndrome, medullary cystic disease)

Miscellaneous (eg, Balkan endemic nephropathy, Chinese herb/aristolochic acid nephropathy)

Lead nephropathy

Environmental and occupational exposure to lead can cause chronic tubulointerstitial nephritis. Occupations in welding, smelting, the battery industry, and mining have all been responsible for lead nephropathy cases. The removal of lead from gasoline in the United States has reduced environmental exposure, but sporadic cases from exposure to lead-based paint is still observed,

particularly among children living in deteriorating older housing in urban areas. Rarely, lead poisoning can be observed in individuals who consume moonshine whiskey and those who drink beverages from imported ceramics painted with leaded glaze.

Obstructive uropathy

A variety of causes contribute to obstructive uropathy, including the following:

Prostate disease in elderly men

Pelvic or colonic tumors involving both ureters, in both sexes

Nephrolithiasis, with or without urinary tract infection

Radiation to the pelvic area

Drugs, such as methysergide, that can cause retroperitoneal fibrosis

Sjögren syndrome

In a study by Maripuri et al, kidney biopsies in 24 patients with primary Sjögren syndrome who also had kidney dysfunction revealed that 17 individuals had tubulointerstitial nephritis as the primary lesion, and 11 of those 17 patients had the chronic form of this nephritis. The investigators suggested these results support the notion that in patients with primary Sjögren syndrome, chronic tubulointerstitial nephritis is the most frequent cause of renal impairment found through kidney biopsy.

Similarly, a prospective study by Jain et al of renal involvement in 70 patients with primary Sjögren syndrome reported that tubulointerstitial nephritis was the most common disorder found on kidney biopsy. Tubulointerstitial nephritis was identified in nine of 17 biopsies in this study.

Balkan endemic nephropathy

Balkan endemic nephropathy is a form of chronic tubulointerstitial nephritis characterized by insidious onset, gradual progression to end-stage renal disease, and frequent association with urothelial carcinoma of the upper urinary tract (UTUC). The disease was reported in the Balkan peninsula of southeastern Europe, in rural areas around tributaries of the Danube River. It was eventually traced to consumption of home-baked bread made with flour contaminated with aristolochic acid from Aristolochia clematitis, a common weed in wheat fields in the region.

Chinese herb/aristolochic acid nephropathy

In the early 1990s, aristolochic acid was recognized as a potent nephrotoxin that was causing rapidly progressive interstitial fibrosis and end-stage renal disease (ESRD) in young women using a Chinese herb as part of a slimming regimen in Belgium. Since then, many other cases of so-called Chinese herb (CH) nephropathy have been reported from around the world.

Chinese herb nephropathy may not be an appropriate name for the disease, however, because aristolochic acid can be present in herbal medicines from any country, and is the environmental

phytotoxin that causes Balkan endemic nephropathy (see above). The term aristolochic acid nephropathy (AAN) more accurately characterizes this form of toxic nephropathy.

As with Balkan endemic nephropathy, AAN from other causes is also associated with UTUC. This appears to occur because aristolochic acid can trigger oncogene mutations, including alterations in the tumor-suppressor gene TP53.

IgG-4-related nephropathy

A recently recognized cause of interstitial kidney disease is immunoglobulin G (IgG)-4-related disease. This multiorgan disorder, characterized by high serum levels of IgG and IgG4, is associated with a tubulointerstitial nephritis with an abundant IgG4-positive plasma cell interstitial infiltration and has a good response to steroids. However, there have been reports of high relapse rates after treatment with corticosteroids.

Diag:

CBC with Differential

Eosinophilia, when present, can be very helpful in the evaluation of tubulointerstitial nephritis. However, this finding is neither specific nor sensitive enough to establish the diagnosis. Although the true incidence of eosinophilia in acute tubulointerstitial nephritis is unknown, it is estimated to be present in approximately half of patients. Typically, eosinophilia is absent in acute tubulointerstitial nephritis that is induced by nonsteroidal anti-inflammatory drugs

Chemistry Panel

A complete set of chemistries, including blood urea nitrogen (BUN) and serum creatinine, provides information on whether renal insufficiency exists. A low bicarbonate level (total carbon dioxide < 24-23 mEq/L) may indicate acidosis. Low serum potassium levels may indicate a proximal tubular disorder, and elevated serum potassium levels with a low bicarbonate level may indicate type 4 renal tubular acidosis, which can be observed with lead nephropathy and nonsteroidal anti-inflammatory drug (NSAID)-induced analgesic nephropathy, among other conditions.

Urine Studies

Urinalysis may reveal proteinuria, hematuria, and the presence of white blood cells (WBCs), with or without bacteria. A microscopic analysis of urine sediment may reveal casts, WBCs, eosinophils, and crystals. If allergic interstitial nephritis is suspected, send a cytopsin specimen to determine if eosinophils are in the urine. In nonsteroidal anti-inflammatory drug (NSAID)-induced acute tubulointerstitial nephritis, eosinophiluria is usually absent. Unfortunately, the absence of eosinophiluria does not rule out the diagnosis, and it can be observed in other diseases, including cholesterol microembolism, urinary tract infections, parasitic disorders, and glomerulonephritis.

Quantitative determination of urine protein may also be helpful. Low-molecular weight proteins, such as beta-2 microglobulin, retinol binding protein (RBP), alpha-1 microglobulin, and immunoglobulin light chains, are increased in chronic tubulointerstitial nephritides. Beta-2 microglobulinuria has been found helpful in the diagnosis of Balkan endemic nephropathy and cadmium nephropathy.

Hettinga and colleagues, in a prospective cohort study of 45 young patients with uveitis, found that urinary β 2-microglobulin (β 2M), urinary protein, and serum creatinine had predictive value for detecting tubulointerstitial nephritis and uveitis (TINU) syndrome. The positive predictive value of increased β 2M levels combined with increased serum creatinine was 100% for detecting patients with definitive and/or probable TINU syndrome. [22]

Urinary N-acetyl- β -D-glucosaminidase (NAG) and matrix metalloproteinases (MMPs) 2 and 9 were significantly inversely correlated with the rate of decline in estimated glomerular filtration rate (GFR) over a period of 11 to 54 months in a study of 54 patients with drug-induced chronic tubulointerstitial nephritis, 10 patients with IgA nephropathy, and 20 healthy controls. These biomarkers may be able to predict deterioration in drug-induced chronic tubulointerstitial nephritis. The areas under the receiver operating characteristic curve for urinary NAG, MMP-9, MMP-2 and α 1-microglobulin for predicting decline in estimated GFR were 0.879, 0.867, 0.735 and 0.709, respectively (all P< 0.05)

Ultrasonography and Radiography

Ultrasonography is noninvasive imaging technique that is extremely helpful in identifying hydronephrosis in obstructive disease as well as calculi in stone disease. Both radiolucent and radiopaque stones can be visualized with this modality. A combination of ultrasonography and flat plate kidney, ureter, and bladder (KUB) radiography is helpful in the workup and identification of radiopaque versus radiolucent stones.

Normal kidney size by ultrasonographic examination generally favors but does not prove a diagnosis of acute (thus potentially reversible) kidney disease. In contrast, small (shrunken) kidneys with increased echogenicity indicate chronic and irreversible kidney disease.

Once widely used, intravenous pyelography seldom plays a role in the workup of kidney diseases in modern medicine. In many instances, similar information can be obtained by ultrasonography without exposing the patient to potentially nephrotoxic contrast dye.

CT Scanning

Computed tomography (CT) scanning provides information similar to ultrasonographic scanning in the workup of kidney disease, generally with greater resolution. However, an ultrasonographic examination is sufficient in most kidney diseases. A high-resolution scan showing microcalcifications in renal papillary tips can be very helpful in diagnosis of analgesic nephropathy. The kidneys may be very small in Balkan endemic nephropathy and aristolochic acid nephropathy.

Kidney Biopsy and Histologic Features

Kidney biopsy is the definitive test for diagnosing acute allergic interstitial nephritis, particularly in cases in which the clinical diagnosis is difficult. Because the differential diagnosis of acute tubulointerstitial nephritis encompasses multiple etiologies, consider kidney biopsy when the diagnosis is not obvious.

