

Pulmonology Disorders

1. Bronchiectasis

<p><u>Clinical Presentation</u></p> <p><i>Symptoms:</i> Cough with Copious & Purulent Sputum Hemoptysis</p> <p><i>Physical Exam:</i> Rales &/or Rhonchi (over obstructed area) Clubbing</p>	<p><u>Lab Presentation</u></p> <p><i>CXR:</i> non-specifically abnormal in area of involvement; may show increased vascular markings or “ring” shadows - CXR is not diagnostic</p> <p><i>HRCT:</i> shows dilated airways with “ring-like” appearance</p> <p><i>ABGs:</i> normal or type B COPD pattern (\downarrow PaO₂ & \uparrow PaCO₂).</p>
<p><u>Etiology and Pathogenesis</u></p> <p><i>Bronchiectasis</i> is an irreversible dilation of the bronchi &/or bronchioles caused by progressive inflammatory damage to the structural components of the airway wall (smooth muscle and elastic matrix); it is usually localized behind an area of specific obstruction (i.e. an aspirated foreign body) or involves the lower lobes bilaterally, preferentially effecting the more vertical airways. The underlying inflammation is most commonly caused by primary lung parenchymal infection (viral, bacterial, or fungal) but may also result from airway obstruction and subsequent recruitment of inflammatory mediators which release proteolytic enzymes (elastase, collagenase, matrix metalloproteases) in a manner similar to that of a local response to infection. Damage to the airway wall is progressive because infection can \rightarrow \uparrow mucous production and \uparrow obstruction, and obstruction (generally by thick mucous plugs) impairs the immune response by impairing the propulsive function of the mucociliary elevator and creating a barrier to cellular and humoral immune clearance of infection (similar to the way abscess formation impairs clearance). Bacterial colonization may be acute or stable over time and exacerbated acutely. Defects in humoral immunity (e.g. hypogammaglobinemia), cellular immunity, or dyskinetic cilia syndrome (as in <i>Kartagener’s syndrome</i>) predispose someone to bronchiectasis, as does pulmonary infection with <i>Staphylococcus aureus</i> or <i>Klebsiella</i>. Because bronchiectasis may be localized or widespread and may or may not present with concurrent generalized airway disease (most often chronic bronchitis), pulmonary function may be normal to severely impaired – similarly, arterial blood gases may be normal or show changes characteristic of type B COPD (hypoxemia with hypercapnia). Three patterns of airway dilation have been described: cylindrical, varicose, and saccular – with dilated airways generally filled with mucoid and/or purulent material. Local inflammation induces pulmonary vascular hypertrophy (with possible increase in number of arteriovenous anastomoses) and inflammatory erosion of the vasculature combined with mechanical trauma due to turbulent flow through obstructed airways may result in <i>hemoptysis</i>. Mucoid obstruction irritates the airways causing <i>productive cough</i>. Symptoms may be episodic and exacerbated acutely by URTIs. A mixed flora may be cultured from the involved bronchi, with staph., strep., enteric anaerobes, H.influenzae, and pseudomonas commonly seen.</p>	
<p><u>Treatment</u></p> <p>Three major aspects of treatment</p> <ol style="list-style-type: none"> 1. Antibiotics 2. Clearance of Airway Secretions 3. Bronchodilators <p>Antibiotics</p> <p>S.pneumoniae & H.influenzae \rightarrow <i>amoxicillin</i>, &/or <i>trimethoprim-sulfamethoxazole</i></p> <p>P.aeruginosa \rightarrow <i>ciprofloxacin</i> - development of resistance is common</p> <p>Clearance of Airway Secretions</p> <p>Chest physical therapy & positioning (postural drainage) Inflatable vests or mechanical vibrators on the chest</p> <p>Bronchodilators</p> <p>- may be useful in pts. with coexisting airway obstruction that is partially reversible</p> <p>Surgery is reserved for pts. with localized bronchiectasis (and no concurrent generalized airways disease) whose symptoms are poorly controlled by medical therapy.</p>	<p><u>Notes</u></p> <p><i>Allergic bronchopulmonary aspergillosis</i> is a form of bronchiectasis characterized by aspergillus colonization primarily of the proximal airways and found almost exclusively in asthmatics.</p> <p>10-20% of pts. have “dry” bronchiectasis (without sputum).</p> <p>Pts. with bronchiectasis often become infected with the uncommon pathogen <i>Pseudomonas aeruginosa</i>; finding this organism suggests the diagnosis.</p> <p>Treatment may begin when there is a change in the quantity or quality of sputum or may be given to control a chronic infection.</p> <p>Important complication in Cystic Fibrosis.</p> <p>HRCT gives definite diagnosis.</p>