Kidney biopsy shows mononuclear and often eosinophilic cellular infiltration of the renal parenchyma with sparing of the glomeruli (see the following images). Sometimes, interstitial

changes such as fibrosis and atrophy are also present (eg, Renal biopsies have shown severe interstitial fibrosis in patients with Chinese herb/aristolochic acid nephropathy).

Treatment and management:

Management of Acute Tubulointerstitial Nephritis

In cases of acute tubulointerstitial nephritis due to hypersensitivity reactions (allergic interstitial nephritis), early recognition and prompt discontinuation of the offending drug are helpful; cessation of the offending agent usually, but not always, results in complete recovery in patients. However, the rate of recovery is variable, and, in some patients, renal failure persists for many weeks before renal function improves. Some patients may progress to chronic renal insufficiency.

Obtain a thorough history of previously documented drug allergies before prescribing a new drug.

If no sign of improvement is observed within a few days of discontinuation of the offending agent, consider therapy with steroids. Although controlled trials are lacking, many authors suggest using prednisone at relatively high doses (eg, 1 mg/kg for 4-6 wks with rapid tapering of the dose). This intervention may improve the outcome, speeding renal recovery and reducing the requirement for dialysis.

A systematic review concluded that limited evidence does not support the use of corticosteroids in the treatment of drug-induced cases. The review included eight studies with 430 patients (300 of whom received corticosteroids and 130 of whom did not): four studies showed no difference in serum creatinine levels between the corticosteroid and comparator arms, while four studies found a benefit

Treatment:

Glucocorticoids

Class Summary

Glucocorticoid agents have immunosuppressant effects and are used for treatment of autoimmune disorders.

Prednisone (Sterapred)

Prednisone has anti-inflammatory properties and causes profound and varied metabolic effects by modifying the body's immune response to diverse stimuli. This agent may decrease inflammation by reversing increased capillary permeability and suppressing polymorphonuclear lymphocyte (PMN) activity. Prednisone also stabilizes lysosomal membranes and suppresses lymphocytes and antibody production.

Chelating agents

Class Summary

These agents promote the excretion of lead.

Succimer (Chemet)

Succimer is a metal chelator, an analogue of dimercaprol that is used in lead poisoning. This agent is particularly useful in children with lead blood levels > 45 mcg/dL. Succimer is approved for chelation therapy in children for lead poisoning. However, its value in chronic lead nephropathy is not established.

Eddetate calcium disodium (Calcium Disodium Versenate)

Eddetate is used for lead chelation; only the calcium disodium preparation should be used. In the context of this article, use of this medication is confined to testing (ie, to perform the ethylenediaminetetraacetic acid [EDTA] lead mobilization test for diagnosing lead as the etiology of chronic tubulointerstitial nephritis). Extended therapy with this agent to reduce body lead stores may be of possible benefit.

101. Chronic pyelonephritis. Etiology and pathogenesis. The role of focal infection. Clinic.

Etiology and Pathophysiology

Chronic pyelonephritis is associated with progressive renal scarring, which can lead to end-stage renal disease (ESRD). For example, in reflux nephropathy, intrarenal reflux of infected urine is suggested to induce renal injury, which heals with scar formation. [5] In some cases, scars may form in utero in patients with renal dysplasia with perfusion defects. Infection without reflux is less likely to produce injury. Dysplasia may also be acquired from obstruction. Scars of high-pressure reflux can occur in persons of any age. In some cases, normal growth may lead to spontaneous cessation of reflux by age 6 years.

Factors that may affect the pathogenesis of chronic pyelonephritis are as follows: (1) the sex of the patient and his or her sexual activity; (2) pregnancy, which may lead to progression of renal injury with loss of renal function; (3) genetic factors; (4) bacterial virulence factors; and (5) neurogenic bladder dysfunction. In cases with obstruction, the kidney may become filled with abscess cavities (see Pyonephrosis)

Complications of chronic pyelonephritis can also include the following:

Proteinuria

Focal glomerulosclerosis

Progressive renal scarring leading to end-stage renal disease

Xanthogranulomatous pyelonephritis (XPN) - May occur in approximately 8.2% of cases and in 25% of patients with pyonephrosis; XPN can be confused with renal cancer

Pyonephrosis - May occur in cases of obstruction

Progressive renal scarring (reflux nephropathy)

Clinical:

History and Physical Examination

Some children with chronic pyelonephritis may report the following:

- Fever

- Lethargy
- Nausea and vomiting
- Flank pain or dysuria

The following may be noted on physical examination:

- Hypertension
- Failure to thrive in young children
- Flank tenderness

102. Diagnosis of chronic pyelonephritis. Outcomes of the disease.

Diagnostic Considerations

Chronic pyelonephritis may resemble the following [18] :

Analgesic abuse nephropathy

Renal tuberculosis

Renal dysplasia

Xanthogranulomatous pyelonephritis

Renal malakoplakia

In malakoplakia, however, characteristic inclusions called Michaelis-Gutmann bodies are seen on biopsy.

Differential Diagnoses

Acute Pyelonephritis

Azotemia

Chronic Kidney Disease

Hypertension

Nephrolithiasis

Perinephric Abscess

Pyonephrosis

Tuberculosis (TB)

Uremia

Xanthogranulomatous Pyelonephritis Imaging

Imaging Studies:

On an intravenous urogram, caliceal dilatation and blunting with cortical scars helps to establish the diagnosis of pyelonephritis. Ureteral dilatation and reduced renal size also may be evident.

Voiding cystourethrogram (VCUG) findings may document the reflux of urine to the renal pelvis and ureteral dilatation in children with gross reflux. [19] To strike the balance between obtaining high-quality images and minimizing radiation exposure, radiology departments should observe the “as low as (is) reasonably achievable” (ALARA) Image Gently guidelines.

Radioisotopic scanning with technetium dimercaptosuccinic acid (DMSA) is the gold standard for detecting renal scars and is more sensitive than intravenous pyelography. [21]

Cystoscopy findings show evidence of previous reflux at the ureteral orifices, even if VCUG images show no reflux because of the spontaneous cessation of reflux due to puberty.

Computed tomography (CT) scanning is the procedure of choice to help diagnose XPN. [14, 22] Renal ultrasonographic images may show calculi, but ultrasonography is not a sensitive screening procedure for reflux nephropathy. However, many cases of VUR are suggested by prenatal ultrasonographic findings.

Outcomes:

Favorable: cure

Unfavorable:

chronic kidney disease. If the infection continues, the kidneys may be permanently damaged. Although rare, it's also possible for the infection to enter the bloodstream. This can result sepsis.

103. Treatment of chronic pyelonephritis: regimen, diet, antibiotics.

The penicillins (amoxicillin) and first-generation cephalosporins are the drugs of choice for chronic pyelonephritis because of good activity against gram-negative rods and good oral bioavailability. In infants, the choice of antibiotics is either amoxicillin or a first-generation cephalosporin. In patients aged 3-6 months, therapy can be changed to sulfamethoxazole or nitrofurantoin. Older children and adults may be treated with trimethoprim-sulfamethoxazole (Bactrim).

Once one antibiotic is chosen, frequent changes in the antibiotic regimen are discouraged, to help prevent the development of resistance.

Indications for surgical treatment. Forecast. Prevention.

Antibiotics:

Class Summary

Antibiotic therapy must be comprehensive and cover all likely pathogens in the context of this clinical setting.

Amoxicillin (Moxatag)

Amoxicillin interferes with the synthesis of cell wall mucopeptides during active multiplication, resulting in bactericidal activity against susceptible bacteria..

Cephalexin (Keflex)

Cephalexin is a first-generation cephalosporin that arrests bacterial growth by inhibiting bacterial cell wall synthesis. It has bactericidal activity against rapidly growing organisms.

Trimethoprim/sulfamethoxazole (Bactrim DS, Septra DS, Sulfatrim)

Trimethoprim/sulfamethoxazole inhibits bacterial growth by inhibiting the synthesis of dihydrofolic acid. Bacterial species it acts against include common urinary tract pathogens, except *Pseudomonas aeruginosa*.

Nitrofurantoin (Furadantin, Macrodantin, Macrobid)

This is a synthetic nitrofuran that interferes with bacterial carbohydrate metabolism by inhibiting acetylcoenzyme A. Nitrofurantoin is bacteriostatic at low concentrations (5-10 mcg/mL) and bactericidal at higher concentrations.

Surgical Care:

Endoscopic Injections

Endoscopic injection have advantages over open surgery, including less postoperative pain and fewer bladder spasms and infections, and the absence of surgical scarring. Endoscopic injection can be performed in a shorter operation time, in an outpatient setting, and with minimal use of postoperative analgesics and is preferred as the first-line treatment for children with VUR. [23]

The American Urological Association (AUA) Vesicoureteral Reflux Guideline Update Committee analyzed data from 17,972 patients, and reported that the overall success rate of a single endoscopic treatment was 83.0% compared to 98% success rates for open surgery. [4] When an injection treatment fails, open ureteral reimplantation may be needed to treat persistent VUR.

Open Ureteral Reimplantation

Surgery entails the reimplantation of the ureters, with the creation of an adequate submucosal tunnel and detrusor support. Open reimplantation surgery may be a primary treatment or may be performed as second-line therapy after endoscopic injection failure. Studies have reported no adverse effect on success rates, operation time, or complications when open reimplantation follows endoscopic injection treatment.

Laparoscopic Ureteral Reimplantation

Robot-assisted laparoscopic extravesical ureteral reimplantation has been proposed as a minimally invasive alternative to open ureteral reimplantation for correcting primary vesicoureteral reflux in children. However, the current literature contains conflicting data regarding the safety and efficacy of this approach. In a multi-institutional review, a success rate of 87.9% was reported in a series of 260 patients who underwent robot-assisted laparoscopic extravesical ureteral reimplantation for primary vesicoureteral reflux.

Diet:

Normalization of metabolism. Moreover, both in the kidneys and in other internal organs.

Reduced edema.

Excretion of toxins, nitrogenous substances and salts.

Lowering blood pressure.

The diet for pyelonephritis corresponds to table No. 7 according to the Pevzner table. In short, the regimen is aimed at reducing the amount of protein consumed, increasing the volume of vitamins and maintaining the previous norm of fats and carbohydrates. If translated into numbers, then the daily recommendations look like this:

Free liquid - 2-3 liters.

Fats - 90-100 g. At the same time, 25% should be vegetable.

Proteins - 80 g. Of this amount, 50-60% should be animals.

Carbohydrates - 400-450 g. They should account for about 80-90 grams of sugar.

In this mode, the daily calorie content will be about 2400-2700 kcal.

104. Urinary tract infection: clinical manifestations, diagnosis, treatment. Peculiarities of management of pregnant women with urinary tract infection.

• Lower Urinary Tract Infections

A. General characteristics

1. Urinary tract infections (UTIs) are much more common in women than in men. Up to 33% of all women experience a UTI in their lifetime. The most common UTI is uncomplicated acute cystitis.
2. The majority of UTIs are caused by ascending infection from the urethra. Colonization of the vaginal area by pathogens from the fecal flora leads to ascension via the urethra into the bladder.
3. Common organisms.
 - a. *E. coli* (most common)—causes 80% of cases.
 - b. Other organisms—*Staphylococcus saprophyticus*, *Enterococcus*, *Klebsiella*, *Proteus* spp., *Pseudomonas*, *Enterobacter*, and yeast (such as *Candida* spp.)

B. Risk factors

1. Female gender—greater risk due to the shorter female urethra and vaginal colonization of bacteria
2. Sexual intercourse
 - a. Often the trigger of a UTI in women, thus the term “honeymoon cystitis”
 - b. Use of diaphragms and spermicides increases risk further (alters vaginal colonization)
3. Pregnancy
4. Indwelling urinary catheters—risk factor for hospitalized patients
5. Personal history of recurrent UTIs
6. Host-dependent factors—increase risk for recurrent or complicated UTIs
 - a. Diabetes—diabetic patients are at risk for upper UTI
 - b. Patients with spinal cord injury
 - c. Immunocompromised state
 - d. Any structural or functional abnormality that impedes urinary flow (e.g., incomplete voiding, neurogenic bladder, BPH, vesicoureteral reflux, calculi)
7. Male risk factors
 - a. Uncircumcised males are at higher risk due to bacterial colonization of the foreskin

- b. Anal intercourse
- c. Vaginal intercourse with a female colonized with uropathogens

C. Clinical features

1. Dysuria—commonly expressed as burning on urination
2. Frequency
3. Urgency
4. Suprapubic tenderness
5. Gross hematuria is sometimes present
6. In lower UTIs, fever is characteristically absent

D. Diagnosis

1. Dipstick urinalysis
 - a. Positive urine leukocyte esterase test—presence of leukocyte esterase reflects pyuria
 - b. Positive nitrite test for presence of bacteria (gram-negative)—nitrite test is sensitive and specific for detecting Enterobacteriaceae. But it lacks sensitivity for other organisms, so a negative test should be interpreted with caution
 - c. Combining the above two tests yields a sensitivity of 85% and specificity of 75%
2. Urinalysis (clean-catch midstream specimen)
 - a. Adequacy of collection
 - The presence of epithelial (squamous) cells indicates vulvar or urethral contamination
 - If contamination is suspected, perform a straight catheterization of the bladder
 - b. Criteria for UTI
 - Bacteriuria: >1 organism per oil-immersion field. Bacteriuria without WBCs may reflect contamination and is not a reliable indicator of infection
 - Pyuria is the most valuable finding for diagnosis: Greater than or equal to 10 leukocytes/ μL is abnormal
 - c. Other findings—hematuria and mild proteinuria may be present. Hematuria in and of itself does not require extended therapy
3. Urine Gram stain
 - a. A count of $>10^5$ organisms/mL represents significant bacteriuria
 - b. It is 90% sensitive and 88% specific
4. Urine culture
 - a. Confirms the diagnosis (high specificity). Obtaining a urine culture is warranted if symptoms are not characteristic of UTI, if a complicated infection is suspected, or if symptoms persist despite prior antibiotic treatment
 - b. Traditional criteria: $\geq 10^5$ CFU/mL of urine from a clean-catch sample; misses up to one-third of UTIs
 - c. Colony counts as low as 10^2 to 10^4 CFU/mL are adequate for diagnosis if clinical symptoms are present
5. Blood cultures—only indicated if patient is ill and urosepsis is suspected
6. IVP, cystoscopy, and excretory urography are not recommended unless structural abnormalities or obstruction is suspected

E. Complications

1. Complicated UTI
 - a. Any UTI that spreads beyond the bladder (e.g., pyelonephritis, prostatitis, urosepsis)—risk factors for upper UTI: pregnancy, diabetes, and vesicoureteral reflux
 - b. Any UTI caused by structural abnormalities, metabolic disorder, or neurologic dysfunction
2. UTI during pregnancy—increased risk of preterm labor, low birth weight, and other complications, especially in advanced pregnancy
3. Recurrent infections
 - a. Usually due to infection with new organism, but sometimes is a relapse due to unsuccessful treatment of the original organism

- b. Risk factors include impaired host defenses, pregnancy, vesicoureteral reflux, and sexual intercourse in women
- c. Generally the consequences are not significant unless the patient is at risk for upper UTI

F. Treatment

1. Acute uncomplicated cystitis—that is, nonpregnant women. Several options exist:
 - a. Oral TMP/SMX (Bactrim) for 3 days.
 - b. Nitrofurantoin (5 to 7 days)—do not give if early pyelonephritis is suspected.
 - c. Fosfomycin (single dose)—do not give if early pyelonephritis is suspected.
 - d. Amoxicillin is a less popular alternative due to increasing antimicrobial resistance.
 - e. Fluoroquinolones (ciprofloxacin in 3-day regimen) is a reasonable alternative to the above-mentioned agents.
 - f. Treat presumptively for pyelonephritis if the condition fails to respond to a short course of antibiotics.
 - g. Phenazopyridine (Pyridium) is a urinary analgesic; it can be given for 1 to 3 days for dysuria.
2. Pregnant women with UTI.
 - a. Treat with ampicillin, amoxicillin, or oral cephalosporins for 7 to 10 days.
 - b. Avoid fluoroquinolones (can cause fetal arthropathy).
3. UTIs in men.
 - a. Treat as with uncomplicated cystitis in women, but for 7 days.
 - b. Urologic workup is required in all men presenting with UTI unless there is an obvious underlying risk factor (catheterization, etc.).
4. Recurrent infections.
 - a. If relapse occurs within 2 weeks of cessation of treatment, continue treatment for 2 more weeks and obtain a urine culture.
 - b. Otherwise treat as for uncomplicated cystitis. If the patient has more than two UTIs per year, give chemoprophylaxis.
 - Single dose of TMP/SMX after intercourse or at first signs of symptoms.
 - Alternative low-dose prophylactic antibiotics (e.g., low-dose TMP/SMX) for 6 months.