2. Cystic Fibrosis

<p>Clinical Presentation</p> <p><i>Symptoms:</i> Dyspnea / Cough / Hemoptysis</p> <p><i>Complications:</i> Pneumothorax / Cor Pulmonale</p> <p><i>Physical Exam:</i> Wheezing Coarse Rales Rhonchi Clubbing (possible)</p>	<p>Lab Presentation</p> <p>Elevated sweat chloride concentration (> 60mEq/L)</p> <p><i>CXR:</i> may show findings of <i>bronchiectasis</i> or <i>pneumonitis</i></p> <p><i>Spirometry:</i> ↑ RV, ↑ FRC ↓ FEV₁, ↓ FEV₁/FVC; normal TLC</p> <p><i>ABGs:</i> ↓ PaO₂ & ↑ PaCO₂; metabolic alkalosis (↑ HCO₃⁻)</p> <p><i>Abnormal Nasal Potential Difference</i></p>
<p>Etiology and Pathogenesis</p> <p>CF is characterized by thick, tenacious secretions from the exocrine glands (especially those in the airways and pancreatic ducts) and elevated concentrations of Na, Cl, and K in the sweat due to an abnormal <i>cystic fibrosis transmembrane conductance regulator</i> (CFTR) chloride-transport protein. Reduced epithelial permeability to Cl export is responsible for the characteristic viscous secretions and elevated electrolyte concentrations in sweat. The most common genetic defect is a 3-nucleotide deletion that results in the loss of a phenylalanine at position 508, though there are more than 800 different CF mutations. In the pancreas, obstruction of the ducts by mucous plugs causes fibrosis, atrophy of the acini, and cystic changes that eventually result in pancreatic insufficiency (with maldigestion and malabsorption of food, especially fats). In the airways, mucous plugging obstructs both airflow and normal tracheobronchial drainage. Early in the course of the disease, the airway changes are found mostly in the bronchioles – later findings are more extensive with pneumonitis, bronchiectasis, and abscess formation likely; cor pulmonale with RVH frequently occurs as well. Recurrent episodes of tracheobronchial infection (esp. <i>pseudomonas</i>) and bronchiectasis are the most serious pulmonary complications of CF – In addition to the obstructive changes, the CFTR mutation contributes to airway infection by altering the binding and clearance of airway epithelial cells and impairing the activity of endogenous antimicrobial peptides (such as β-defensin-1). The humoral immune system appears to be intact in CF, however. CF patients also show pathophysiologic changes similar to type B COPD (V/Q mismatch, hypoxemia, possible hypercapnea, pulmonary HTN w/ cor pulmonale) and functional changes characteristic of obstructive disease and airway trapping (↑ RV & ↑ FRC, ↓ FEV₁ & ↓ FEV₁/FVC) that progressively worsen over time. Because emphysematous changes usually do not occur in CF, elastic recoil is preserved and TLC is most often normal – and since the alveolar-capillary interface remains relatively preserved, diffusing capacity is normal as well.</p>	
<p>Treatment</p> <p>Similar to treatment of <i>brochiectasis</i> (see # 1).</p> <ol style="list-style-type: none"> 1. Antibiotics 2. Clearance of Airway Secretions 3. Bronchodilators <p>Also:</p> <ol style="list-style-type: none"> 4. <i>Recombinant DNase</i> - to decrease sputum viscosity by degrading the large amount of DNA released from lysed inflammatory cells. <p>Possibly:</p> <ol style="list-style-type: none"> 5. <i>Bilateral lung transplant</i> - post-transplant survival is similar to that of non-CF patients, despite concerns about chronic pulmonary infection in CF. <p>Nutritional Therapy: High fat/calorie diet Pancreatic enzyme supplementation Fat-soluble vitamin supplementation</p> <p>For Acute Exacerbations: ↑ ↑ airway clearance IV &/or inhaled antibiotics: 2 agents against all gram negatives for at least 2 weeks</p>	<p>Notes</p> <p>Epidemiology:</p> <ul style="list-style-type: none"> • most common lethal genetic ds in white population; inherited as autosomal recessive in 1 in 2,500 live births. • heterozygous carriers are asymptomatic • onset is most often in childhood • the major organisms that eventually colonize CF airways are <i>Staphylococcus aureus</i> and <i>Pseudomonas aeruginosa</i>. • 71% of pts. are diagnosed in the first year of life; 2% are diagnosed in adulthood. <p>CF presents in 10-20% of patients in the neonatal period as <i>meconium ileus</i> (intestinal obstruction from thick meconium); most others present as children with recurrent pulmonary infections and pancreatic insufficiency.</p> <p>Almost all males with CF are sterile; females may have children but their fertility rate is decreased.</p> <p>Heterozygotes have normal sweat electrolytes.</p>

3. Upper Airway Obstruction

<p><u>Clinical Presentation</u></p> <p><i>Symptoms:</i> Dyspnea / Cough Anxiety & Respiratory Distress</p> <p>Sore throat / dysphagia / drooling / voice change (<i>epiglottitis</i>)</p> <p><i>Physical Exam:</i> Expiratory wheezing (intrathoracic obstruction) Inspiratory stridor (extrathoracic obstruction) Inspiratory & Expiratory stridor/wheezing (fixed obstruction)</p>	<p><u>Lab Presentation</u></p> <p>CXR, CT, or bronchoscopy reveals the obstruction.</p> <p><i>Spirometry Flow-Volume Curve:</i> Intrathoracic obstruction → expiratory plateau Extrathoracic obstruction → inspiratory plateau Fixed obstruction → expiratory & inspiratory plateau</p>
<p><u>Etiology and Pathogenesis</u></p> <p>Upper airway obstruction may be caused acutely by laryngeal inflammation (e.g. epiglottitis due to <i>Haemophilus influenzae</i> or laryngeal edema from anaphylaxis), thermal injury and resulting laryngeal edema from smoke inhalation, or aspiration of a foreign body. It may be caused chronically by hypertrophy of the tonsils, tracheal tumors, tracheal strictures, or vocal cord paralysis.</p> <p>In <i>fixed obstructions</i>, airway diameter does not change over the course of the respiratory cycle and the flow-volume curve correspondingly shows a plateau in both the inspiratory and expiratory phase. In <i>variable obstructions</i>, airway diameter (and thus the extent of obstruction) varies throughout the respiratory cycle: <i>extrathoracic obstructions</i> are located outside of the pleural cavity and as such are made worse during inspiration (& show a plateau in the inspiratory phase on the flow-volume curve) as increasingly negative intrathoracic pressure generated by the respiratory musculature creates a suction that narrows the extrathoracic upper airways; <i>intrathoracic obstructions</i> are located inside the pleural cavity and are made worse in expiration (show a plateau in the expiratory phase on the flow-volume curve) as positive pleural pressures cause narrowing of the intrathoracic airways. Upper airway obstructions can be a medical emergency if the airway is significantly compromised.</p>	
<p><u>Treatment</u></p> <p>Acute, severe upper airway obstruction: - emergency procedures such as <i>endotracheal intubation</i> or <i>tracheostomy</i></p> <p>Chronic airway obstruction: varies with cause of ds.</p>	<p><u>Notes</u></p> <p><i>Sleep apnea syndrome</i> is recurrent, episodic upper airway obstruction during sleep.</p> <p>Use functional evaluation based on the shape of the flow-volume curve for chronic obstructions, not for acute life-threatening obstructions.</p> <p>Obstructions most often occur in the right lower lobe.</p>

4. Asthma

Clinical Presentation	Lab Presentation
<p><i>Symptoms:</i> (episodic; may be associated with known exposure) Cough Dyspnea Wheezing Chest Tightness</p> <p><i>Physical Exam:</i> Tachypnea Prolonged Expiration Wheezing (generally worse on expiration and made more prominent by forced expiration) - wheezing may not be audible in severe airway obstruction</p>	<p><i>Histology:</i> eosinophilia (even when asthma is non-allergic); Charcot-Leyden crystals; pathologic changes as described below.</p> <p><i>Blood Tests:</i> eosinophilia, ↑ serum IgE</p> <p><i>Spirometry:</i> ↓ FEV₁, ↓ FEV₁/FVC, ↓ FEF_{25-75%}; ↑ DLCO ↑ FRC, ↑ RV; may show ↑ TLC.</p> <p><i>CXR:</i> may be normal; may show hyperinflation.</p> <p><i>Provocation Testing:</i> bronchoconstriction when exposed to <i>methacholine</i> or <i>isocaproic hyperpnea</i> (inhalation of cold</p>
<p><i>Asthma</i> is characterized by episodic, reversible airway narrowing associated with hyper-responsive smooth muscle contraction in the presence of a wide variety of stimuli. Hyper-responsiveness is likely due to an underlying inflammatory process and epithelial injury, and because the bronchoconstriction is at least partially reversible the patient experiences episodic exacerbations as well as symptom-diminished and symptom-free periods. Although asthma is often but not always associated with concurrent allergic disease: asthma with an allergic component (Type I hypersensitivity) is called <i>extrinsic asthma</i> whereas asthma with no known allergy is <i>intrinsic asthma</i> – the common feature of both types is hyper-responsive bronchoconstriction with inflammation (with many eosinophils and lymphocytes) and epithelial damage. Mediators that play a role in asthmatic inflammation include: 1) <i>prostaglandin</i> and <i>leukotriene</i> products of arachidonic acid metabolism (leukotrienes are also thought to be responsible for the “late-phase” bronchoconstriction that may occur 2-6 hours after the initial bronchoconstriction in an asthma attack), 2) <i>histamine</i> released from mast cells upon IgE binding, 3) <i>cytokines</i> released from pro-inflammatory cells such as <i>IL-5</i>, which stimulates chemotaxis, proliferation, activation, and degranulation of eosinophils, and <i>IL-4</i>, which activates B-lymphocytes to enhance IgE secretion and promotes differentiation of T_H2 cells, 4) <i>eosinophil granule contents</i> such as <i>major basic protein</i> and <i>eosinophil cationic protein</i> which contribute to epithelial damage (eosinophils also release LTC₄ and PAF and so can continue an allergic asthmatic reaction without continued exposure to antigen), 5) <i>NO</i>, <i>chemokines</i>, and <i>cytokines</i> produced by the damaged epithelium that induce airway edema via causing vasodilation and increased permeability in the pulmonary vasculature, 6) <i>tachykinins</i> such as <i>substance P</i> and <i>neurokinin A</i> released by nerve endings that become exposed in a damaged epithelium.</p> <p>Common stimuli that precipitate bronchoconstriction include: 1) <i>allergen exposure</i> via inhalation, leading to antigen binding IgE and antigen-IgE complex binding IgE receptors on mast cells in the bronchial lumen resulting in degranulation of mediators that induce bronchoconstriction and increase the permeability of the epithelium, allowing antigen to access the larger population of mast cells deeper in the epithelium, 2) <i>inhaled irritants</i> such as cigarette smoke, inorganic dusts, and organic pollutants that stimulate irritant receptors and induce a vagal reflex that results in vasoconstriction, 3) <i>respiratory tract infection</i> which potentiates airway inflammation and epithelial damage, 4) <i>exercise</i>, due to cooling and drying of the upper airways as high minute ventilation demands a high evaporation of water vapor from the tracheobronchial mucosa – this is the same reason breathing cold air exacerbates asthma, though the mechanism that links cold to bronchoconstriction is unknown. Some patients are sensitive to aspirin or other NSAIDs, probably because these shift the balance of arachidonic acid metabolism toward leukotriene production.</p> <p>Pathologic findings in asthma include: 1) edema with cellular infiltrates within the bronchial wall, especially with eosinophils and lymphocytes, 2) epithelial damage, with a “fragile” appearance of the epithelium and detachment of surface epithelial cells from the basal cells, 3) hypertrophy and hyperplasia of the smooth muscle layer in the large & medium airways, 4) thickening of the epithelial basement membrane (does not happen in chronic bronchitis), 5) enlargement of the mucus-secreting apparatus, with hypertrophy of mucous glands and an increased # of goblet cells. These changes are present from the large airways down to the peripheral airways less than 2mm in diameter.</p> <p>As a result of narrowed airways patients have difficulty with airflow in both inspiration & expiration, though expiratory impairment predominates due to airway closure during expiration – this difficulty is most pronounced in forced expiration when increasingly positive pleural pressures exacerbate airway closure. During an attack, spirometry shows ↓ FEV₁, ↓ FEV₁/FVC, ↓ FEF_{25-75%}, ↑ FRC, and ↑ RV – a pattern characteristic of narrowed airways and air-trapping behind airways obstructed by bronchoconstriction, mucus plugging, and inflammatory thickening of the mucosa. Most pronounced is the increase in RV, which may be > 200% of the predicted value. FRC may be increased for two reasons: 1) because more time is required for expiration through increasingly resistant airways, patients may not have sufficient time to exhale completely before needing to take the next breath (dynamic hyperinflation), 2) maintenance of higher-than-normal lung volume in expiration (via persistent activity of the inspiratory musculature) such that airway “back pressure” remains elevated in order to keep small, constricted airways from collapsing completely. TLC is occasionally elevated as well, possibly due to increased contractility of the inspiratory musculature &/or decreased elastic recoil of the lungs during the attack, though the reason for these changes is unknown. Arterial blood gas measurements show hypoxemia & hypocapnia due to V/Q mismatch (↓ V with normal Q) caused by perfusion of obstructed airways (this explains the hypoxemia) and compensatory hyperventilation (this explains the hypocapnia) – this mismatch may be made worse by β-agonist therapy as hypoxic constriction of underventilated capillaries is reversed. When P_{CO2} returns to normal or becomes high, this is usually a bad sign as it means the patient is tiring and can no longer maintain normal-to-high minute ventilation in response to significant airflow obstruction and low P_{O2}. The stimulus for asthmatic hyperventilation is likely an activation of the irritant receptors in the lung.</p> <p>Asthmatic attacks are associated with pulmonary function and gas-exchange changes occurring 30min after antigen exposure and resolving within 2 hours; in many patients a “late-phase” reaction that begins 2-8 hours after exposure and peaks at 6hours also occurs. Between attacks, the pulmonary function of many asthmatics returns to normal, though subtle abnormalities such as a slightly reduced FEF_{25-75%} or increased RV may be present and serve as diagnostic clues. Some patients will have persistently</p>	