The classic symptoms of urinary tract infection (UTI) in the adult are primarily dysuria with accompanying urinary urgency and frequency. A sensation of bladder fullness or lower abdominal discomfort is often present.

Because of the referred pain pathways, even simple lower UTI may be accompanied by flank pain and costovertebral angle tenderness. In the emergency department, however, assume that the presence of these symptoms represents upper UTI.

Bloody urine is reported in as many as 10% of cases of UTI in otherwise healthy women; this condition is called [hemorrhagic cystitis](#). Fevers, chills, and malaise may be noted in patients with cystitis, though these findings are associated more frequently with upper UTI (ie, pyelonephritis).

A history of vaginal discharge suggests that vaginitis, cervicitis, or pelvic inflammatory disease is responsible for symptoms of dysuria; therefore, a pelvic examination must be performed. Important additional information includes a history of prior sexually transmitted disease (STD) and multiple current sexual partners.

Diag:

Urinalysis

The most accurate method to measure pyuria is counting leukocytes in unspun fresh urine using a hemocytometer chamber; greater than 10 white blood cells (WBCs)/mL is considered abnormal. Counts determined from a wet mount of centrifuged urine are not reliable measures of pyuria. A noncontaminated specimen is suggested by a lack of squamous epithelial cells. Pyuria is a sensitive (80-95%) but nonspecific (50-76%) sign of UTI.

White cell casts may be observed in conditions other than infection, and they may not be observed in all cases of pyelonephritis. If the patient has evidence of acute infection and white cell casts are present, however, the infection likely represents pyelonephritis. A spun sample (5 mL at 2000 revolutions per min [rpm] for 5 min) is best used for evaluation of cellular casts.

Proteinuria is commonly observed in infections of the urinary tract, but the proteinuria usually is low grade. More than 2 g of protein per 24 hours suggests glomerular disease.

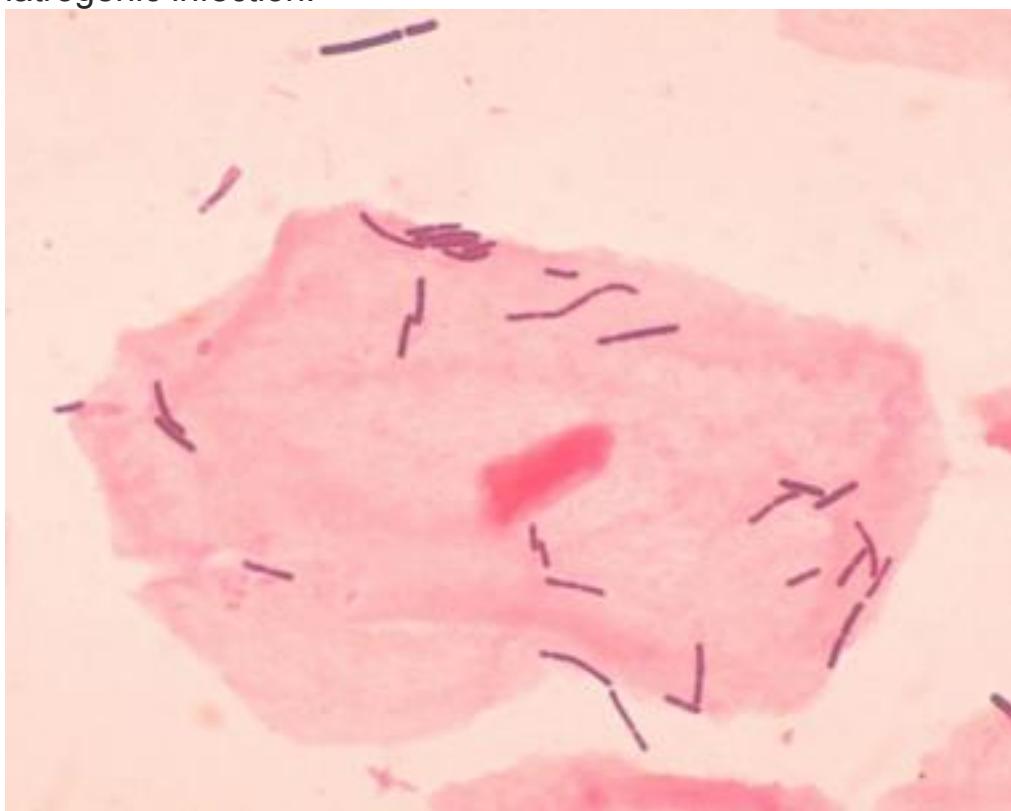
Approximately 70% of patients with corticomedullary abscesses have abnormal urinalysis findings, whereas those with renal cortical abscesses usually have normal findings. Two thirds of patients with perinephric abscesses have an abnormal urinalysis.

Urine specimen collection

Urine specimens may be obtained by midstream clean catch, suprapubic aspiration, or catheterization.

The midstream-voided technique is as accurate as catheterization if proper technique is followed. Instruct the woman to remove her underwear and sit facing the back of the toilet. This promotes proper positioning of the thighs. Instruct the patient to spread the labia with one hand and cleanse from front to back with povidone-iodine or soaped swabs with the other hand; then pass a small amount of urine into the toilet; and finally urinate into the specimen cup. The use of a tampon may allow a proper specimen if heavy vaginal bleeding or discharge is present.

Midstream urine specimens may become contaminated, particularly if the woman has difficulty spreading and maintaining separation of the labia. The presence of squamous cells and lactobacilli on urinalysis suggests contamination or colonization (see image below). Catheterization may be needed in some women to obtain a clean specimen, although it poses the risk of iatrogenic infection. [\[19\]](#)



Lactobacilli and

a squamous epithelial cell are evident on this vaginal smear. The presence of squamous cells and lactobacilli on urinalysis suggests contamination or colonization. Source: Centers for Disease Control and Prevention, Dr. Mike Miller

[View Media Gallery](#)

Although the use of midstream urine specimens is widely advocated, one randomized trial in young women showed that the rate of contamination was nearly identical among those who used midstream clean-catch technique and those who urinated into a container without cleansing the perineum or discarding the first urine output. Use of a vaginal tampon in addition to clean-catch technique had no significant effect on the contamination rate. [\[20\]](#)

Dipstick testing

Dipstick testing should include glucose, protein, blood, nitrite, and leukocyte esterase. Leukocyte esterase is a dipstick test that can rapidly screen for pyuria; it is 57-96% sensitive and 94-98% specific for identifying pyuria. Given this broad range of sensitivity, it is important to consider the possibility of false-positive results, particularly with asymptomatic patients undergoing evaluation for recurrent UTI.

Pyuria, as indicated by a positive result of the leukocyte esterase dipstick test, is found in the vast majority of patients with UTI. This is an exceedingly useful screening examination that can be performed promptly in any ED setting. If pyuria is absent, the diagnosis of UTI should be questioned until urine culture results become available.

In a United Kingdom study, dipstick diagnosis based on findings of nitrite or both leukocyte esterase and blood was 77% sensitive and 70% specific, with a positive predictive value of 81% and a negative predictive value of 65%. [\[4\]](#) Diagnosis on clinical grounds proved less sensitive.

Urine microscopy

A microscopic evaluation of the urine sample for WBC counts, RBC counts, and cellular or hyaline casts should be performed. In the office, a combination of clinical symptoms with dipstick and microscopic analysis showing pyuria and/or positive nitrite and leukocyte esterase tests can be used as presumptive evidence of UTI.

Low-level pyuria (6-20 WBCs per high-power field [hpf] microscopy on a centrifuged specimen) may be associated with an unacceptable level of false-negative results with the leukocyte esterase dipstick test, as Propp et al found in an ED setting. [\[21\]](#)

In females with appropriate symptoms and examination findings suggestive of UTI, urine microscopy may be indicated despite a negative result of the leukocyte esterase dipstick test. Current emphasis in the diagnosis of UTI rests with the detection of pyuria. As noted, a positive leukocyte esterase dipstick test suffices in most instances.