Treatment	Notes
<p><i>Treatment strategies for the various severities of asthma are given in the Notes section.</i></p> <p>For patients whose asthma is provoked by an antigen exposure, <i>antigen avoidance</i> is an important and necessary component of therapy.</p> <p>Medical Therapies:</p> <p>I. <i>Bronchodilators</i></p> <ol style="list-style-type: none"> 1. <i>β₂-agonists</i> (albuterol & salmeterol) <ul style="list-style-type: none"> - ↑ cAMP in bronchial smooth muscle cells promotes relaxation & in mast cells inhibits degranulation. - may be used prophylactically before exertion or exposure. - inhaled, oral, or IV administration 2. <i>Methylxanthines</i> (theophylline & aminophylline) <ul style="list-style-type: none"> - ↑ cAMP via phosphodiesterase inhibition or stimulation of adenylyl cyclase. - theophylline may also have anti-inflammatory activity by inhibiting PDE IV isozyme in inflammatory cells. - oral administration only for theophylline; aminophylline can be given orally or IV. - more side effects than β-agonists because methylxanthines must be given systemically. 3. <i>Anti-cholinergics</i> (ipratropium) <ul style="list-style-type: none"> - used more in COPD than in asthma <p>II. <i>Anti-inflammatories</i></p> <ol style="list-style-type: none"> 4. <i>Corticosteroids</i> (methylprednisone & beclomethasone) <ul style="list-style-type: none"> - suppress inflammation by diminishing the # of eosinophils and lymphocytes infiltrating the airways. - ligand/receptor complex binds TFs such as AP-1 and NF-κB and regulates expression of IL-1, IL-3, IL-4, IL-5, IL-6, TNF-α, iNOS, & iCOX. - methylprednisone given systemically; beclomethasone may be inhaled. - treat underlying pathology as well as symptoms. - corticosteroid tapers are commonly used to treat acute attacks; inhalable corticosteroids avoid many of the side effects of systemic steroids and are now the preferred therapy for preventative maintenance of patients with asthma not controlled by short-acting β₂-agonist 5. <i>Sodium Cromoglycate (Cromolyn)</i> <ul style="list-style-type: none"> - inhibits mediator release from mast cells or the inflammatory action of tachykinins. - used for prevention of attacks, not for tx of acute exacerbation. - given by inhalation 6. <i>Nedocromil</i> <ul style="list-style-type: none"> - inhibits mediator release from mast cells or the inflammatory action of tachykinins. - used for prevention of attacks, not for tx of acute exacerbation. - given by inhalation <p>III. <i>Leukotriene Modifiers</i></p> <ol style="list-style-type: none"> 7. <i>Zafirlukast</i> <ul style="list-style-type: none"> - oral; LTD₄ receptor antagonist 8. <i>Zileuton</i> <ul style="list-style-type: none"> - oral; inhibits 5-lipoxygenase → ↓ LTs <p><i>Omalizumab</i> is a monoclonal Ab against IgE that is</p>	<p>Definitive diagnosis of asthma is made by documenting a history of episodic dyspnea, wheezing, &/or cough along with reversible airflow obstruction shown in pulmonary function tests.</p> <p>Epidemiology</p> <ul style="list-style-type: none"> • occurs in 3-5% of the population • primarily occurs in children & young adults; most common chronic ds in these age groups. • in many patients, esp. those whose asthma began before age 16, the disease eventually regresses. <p>Predisposing factors:</p> <ol style="list-style-type: none"> 1. <i>Genetics</i> <ul style="list-style-type: none"> • history of allergic disease (e.g. eczema & allergic rhinitis) with elevated IgE levels • family history of allergic disease <ul style="list-style-type: none"> - though no clear Mendelian inheritance pattern has been demonstrated • evidence for genetic involvement in asthma: <ul style="list-style-type: none"> - ↑ incidence of asthma in first-degree relatives of asthmatics - ↑ incidence of asthma in monozygotic twins - observed genetic correlations: <ul style="list-style-type: none"> - chromosomes 5q, 11q, 12q, 6p - 11q → β-subunit gene of IgE receptor - 5q → cytokine gene cluster & β₂ receptor gene • specific gene: some asthmatics do not have the gene <i>T-bet</i>, which codes for a transcription factor for IFN-γ (which drives the helper T-cell population to the T_{H1} phenotype; the T_{H2} cells are active in asthma). 2. <i>Environmental factors</i> <ul style="list-style-type: none"> • exposure to allergens during critical period in childhood • maternal cigarette smoking <p>Classification of Asthma by Severity, Presentation, & Treatment:</p> <p><i>Mild intermittent:</i> symptoms < 2x per week; asymptomatic and normal PEFr between exacerbations; PEFr variability < 20%; nighttime symptoms < 2x per month; tx → inhaled short-acting β₂-agonist prn.</p> <p><i>Mild persistent:</i> symptoms > 2x per week but < daily; nighttime symptoms > 2x per month, exacerbations may affect activity; FEV₁ or PEFr < 80% predicted, PEFr variability 20-30%; tx → anti-inflammatory (inhaled corticosteroid or cromolyn) or sustained release theophylline or LT-modifier (zafirlukast) plus inhaled short-acting β₂-agonist prn.</p> <p><i>Moderate persistent:</i> daily symptoms, daily use of plus inhaled short-acting β₂-agonist, exacerbations that affect activity > 2x per week and may last for days; nighttime symptoms > once per week; FEV₁ or PEFr 60-80% predicted, PEFr variability > 30%; tx → anti-inflammatory with or without addition of an LT-modifier (zafirlukast) and with or without an inhaled long-acting bronchodilator (β₂-agonist or theophylline) plus the inhaled short-acting β₂-agonist prn.</p> <p><i>Severe persistent:</i> continual symptoms, frequent nighttime symptoms, limited physical activity with frequent exacerbations; FEV₁ or PEFr < 60% predicted, PEFr variability > 30%; tx → high-dose inhaled corticosteroids</p>

5. Chronic Obstructive Pulmonary Disease (COPD) - Chronic Bronchitis & Emphysema

Clinical Presentation	Lab Presentation
<p><i>Symptoms:</i> (May be asymptomatic with dx based on PFTs)</p> <p>Dyspnea (primary in type A)</p> <p>Productive Cough (primary in type B)</p> <p>Respiratory Failure</p> <ul style="list-style-type: none"> - often follows acute exacerbations - type B pts. more sensitive to exacerbations <p><i>Physical Exam:</i></p> <p>Type A (pink puffer) → cachectic (wasted) appearance; may be leaning forward and resting on extended arms; use of accessory muscles in breathing; hyperpnea</p> <p>Type B (blue bloater) → obese, cyanotic, may show right-heart failure, generally in less respiratory distress than type A, rhonchi heard over areas of profuse mucus secretion</p> <p>General COPD → lung hyperinflation (↑ AP diameter of chest); prolonged expiration ↓ diaphragmatic excursion wheezing</p>	<p><i>Spirometry:</i></p> <p><i>Chronic Bronchitis:</i> ↓ FEV₁, ↓ FVC, ↓ FEV₁/FVC, ↓ FEF_{25-75%}; ↑ RV, ↑ FRC,</p> <p><i>Emphysema:</i> as above plus ↓ Diffusing Capacity & ↑ TLC</p> <p><i>ABGs:</i></p> <p><i>Type A:</i> normal P_{O2}, normal P_{CO2}</p> <p><i>Type B:</i> ↓ P_{O2}, ↑ P_{CO2}, ↑ HCO₃⁻</p> <p><i>CXR:</i> (2 patterns – see P&E below for explanation)</p> <p>Hyperinflation / Flat diaphragms / ↑ AP diameter / ↓ markings</p> <p>or</p> <p>↑ vascular markings / RVH (from cor pulmonale)</p>

Etiology and Pathogenesis

Chronic Bronchitis is a fundamentally clinical diagnosis used for patients with chronic cough & sputum production present on most days for 3 consecutive months per year for at least 2 consecutive years. CB patients frequently have periods of exacerbation with progressive residual disease present between them (unlike most asthmatics, whose lung function returns to normal between exacerbations). *Emphysema* is formally a pathologic diagnosis characterized by destruction of the lung parenchyma and enlargement of air spaces distal to the terminal bronchiole. Since many patients have elements of both chronic bronchitis and emphysema, the term COPD is used to include either or both of these disorders. Cigarette smoking is the primary etiology of COPD (though only 15% of smokers will develop severe disease) with environmental pollutants and RTIs likely to cause exacerbations.