According to Stamm et al, levels of pyuria as low as 2-5 WBCs/hpf in a centrifuged specimen are important in females with appropriate symptoms. The presence of bacteriuria is significant. However, the presence of numerous squamous epithelial cells raises the possibility of contamination. [\[19\]](#) Low-level or, occasionally, frank hematuria may be noted in otherwise typical UTI; however, its positive predictive value is poor.

Nitrite test

Nitrite tests detect the products of nitrate reductase, an enzyme produced by many bacterial species. These products are not present normally unless a UTI exists. This test has a sensitivity and specificity of 22% and 94-100%, respectively. The low sensitivity has been attributed to enzyme-deficient bacteria causing infection or low-grade bacteriuria.

A positive result on the nitrite test is highly specific for UTI, typically because of urease-splitting organisms, such as *Proteus* species and, occasionally, *E coli*; however, it is very insensitive as a screening tool, as only 25% of patients with UTI have a positive nitrite test result.

Urine Culture Complete Blood Cell Count Diagnostic Catheterization

Treatment:

Sulfonamides

Class Summary

Sulfonamides inhibit bacterial dihydropteroate synthase by competing with para-aminobenzoic acid (PABA). This action interferes with the uptake of PABA into folic acid, an essential component of bacterial development.

Trimethoprim-sulfamethoxazole (Bactrim, Bactrim DS, Septra, Septra DS)

Trimethoprim-sulfamethoxazole (TMP-SMX) is designed to take advantage of the synergy between trimethoprim and sulfonamides. TMP-SMX activity includes common urinary tract pathogens, both aerobic gram-positive and gram-negative bacteria, except *Pseudomonas aeruginosa*. Empiric therapy with TMP-SMX should be avoided if the prevalence of resistance is greater than 20%. This agent has been given an A-I rating in the 2010 Infectious Disease Society of America (IDSA) guidelines for treating cystitis. [1] General dosing recommendations include administering 1 tablet (160 mg/800 mg) twice a day for 3 days in patients with uncomplicated cystitis.

Antibiotics, Other Class Summary

Empiric antimicrobial therapy should cover all likely pathogens in the context of this clinical setting. Antibiotics that have been used include nitrofurantoin, fosfomycin, or trimethoprim.

Nitrofurantoin (Furadantin, Macrobid, Macrodantin)

Nitrofurantoin is bacteriocidal in urine at therapeutic doses. It is indicated for the treatment of cystitis when caused by susceptible strains of *E coli*, *enterococci*, *Staphylococcus aureus*, and certain strains of *Klebsiella* and *Enterobacter* species. It is a good treatment option because of minimal resistance and propensity for collateral damage.

This agent has been given an A-I rating in the 2010 Infectious Disease Society of America (IDSA) guidelines for treating cystitis. [1] Nitrofurantoin should be avoided if there is suspicion for early pyelonephritis, and it is contraindicated when creatinine clearance is less than 60 mL/min.

Nitrofurantoin is manufactured in different forms to facilitate durable concentrations in the urine: macrocrystals (Macrodantin) and microcrystal suspension (Furadantin). A combined preparation of monohydrate/monocrystals (Macrobid) is indicated only for the treatment of acute cystitis caused by susceptible strains of *E coli* or *S saprophyticus* in patients 12 years of age and older.

General dosing recommendations for patients with uncomplicated cystitis include nitrofurantoin monohydrate/macrocystals, 100 mg twice a day for 5-7 days, or nitrofurantoin macrocrystals, 50-100 mg 4 times a day for 7 days.

Fosfomycin (Monurol)

Fosfomycin is a bactericidal agent that is used for the treatment of uncomplicated cystitis in susceptible strains of *E coli* and *Enterococcus faecalis*. Little cross-resistance between fosfomycin and other antibacterial agents exists. It is primarily excreted unchanged in the urine, and concentrations remain high for 24-48 hours after a single dose. This agent has been given an A-I rating in the 2010 IDSA guidelines for treating cystitis.^[1] Fosfomycin can be administered at a dose of 3 g as a single dose with 3-4 oz of water for uncomplicated cystitis.

Trimethoprim (Primsol)

Trimethoprim inhibits bacterial growth by inhibiting synthesis of dihydrofolic acid. It is active in vitro against a broad range of gram-positive and gram-negative bacteria, including uropathogens, such as Enterobacteriaceae and *S saprophyticus*. Resistance usually is mediated by decreased cell permeability or alterations in the amount or structure of dihydrofolate reductase. It demonstrates synergy with the sulfonamides, potentiating the inhibition of bacterial tetrahydrofolate production.

Fluoroquinolones Class Summary

Fluoroquinolones are highly effective against gram-negative and gram-positive bacteria. A major concern with fluoroquinolones is the development of resistance among uropathogens and other organisms.^[44] For that reason, these agents should be reserved as alternative therapies for acute cystitis. Fluoroquinolones are effective in 3-day regimens. In the 2010 IDSA guidelines, quinolones have an A-III rating for treating cystitis.^[1]

Ciprofloxacin (Cipro. Proquin XR)

Ciprofloxacin is used to treat cystitis that is caused by *E coli* or *S saprophyticus*. For acute uncomplicated cystitis, the recommended dosage is 250 mg twice daily for 3 days. As the severity of the condition worsens, the duration of therapy is extended.

Ofloxacin

Ofloxacin is indicated for the treatment of both uncomplicated and complicated cystitis. Like other fluoroquinolones, it is most effective against gram-negative organisms such as *E coli*, *Citrobacter diversus*, *C freundii*, *Enterobacter cloacae*, *Klebsiella* species, *Proteus* species, and *Shigella* species. The usual regimen for uncomplicated cystitis is 200 mg given twice daily for 3 days. Complicated cystitis can be treated for 10 days.

Levofloxacin (Levaquin)

Levofloxacin is indicated for the treatment of uncomplicated and complicated cystitis. It is used to treat cystitis caused by *E coli*, *S saprophyticus*, or *Klebsiella* species. Levofloxacin can be given for uncomplicated cystitis at a dose of 250 mg every 24 hours for 3 days. It can also be given for complicated cystitis at a dose of 750 mg daily for 5 days or a dose of 250 mg daily for 10 days.

Penicillins, Amino Class Summary

Penicillins such as amoxicillin and ampicillin are not recommended as empiric therapy for uncomplicated cystitis. However, amoxicillin-clavulanate may be used in uncomplicated cystitis as an alternative therapy.

Amoxicillin-clavulanate (Augmentin, Augmentin XR)

A beta-lactam antibiotic such as amoxicillin-clavulanate in 3-7 day regimens is recommended for the treatment of uncomplicated cystitis when other agents are not appropriate. In the 2010 IDSA guidelines, amoxicillin-clavulanate has a B-I rating for treating cystitis. [1]

Ampicillin

Ampicillin has activity against anaerobes and gram-negative aerobes. Ampicillin can be given intravenously or intramuscularly and is generally used in combination with an aminoglycoside (gentamicin) for empiric or directed activity against *E faecalis* in patients with complicated cystitis who cannot tolerate oral therapy or in patients in whom infection with resistant organisms is suspected.

Cephalosporine
Management of woman with uti:

Women presenting with recurrent lower urinary tract infections (rUTI) should undergo a complete patient history and pelvic examination.

A diagnosis of rUTI must be based on documented positive urine culture results in association with prior symptomatic episodes.

An initial urine specimen that may be contaminated should prompt a repeat urine study; collection of a catheterized specimen should be considered.

Index patients presenting with rUTI should not routinely undergo upper tract imaging and cystoscopy.

Before beginning treatment in patients with rUTI, urinalysis, urine culture, and sensitivity should be performed for each symptomatic acute cystitis episode.

Select patients with rUTI with acute episodes may be offered patient-initiated treatment (self-start treatment) while urine culture results are pending.

Asymptomatic bacteriuria

Surveillance urine testing, including urine culture, should not be performed in asymptomatic patients with rUTI.

Asymptomatic bacteriuria should not be treated.

Antibiotic treatment

Symptomatic UTIs in women should be treated with first-line therapy (ie, nitrofurantoin, TMP-SMX, fosfomycin) and should depend on local antibiogram.