Smoking causes the following pathologic changes in the lung: 1) ↑ in the number and size of the bronchial mucous glands in the larger airways resulting in ↑ ed mucus secretion and thickening in the airway wall from hypertrophied/hyperplastic mucous glands – both of these effects act to reduce airway diameter and impair airflow, 2) ↓ ciliary function and mucociliary clearance, which worsens the problem of excessive airway mucus, 3) recruitment of inflammatory cells (esp. macrophages, neutrophils, and CD8⁺Tcells) into the airway wall, which subsequently release mediators (LTB₄, IL-8, TNF- α) that further inflammation and promote bronchoconstriction, 4) bronchiolar narrowing, fibrosis, and inflammation, 5) squamous metaplasia of the lung epithelium, and 6) destruction of the pulmonary parenchyma (emphysema) as neutrophil-released *elastase* and macrophage-released *matrix metalloproteases* break down the alveolar wall (especially *elastin*) faster than can be inhibited by endogenous α_1 -antitrypsin and *tissue inhibitors of matrix metalloproteases*, respectively – this imbalance occurs in smokers as large numbers of neutrophils and macrophages are recruited to the lung and oxidants from cigarette smoke and inflammatory cells oxidize and impair endogenous protease inhibitors; neutrophil elastase also promotes further secretion of mucus in the airways. Genetic variation in the activity of the protease inhibitors may explain variability in COPD incidence and course in smokers – Patients who are homozygous for α_1 -antitrypsin deficiency (Pi ZZ genotype) have circulating α_1 -antitrypsin levels 15% of normal because secretion of the mutant enzyme from the liver is impaired; they may develop emphysema as early as their 30s-40s, especially if they smoke. Lung damage due to childhood respiratory infections has also been associated with development of COPD in adult smokers, and some data suggests patients with increased bronchial hyper-responsiveness also have an increased risk of developing COPD.

Pathologic findings in chronic bronchitis include hypertrophy and hyperplasia of the mucus-secreting glands as well as inflammation in the bronchi (large airways) with fibrosis, cellular infiltration, smooth muscle hypertrophy, and goblet-cell hyperplasia in the bronchioles (small airways). Because the resistance of airways varies inversely with the fourth power of the radius, even a small change in airway diameter from any of the above causes can significantly decrease flow. Parenchymal destruction in emphysema shows two distributions in the airway: *panlobular emphysema* uniformly and diffusely involves all structures distal to the terminal bronchiole, whereas *centrilobular emphysema* is generally confined to the respiratory bronchioles (all emphysema is restricted to the acinus). Panlobular and centrilobular emphysema are associated primarily (but not exclusively) with α_1 -antitrypsin deficiency and smoking, respectively. Panlobular emphysema generally involves the lower lung, whereas centrilobular emphysema generally involves the upper lung.

The productive cough that is characteristic of chronic bronchitis results from large airway inflammation and mucus-plugging, but when airway obstruction is present it appears that obstruction in the small airways &/or emphysematous alveolar destruction play a greater role in functional impairment. When pathology is confined to the peripheral airways (only 10-20% of total lung resistance), functional impairment may be mild or non-existent; if impairment exists, spirometry reveals a pattern consistent with obstructive disease: in pure airways disease (chronic bronchitis) FEV₁, FEV₁/FVC, and FEF_{25-75%} are decreased due to flow across increased resistance, and though TLC and FRC may remain normal because inspiratory strength and lung elastic recoil are unchanged, FRC will be elevated if expiration is prolonged (due to reduced airflow across increasing resistance) such that the lung cannot empty to FRC before the next breath occurs (this is similar to asthma and is a major cause for exertional dyspnea). RV will also be elevated if air-trapping behind obstructed airways occurs. If emphysema is present, there is increased RV, FRC, and TLC due to air-trapping behind easily collapsible small airways and decreased expiratory pressures and pressures opposing chest-wall expansion (at FRC) generated by less elastic lungs. Hyperinflation may result in the diaphragm being displaced downward and rendered less effective by less length-of-contraction. Nonuniformity in airway collapse and mucus-plugging across the lung results in areas of ventilation-perfusion mismatch (↓ V with normal Q) that result in arterial hypoxemia and hypercapnea.

Pulmonary hypertension may develop in COPD from hypoxic & hypercapnic pulmonary arterial vasoconstriction (the major cause), emphysematous destruction of the pulmonary vasculature, and compensatory polycythemia; long-standing pulmonary HTN can then cause *cor pulmonale* characterized by right-heart functional impairment.

Two common clinical presentations of COPD have been identified: *type A* (pink puffer) physiology is associated with predominantly emphysematous COPD and is characterized by a generally normal P_{O_2} (due to simultaneous and matched loss of ventilation and perfusion when alveolar walls are destroyed) and hyperpnea (due to need of high minute ventilation to sustain P_{O_2}). Because hypoxia is not a feature of type A COPD, pulmonary HTN and polycythemia are not seen. *Type B* (blue bloater) physiology is associated with predominantly chronic bronchitis and is characterized by hypoxemia & hypercapnia due to perfusion of non-ventilated airways – as mentioned above, this results in pulmonary HTN, right-heart failure, and polycythemia (\uparrow hematocrit).

The large majority of COPD patients present with a combination of type A & type B findings.

Chest radiography in COPD shows two patterns: The first is the *arterial deficiency* pattern which is associated primarily with panlobular emphysema (& α_1 -antitrypsin deficiency) and consists of hyperinflation, flat diaphragms, \uparrow AP diameter, and loss of vascular markings due to vascular obliteration and hyperinflation. The second is the *increased markings* pattern which is associated primarily with type B physiology and centrilobular emphysema and consists of prominent vascular markings with RVH due to pulmonary hypertension (as discussed above, type B pts. show pulmonary HTN primarily due to hypoxic/hypercapnic arterial vasoconstriction).

Arterial blood gas findings also show two patterns: type A patients show normal or slightly reduced P_{O_2} with normal to slightly elevated P_{CO_2} , whereas type B patients show marked reductions in P_{O_2} and increases in P_{CO_2} ; over time, the kidneys retain bicarbonate in order to compensate for the pH reduction caused by respiratory CO_2 retention. Failure of this metabolic compensation to keep pH nearly normal may indicate an exacerbation or a progressive worsening of the disease.

Treatment	Notes															
<p>Drug Therapy (see # 4 – Asthma for drug info)</p> <ul style="list-style-type: none"> • <i>Ipratropium</i> is a first-line therapy; it is at least as effective as β-agonists and has less side-effects. • Exacerbations are often treated with antibiotics, even when there is no clear bacterial infection. <ul style="list-style-type: none"> - most common bacterial infections in COPD: <i>Streptococcus pneumoniae</i>, <i>Haemophilus influenzae</i>, <i>Moraxella catarrhalis</i>. • A short course of systemic corticosteroids is often beneficial in acute exacerbations, but are less effective as maintenance therapy; inhaled corticosteroids are not useful at all for COPD. <p>Other Medical Therapy</p> <ul style="list-style-type: none"> • <i>Supplemental O₂</i> is given to patients with $P_{O_2} < 55$mmHg <ul style="list-style-type: none"> - COPD often responds to low amounts of O₂ (24-28% O₂) or 1-2L/min by nasal canula. - O₂ is particularly important in patients with hypoxia-induced polycythemia. - O₂ is the only COPD tx that prolongs survival. • <i>Smoking Cessation</i> counseling & treatment is crucial. • <i>Vaccination</i> against H.flu & Pneumococcus for all pts. • Chest physiology followed by postural changes to loosen secretions may or may not help. • IV α_1-antitrypsin may or may not help. <p>Surgical Therapy</p> <ul style="list-style-type: none"> • <i>Lung volume reduction surgery</i> to diminish overall thoracic volume (which allows diaphragm to return to its normal position) and improve overall lung elastic recoil (by removing the most damaged areas of the lung). <ul style="list-style-type: none"> - overall benefit and long-term survival are unknown. • <i>Lung transplantation</i> <ul style="list-style-type: none"> - good for emphysema pts. with α_1-antitrypsin deficiency who develop disease at an early age. <p>Patients in respiratory failure may need mechanical ventilation by <i>non-invasive positive pressure ventilation</i> (O₂ tank and mask) or <i>endotracheal intubation</i>.</p>	<p><i>Asthmatic Bronchitis</i> refers to chronic bronchitis with a prominent component of airways hyperactivity; it responds better than non-asthmatic COPD to bronchodilator therapy.</p> <p>In COPD patients with respiratory failure, fatigue of the diaphragm likely contributes to alveolar hypoventilation and CO₂ retention.</p> <p>Epidemiology of COPD</p> <ul style="list-style-type: none"> • 4th leading cause of death in US • 2nd leading cause of disability in US • US prevalence of COPD = 16 million patients • US prevalence of smoking = 50 million people • 110,000 deaths per year in US • Since 1964, smoking prevalence has gone from 40% to 25% <p>In the larger airways, <i>secretory leukoprotease inhibitor</i> (not α_1-antitrypsin) inhibits neutrophil elastase.</p> <p>The <i>Reid Index</i> is the ratio of the thickness of mucous glands to the thickness of the airway wall; it is elevated in COPD</p> <p>Viral infections appear to be more responsible for COPD exacerbations than do bacterial infections, though many patients will have bacterial superinfection with a primary viral infection.</p> <p>Reduced IC accords more with dyspnea than does \downarrowed FEV₁.</p> <p>GOLD Therapy Recommendations (values relative to predicted):</p> <table border="1" data-bbox="852 1654 1404 1806"> <thead> <tr> <th>FEV₁</th> <th>FEV₁/FVC</th> <th>Treatment</th> </tr> </thead> <tbody> <tr> <td>>80%</td> <td><70%</td> <td>Ipratropium prn</td> </tr> <tr> <td>50-80%</td> <td><70%</td> <td>Ipratropium maintenance</td> </tr> <tr> <td>30-50%</td> <td><70%</td> <td>add Corticosteroids prn</td> </tr> <tr> <td><30%</td> <td><70%</td> <td>add O₂ if in respiratory failure consider surgery</td> </tr> </tbody> </table> <p>(all COPD pts. get flu vaccine)</p>	FEV ₁	FEV ₁ /FVC	Treatment	>80%	<70%	Ipratropium prn	50-80%	<70%	Ipratropium maintenance	30-50%	<70%	add Corticosteroids prn	<30%	<70%	add O ₂ if in respiratory failure consider surgery
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6a. Pneumonconiosis (& diffuse parenchymal lung disease in general)