The duration of antibiotic therapy for rUTI in patients with acute cystitis episodes should be as short as is reasonable (typically no longer than 7 days).

rUTIs in patients with acute cystitis that has shown resistance to oral antibiotics on urine culture may be treated with culture-directed parenteral antibiotics for as short a course as is reasonable (typically no longer than 7 days).

Antibiotic prophylaxis

After discussing the risks, benefits, and alternatives, antibiotic prophylaxis may be prescribed to reduce the risk of future UTIs in women of all ages previously diagnosed with UTI.

Nonantibiotic prophylaxis

Cranberry prophylaxis may be offered to women with rUTI.

Follow-up evaluation

Posttreatment urinalysis or urine culture to test for cure should not be performed in asymptomatic patients.

UTI symptoms that persist after antimicrobial therapy should prompt repeat urine culture to guide further treatment.

Estrogen therapy

Vaginal estrogen therapy with no contraindications should be recommended to perimenopausal and postmenopausal women with rUTIs to reduce the risk of future UTI.

105. Chronic kidney disease. Classification. The main diseases leading to the development of CKD.

The term “chronic kidney disease” means lasting damage to the kidneys that can get worse over time. If the damage is very bad, your kidneys may stop working. This is called kidney failure, or end-stage renal disease (ESRD). If your kidneys fail, you will need dialysis or a kidney transplant in order to live.

The main diseases:

Diabetes

High blood pressure (hypertension)

Heart disease

Having a family member with kidney disease

Being African-American, Hispanic, Native American or Asian

Being over 60 years old

Stages:

The stages of kidney disease are based on the eGFR number.

Stage 1 CKD: eGFR 90 or Greater, normal

Stage 2 CKD: eGFR Between 60 and 89, mild

Stage 3 CKD: eGFR Between 30 and 59, moderate

Stage 4 CKD: eGFR Between 15 and 29, severe

Stage 5 CKD: eGFR Less than 15, failure

106. Renal failure (acute and chronic). Etiology of acute and chronic renal failure (CRF).

Acute kidney failure happens when your kidneys suddenly lose the ability to eliminate excess salts, fluids, and waste materials from the blood. This elimination is the core of your kidneys' main function. Body fluids can rise to dangerous levels when kidneys lose their filtering ability.

Symptoms of Acute Kidney Failure

Sometimes, there aren't any.

If you do have symptoms, they'll depend on how bad your loss of kidney function is, how quickly you lose kidney function, and the reasons for your kidney failure. You may experience the following:

Peeing less than normal

Swelling in your legs, ankles, and feet (caused by your body holding on to fluid)

Drowsiness or feeling very tired

Shortness of breath

Itching

Joint pain, swelling
Loss of appetite
Confusion
Throwing up or feeling like you're going to
Chest pain or pressure
Muscle twitching
Seizures or coma (in severe cases)
Stomach and back pain
Fever
Rash
Nosebleed

Causes of Acute Kidney Failure:

There are three main reasons your kidneys fail all of a sudden:

1. Something is stopping blood flow to your kidneys. It could be because of:
An infection
Liver failure
Medications (aspirin, ibuprofen, naproxen, or COX-2 inhibitors, like Celebrex)
Blood pressure medications
Heart failure
Severe burns or dehydration
Blood or fluid loss

2. You have a condition that's blocking urine from leaving your kidneys. This could mean:

Bladder, cervical, colon or prostate cancer

Blood clots in your urinary tract

An enlarged prostate

Kidney stones

Nerve damage in your bladder

3. Something has directly damaged your kidneys, like:

Blood clots

Cholesterol deposits

Medications that can directly damage kidneys, including NSAIDs like ibuprofen and naproxen, chemotherapy, and antibiotics

Glomerulonephritis (inflamed kidney filters; can be caused by an infection, autoimmune disease (like lupus), multiple myeloma, scleroderma, chemotherapy drugs, antibiotics, or other toxins)

Diseases and conditions that cause chronic kidney disease include:

- Type 1 or type 2 diabetes
- High blood pressure
- Glomerulonephritis (glo-mer-u-low-nuh-FRY-tis), an inflammation of the kidney's filtering units (glomeruli)
- Interstitial nephritis (in-tur-STISH-ul nuh-FRY-tis), an inflammation of the kidney's tubules and surrounding structures
- Polycystic kidney disease
- Prolonged obstruction of the urinary tract, from conditions such as enlarged prostate, kidney stones and some cancers
- Vesicoureteral (ves-ih-koe-yoo-REE-tur-ul) reflux, a condition that causes urine to back up into your kidneys
- Recurrent kidney infection, also called pyelonephritis (pie-uh-low-nuh-FRY-tis)

Diag:

Your doctor will start with a physical exam. Then, he'll order tests of your blood, urine, and kidneys.

Blood tests. These measure two substances in your blood -- creatinine and urea nitrogen.

Urine tests. Your doctor will check your pee for blood and protein. He'll also look for certain electrolytes (chemicals that control important body functions). The results help him understand what's causing your kidney failure.

Imaging tests. Some tests, like ultrasonography or a CT scan, can show whether your kidneys are enlarged or there's a blockage in your urine flow. An angiogram can tell your doctor if the arteries or veins that lead to your kidneys are blocked. An MRI can show the same thing.

Kidney Failure Treatment:

If there aren't any other problems, the kidneys may heal themselves.

In most other cases, acute kidney failure can be treated if it's caught early. It may involve changes to your diet, the use of medications, or even dialysis.

Diet. Your doctor will limit the amount of salt and potassium you can take in until your kidneys heal. That's because both of these substances are removed from your body through your kidneys. Changing how and what you eat won't reverse acute kidney failure. But your doctor may modify your diet while he deals with the conditions that caused it. This may mean treating a health problem like heart failure, taking you off certain medications, or giving you fluids through an IV if you're dehydrated.

Medications. Your doctor may prescribe medicines that regulate the amount of phosphorous and potassium in your blood. When your kidneys fail, they can't remove these substances from your body. Medications won't help your kidneys, but they may reduce some of the problems kidney failure causes.

Dialysis . If your kidney damage is severe enough, you may require hemodialysis until your kidneys can heal. Dialysis does not help kidneys heal but takes over the work of kidneys until they do. If your kidneys don't heal, dialysis could be long-term.

107. The main clinical syndromes in chronic renal failure. Classification of chronic kidney disease.

Symptoms

Signs and symptoms of chronic kidney disease develop over time if kidney damage progresses slowly. Signs and symptoms of kidney disease may include:

- Nausea
- Vomiting
- Loss of appetite
- Fatigue and weakness
- Sleep problems
- Changes in how much you urinate
- Decreased mental sharpness
- Muscle twitches and cramps
- Swelling of feet and ankles
- Persistent itching
- Chest pain, if fluid builds up around the lining of the heart
- Shortness of breath, if fluid builds up in the lungs
- High blood pressure (hypertension) that's difficult to control

Signs and symptoms of kidney disease are often nonspecific, meaning they can also be caused by other illnesses. Because your kidneys are highly adaptable and able to compensate for lost function, signs and symptoms may not appear until irreversible damage has occurred.

Stage	Description	Classification by severity		Classification by treatment
		GFR mL/min/1.73 m ²	Related terms	
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, proteinuria, hematuria	
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria, proteinuria, hematuria	
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency, early renal insufficiency	T if kidney transplant recipient
4	Severe ↓ GFR	15–29	Chronic renal insufficiency, late renal insufficiency, pre-ESRD	
5	Kidney failure	<15 (or dialysis)	Renal failure, uremia, end-stage renal disease	D if dialysis (hemodialysis, peritoneal dialysis)

Abbreviations are: GFR, glomerular filtration rate; ESRD, end-stage renal disease.
Related terms for CKD stages 3 to 5 do not have specific definitions, except ESRD.

108. Nephrotic syndrome. Diagnostics.

Nephrotic syndrome is the combination of nephrotic-range proteinuria with a low serum albumin level and edema. Nephrotic-range proteinuria is the loss of 3 grams or more per day of protein into

the urine or, on a single spot urine collection, the presence of 2 g of protein per gram of urine creatinine.

Nephrotic syndrome has many causes, including primary kidney diseases such as minimal-change disease, focal segmental glomerulosclerosis, and membranous glomerulonephritis. Nephrotic syndrome can also result from systemic diseases that affect other organs in addition to the kidneys, such as diabetes, amyloidosis, and lupus erythematosus. [1]

Nephrotic syndrome may affect adults and children of both sexes and of any race. It may occur in typical form, or in association with nephritic syndrome. The latter term connotes glomerular inflammation, with hematuria and impaired kidney function.

The first sign of nephrotic syndrome in children is usually swelling of the face; this is followed by swelling of the entire body. Adults can present with dependent edema. Fatigue and loss of appetite are common symptoms.

Classification

- Minimal-change nephropathy
- Focal glomerulosclerosis
- Membranous nephropathy
- Hereditary nephropathies

Secondary causes include the following, again in order of approximate frequency:

- Diabetes mellitus
- Lupus erythematosus
- Viral infections (eg, hepatitis B, hepatitis C, human immunodeficiency virus [HIV])
- Amyloidosis and paraproteinemias
- Preeclampsia
- Allo-antibodies from enzyme replacement therapy

Diagnostic studies for nephrotic syndrome may include the following:

- Urinalysis
- Urine sediment examination
- Urinary protein measurement
- Serum albumin
- Serologic studies for infection and immune abnormalities
- Renal ultrasonography
- Renal biopsy

Urinalysis

Urinalysis is the first test used in the diagnosis of nephrotic syndrome. Nephrotic-range proteinuria will be apparent by 3+ or 4+ readings on the dipstick, or by semiquantitative

testing by sulfosalicylic acid. A 3+ reading represents 300 mg/dL of urinary protein or more, which correlates with a daily loss of 3 g or more and thus is in the nephrotic range. The chemistry of the dipsticks is such that albumin is the major protein that is tested. Glucosuria points to diabetes.

Urine sediment examination

The urine sediment exam may show cells and/or casts.

Waxy casts mark proteinuric renal disease. By use of a polarizing microscope, one can see oval fat bodies and also fatty casts. These point to the nephrotic syndrome. They occur because of glomerular filtration of lipoproteins; the tubular cells that endocytose these lipoproteins then fall off into the urine. Viewed by polarizer, the oval fat bodies and fatty casts cause a "Maltese cross" appearance.

The presence of more than 2 red blood cells (RBCs) per high power field is indicative of microhematuria. Microhematuria may occur in membranous nephropathy but not in minimal-change nephropathy.

Glomerular disease may allow RBCs to traverse the damaged glomerular basement membrane, and the RBCs in the sediment may then be deformed, or dysmorphic. This points to glomerular disease with inflammation and destruction of the normal structures (ie, a nephritis, and thus a nephritic picture, with hematuria, oliguria, azotemia, and hypertension). This could occur in, for example, nephrotic syndromes associated with IgA nephropathy or proliferative glomerulonephritis.

More than 2 granular casts in the entire sediment is a biomarker for renal parenchymal disease. Variable-caliber and broad granular casts point to reduced renal function.

Urinary protein measurement

Urinary protein is measured by a timed collection or a single spot collection. [38] A timed collection is typically done over a 24-hour period, starting at 7 am and finishing the next day at the same time. In healthy individuals, less than 150 mg of total protein is present in a 24-hour urine collection.

A single spot urine collection is much easier to obtain. When the ratio of urine protein to urine creatinine is greater than 2 g/g, this corresponds to 3 g of urinary protein per day or more.

The exact type of urine protein is of potential interest. This can be tested by urine protein electrophoresis. Proteinuria that does not include albumin may point to overflow proteinuria that occurs in paraproteinemias, such as [multiple myeloma](#).

There has been intermittent interest in establishing whether proteinuria is "selective" for albumin (ie, >85% albumin), as opposed to nonselective. In the case of selective proteinuria, a charge-selective leak of albumin across the glomerular barrier may be occurring, perhaps due to reduced negative charges on that barrier, whereas nonselective proteinurias point to more substantial glomerular injury and perhaps also predict lesser response to prednisone treatment.

Renal Biopsy

For childhood nephrotic syndrome, a renal biopsy is indicated for the following:

- Congenital nephrotic syndrome
- Children older than 8 years at onset
- Steroid resistance
- Frequent relapses or steroid dependency
- Significant nephritic manifestations

- **Laboratory Studies**
- **Kidney function**
 - Serum tests for kidney function are essential. Serum creatinine will be in the normal range in uncomplicated nephrotic syndrome, such as that occurring in minimal-change nephropathy. In children, the serum creatinine level will be lower than it is in adults. The normal adult serum creatinine level is approximately 1 mg/dL, whereas that of a child aged 5 years will be about 0.5 mg/dL. Values higher than this in children indicate reduced kidney function.
- **Serum albumin**
 - The serum albumin level is classically low in nephrotic syndrome, being below its normal range of 3.5-4.5 g/dL. In a single-center study of patients who underwent kidney biopsy for idiopathic proteinuria, Gupta et al found that the frequency of focal and segmental glomerulosclerosis increased to three-quarters of the cases when patients had near-normal serum albumin levels.
- **Serologic studies**
 - In adults with nephrotic syndrome, tests for hepatitis B and C, HIV, and even syphilis may be useful. Tests for lupus, including antinuclear antibody (ANA), anti-double stranded DNA (anti-dsDNA) antibodies, and complement, may be useful. Testing for antineutrophil cytoplasmic antibodies (ANCA) is not indicated in typical nephrotic syndrome, because that test is associated with [rapidly progressive glomerulonephritis](#), which presents with a nephritic picture rather than one that is typically nephrotic.
 - Tests for previous streptococcal infection, such as antistreptolysin O, are not usually indicated for nephrotic syndrome, since postinfectious glomerulonephritis usually causes a nephritic rather than a nephrotic syndrome.
- **Phospholipase A2 receptor**
 - Phospholipase A₂ receptor (PLA₂ R) is a cell surface transmembrane receptor expressed on the surface of podocytes. Seventy percent of patients with idiopathic membranous nephropathy have autoantibodies directed against PLA₂ R. [40] Levels of this antibody have a strong correlation with clinical disease activity and thus help in monitoring disease activity and treatment efficacy. [41] Absence of these antibodies may suggest secondary membranous nephropathy such as that associated with cancers.
 - During treatment, the levels of the antibodies generally decline before remission of proteinuria. After treatment, about half the patients who are PLA₂R negative remain in remission for 5 years, but those who remain PLA₂R positive relapse in just 2 years. Use of the PLA₂R antibody test has changed the diagnosis and treatment of idiopathic membranous nephropathy.

Ultrasonography

Ultrasonographic scanning shows whether a patient has two kidneys. Individuals with a single kidney may be prone to developing focal glomerulosclerosis.

Having only one kidney is also a relative contraindication to kidney biopsy.

Ultrasonography also demonstrates renal echogenicity. Increased renal echogenicity is consistent with intrarenal fibrosis (ie, chronic disease with reduced kidney function).

109. Amyloidosis of the kidneys. Clinic. Diagnostics. Treatment.

Amyloidosis (am-il-oyd-OH-sis) causes proteins called amyloids to build up and form clumps inside your organs and tissues, causing damage. These clumps can form in the kidneys, heart, brain, liver, and intestines. There are two types of amyloidosis that often affect the kidneys: Primary amyloidosis and dialysis-related amyloidosis. Primary amyloidosis can cause kidney disease, and dialysis-related amyloidosis can happen by being on dialysis for a long time.

The two types of amyloidosis that often affect the kidneys are called primary amyloidosis and dialysis-related amyloidosis. Doctors and researchers are not sure what causes primary amyloidosis. Dialysis-related amyloidosis happens to people who have kidney failure and have been on dialysis for a long time. Dialysis does a good job cleaning your blood, but it does not work as well as healthy kidneys. It cannot remove all of a protein called beta-2-microglobulin, so this protein builds up in the blood and forms clumps in organs and tissues.

The most common sign of primary amyloidosis is nephrotic syndrome, which is a group of symptoms that includes:

Protein in the urine

High levels of fat and cholesterol in the blood

Swelling

Low levels of protein in the blood

The most common symptoms of dialysis-related amyloidosis are:

Joint pain and stiffness

Cysts (fluid-filled sacs) in bones

Numbness or tingling in hands and fingers

If your doctor thinks you might have primary amyloidosis, you might need to have blood and urine tests and a kidney biopsy. If your doctor thinks you might have dialysis-related amyloidosis, you may need blood and urine tests , as well as imaging tests, such as X-rays and CT scans.

Both primary and dialysis-related amyloidosis can be treated. Primary amyloidosis can be treated using medicine called chemotherapy. It can also be treated by having a stem cell transplant. Other treatment can help you manage the side effects of primary amyloidosis. Dialysis-related amyloidosis can be treated using medicine, better hemodialysis filters, surgery or a kidney transplant.

Diag:

A health care provider can use urinalysis and blood tests to detect the amount of amyloid proteins in urine and blood. Imaging tests, such as x-rays and CT scans, can provide pictures of bone cysts and amyloid deposits in bones, joints, tendons, and ligaments.

Diagnostic **testing** for AL **amyloidosis** involves blood **tests**, urine **tests** and biopsies. Blood and/or urine **tests** can indicate signs of the **amyloid** protein, but only bone marrow **tests** or other small biopsy samples of tissue or organs can positively confirm the diagnosis of **amyloidosis**.

Treatment:

There is no cure for amyloidosis. Your doctor will prescribe treatments to slow the development of the amyloid protein and manage your symptoms. If amyloidosis is related to another condition, then treatment will include targeting that underlying condition.

Specific treatment depends on what type of amyloidosis you have and how many organs are affected.

- High-dose chemotherapy with stem cell transplant can help remove the substance that leads to amyloid formation in some people with primary AL amyloidosis. Chemotherapy medicines alone may be used to treat other patients with primary AL amyloidosis.
- Secondary (AA) amyloidosis is treated by controlling the underlying disorder and with powerful anti-inflammatory medicines called steroids, which fight inflammation.
- A liver transplant may treat the disease if you have certain types of hereditary amyloidosis.
- New therapies can slow the production of the abnormal protein TTR.
- Your doctor might also recommend a kidney transplant.

Other treatments to help with symptoms include:

- Diuretic medicine to remove extra water from your body
- Thickeners to add to fluids to prevent choking if you have trouble swallowing
- Compression stockings to relieve swelling in your legs or feet
- Changes to what you eat, especially if you have gastrointestinal amyloidosis

110. Treatment of chronic renal failure (regimen, diet, water-salt regimen, correction of acidosis, detoxification therapy, the possibility of symptomatic treatment). Indications for hemodialysis and kidney transplantation.

Medication

Kidney failure is linked to high blood pressure, so your doctor may put you on blood pressure medication. You might also need medications called statins to lower your cholesterol level.

Often people with chronic kidney failure experience anemia. Anemia occurs when your body doesn't produce enough red blood cells. You may need a supplement to help increase your red blood

cell production. Because your body needs iron to manufacture blood cells, your doctor might also prescribe iron pills or shots. In some cases, you may need a blood transfusion to improve your red blood cell health.

If your kidney problem is causing fluid retention, diuretics can help relieve your swelling. This medicine makes you urinate frequently.

Calcium and vitamin D supplements help to protect your bones. If you have chronic kidney disease, you will have lower-than-normal levels of Vitamin D, which is essential for calcium absorption. Taking Vitamin D will reduce your risk of bone fractures. Phosphate is elevated in kidney failure, and this can also reduce your body's absorption of calcium. Your doctor may prescribe phosphate binders, a type of medicine to control your phosphate level.

Antihistamines can relieve the symptom of itchy skin.

Antiemetics can help with nausea.

Diet

Dietary changes might also be necessary. People with chronic kidney failure usually need to reduce their protein intake. As your body processes protein, it creates waste products. Your kidneys are responsible for filtering this waste. A lower-protein diet makes their job easier.

You might also need to monitor your levels of salt, potassium, and phosphate. Work with a dietitian to find out how much of these substances you should eat.

Get in the habit of reading labels. Even if you don't add table salt to your food, many prepared foods, such as canned soup or fast food, are already high in sodium.

Learn which foods are high in potassium and which are low. Your kidneys are responsible for filtering excess potassium out of your body. When they're not functioning well, they won't be able to filter potassium properly. In people with chronic kidney failure, high levels of potassium (hyperkalemia) can be life threatening. It can lead to abnormal heart functioning or paralysis.

Your kidneys may not be able to process phosphate either. Phosphate can also diminish your body's ability to absorb calcium. High-phosphate foods include fish, dairy products, eggs, and meat. You may need to eat less of these.

You may also need to limit your fluids, so your kidneys don't have to work too hard.

People with chronic kidney failure often lose weight. Make sure you're consuming enough calories from foods that your dietitian has approved and recommended.

Lifestyle

You should also avoid smoking and keep up to date on your vaccinations, including your flu shots. Discuss supplements and over-the-counter medications with your doctor before taking them. If you see other doctors for different conditions, always inform them of your kidney situation.

End-Stage Treatment

If attempts to control your condition through diet and medication fail, you might face end-stage kidney disease. This occurs when your kidneys are operating at only 10 to 15 percent of their full capacity. At this stage, your kidneys can no longer eliminate waste as fast as you're producing it.

There are two treatment options for end-stage kidney disease: dialysis and kidney transplant. Doctors try to postpone these options as long as possible because both carry serious risks.

Dialysis is a system for filtering waste products and excess fluids out of your blood. There are several ways to do this. The two main types of dialysis are hemodialysis and peritoneal dialysis. In hemodialysis, your blood is filtered outside of your body, in a machine. In peritoneal dialysis, you fill your abdominal cavity with a special solution via a catheter. The solution absorbs excess fluid and waste before it's drained from your body. Because dialysis usually needs to be done several times a week, it's a big lifestyle change. Dialysis also carries a risk of infection.

Kidney transplant is more convenient than dialysis, if you can find an appropriate donor kidney. The donor needs to have the same blood type as you. A kidney from a living sibling or other close relative is usually best. You could also get your kidney from a deceased donor. However, kidney transplants also carry a large risk of infection because you will need lifelong immunosuppression.

Long-Term Outlook for Chronic Kidney Failure

Some people with chronic kidney failure manage to live for many years. This can only be accomplished if you keep your kidneys from getting worse through lifestyle changes and medication. You will need to maintain a kidney-healthy regimen for the rest of your life.

If you reach end-stage kidney disease, you will need dialysis or a kidney transplant. Without such interventions, the disease is fatal.

The health of your kidneys affects your other organs and systems, too. Possible complications of kidney failure include heart and liver failure, damage to your nerves, stroke, fluid buildup in your lungs, infertility, erectile dysfunction, dementia, and bone fractures.

Children with kidney failure may not grow properly because their kidneys can't activate vitamin D. Vitamin D is essential for bone growth.

Kidney failure also poses serious risks to pregnant women and their unborn babies. Pregnant women with kidney failure face a higher incidence of preeclampsia. Preeclampsia is a spike in blood pressure that can lead to brain or liver hemorrhage in pregnant women. This can potentially kill pregnant women and their unborn babies.

Preventing Chronic Kidney Failure

You can prevent kidney failure by making healthy lifestyle changes. Here are some general guidelines for healthy living:

Women and men over 65 should limit themselves to no more than one alcoholic drink per day. Men who are younger than 65 should stop at two drinks.

Maintain good control of your blood pressure.

If you have diabetes, control your blood sugar.

If you're overweight, try to get down to a healthy weight. This usually means consuming fewer calories and being more active.

Over-the-counter pain relievers can cause kidney damage. Follow the directions on the packages, only them take as needed, and discuss the use of pain relievers with your doctor if you have any kidney concerns.

If you smoke cigarettes, quit today.

Indications for kidney transplant:

Indications for kidney transplantation include chronic kidney disease (CKD) and renal tumors. Studies show that kidney transplantation prolongs patient lifespan compared with dialysis. Although perhaps only 25% of adult patients on dialysis are being referred for transplant evaluation (probably 95% of pediatric patients with ESRD will be referred), the number of potential candidates has resulted in burgeoning waitlists and longer waiting times for patients in need of kidney transplants.

Correction of acidosis:

using sodium bicarbonate to treat the chronic acidosis of CKD, usually starting with 650 mg twice daily (15.5 mEq/day of bicarbonate) and titrating upward based on the response