Clinical Presentation	Lab Presentation
<p><i>Symptoms:</i> Dyspnea (May show non-productive cough &/or cor pulmonale)</p> <p><i>Physical Exam:</i> Hyperpnea Rales or dry crackles audible at the base of the lungs. (May show pulmonary hypertension)</p> <p>Clubbing (more likely in asbestosis)</p> <p>Asbestosis → pleural effusion/thickening; pleuritic pain diffuse fibrosis, basilar rales</p>	<p><i>Spirometry:</i> ↓ RV, ↓ FRC, ↓ TLC, ↓ VC; normal-to-high FEV₁/FVC, normal FEF_{25-75%};</p> <p><i>ABGs:</i> ↓ P_{O₂}, normal P_{CO₂}</p> <p><i>CXR:</i> Silicosis & CWP → small nodules (simple pneumoconiosis); large & coalescent nodules (complicated)</p> <p>Asbestosis → reticular streaking at the lung bases; maybe cystic changes or honeycombing; often shows diffuse pleural thickening or localized plaques.</p> <p>Berylliosis → hilar & mediastinal lymph node enlargement, granulomas may be seen.</p> <p><i>Histology:</i> Silicosis → silicotic nodules</p>
<p>Etiology and Pathogenesis</p>	
<p>Diffuse parenchymal lung diseases in general are associated with varying degrees of alveolitis and fibrosis resulting in characteristic pathophysiologic findings: 1) <i>decreased lung compliance</i> (↑ elastic recoil) due to fibrosis causing patients to breath rapidly at low tidal volumes to reduce the work of breathing, 2) <i>generalized decrease in lung volume</i> as increased elastic recoil causes FRC stabilizes at a lower lung volume, 3) <i>diffusion impairment</i> caused primarily by destruction of the alveolar-capillary interface and minimally by fibrotic expansion of the alveolar wall, 4) <i>abnormalities in small airways function</i> that may induce V/Q mismatch and hypoxemia without corresponding large airways obstruction (and so without abnormal FEV₁/FVC), 5) <i>disturbances in gas-exchange</i> usually resulting in hypoxemia without hypercapnia as high minute ventilation compensates for ↓ P_{O₂} and keeps P_{CO₂} normal; hypoxemia worsens during exercise because of ↓ diffusing capacity but usually P_{CO₂} is kept normal by hyperpnea, and 6) <i>pulmonary hypertension</i> may be caused by arterial hypoxemia & obliteration of small blood vessels. Clinical findings include dyspnea with possible non-productive cough, hyperpnea, audible rales primarily at the lung bases, possible pulmonary HTN, functional tests consistent with restrictive disease (↓ RV, ↓ FRC, ↓ VC & ↓ TLC with normal-to-high FEV₁/FVC, normal-to-high FEF_{25-75%}, and low-to-normal FEV₁). CXR reveals a reticular or reticulo-nodular pattern in 90% of patients but cannot distinguish primarily alveolitic from primarily fibrotic processes (CT can in some cases). In severe end-stage disease, fibrosis may be so extensive that “honeycombing” of the lung tissue (due to retraction of fibrotic areas) is seen and/or evidence of alveolitis disappears. Pulmonary fibrosis may also lead to contraction atelectasis (lung collapse due to ↑ ↑ elastic recoil).</p> <p>Four pathologic patterns are observed in diffuse parenchymal lung disease: 1) <i>Usual interstitial pneumonia</i> is characterized by patchy areas of interstitial inflammation & fibrosis interspersed between areas of preserved tissue; fibrosis is prominent with “fibroblastic foci” (focal collections of proliferating fibroblasts) present, and the inflammatory process in alveolar walls is nonspecific & typically composed of lymphocytes/MPs/plasma cells with hyperplasia of type II pneumocytes, presumably to replace damaged type I cells; CXR/CT shows subpleural involvement; the pathologic appearance of UIP can result from exposure to some inhaled dusts (esp. asbestos), drug-induced lung ds, systemic rheumatic ds, or can be idiopathic, 2) <i>Desquamative interstitial pneumonia</i> is characterized by large #s of intra-alveolar macrophages with less prominent inflammation of the alveolar walls, minimal fibrosis, “ground-glass” appearance on CT, and a more homogenous appearance than UIP; this pattern is strongly associated with smoking, 3) <i>Non-specific interstitial pneumonia</i> is characterized by uniform mononuclear cell infiltrate within alveolar walls with predominant inflammation and variable fibrosis; CT shows a “ground glass” appearance; NSIP may be idiopathic or associated with connective tissue disease, and 4) <i>Acute interstitial pneumonia</i> seen in acute respiratory distress syndrome and characterized by fibroblast proliferation & type II pneumocyte hyperplasia representing the fibrotic (organizing) stage of diffuse alveolar damage; ground-glass appearance is seen on CT along with areas of alveolar filling (as opposed to purely interstitial disease); AIP may occur without a typical inciting event of ARDS.</p> <p><i>Pneumonconiosis</i> is diffuse parenchymal lung disease caused by inhalation of inorganic dusts. <i>Silicosis</i> results from exposure to silica; persons at risk include sandblasters, miners, quarry workers, and stonecutters – Alveolar macrophages are activated and killed in digesting the inhaled silica, and cytokines they release are thought to be responsible for the alveolitis which in turn induces fibrosis (activated immune cells release proteases that degrade the normal extracellular matrix as well as cytokines such as TGF-β and PDGF that recruit and activate fibroblasts). Pathologically, silicotic inflammation is initially localized in the respiratory bronchioles but eventually becomes diffuse; histologically there is a characteristic a cellular nodule (the <i>silicotic nodule</i>) which is composed of connective tissue and at first are small & discrete but upon progression of silicosis become larger and may coalesce. These nodules may be visible on chest radiographs and if so can help classify silicosis into a <i>simple</i> (small, rounded nodules) or <i>complicated</i> (large and coalescent nodules) <i>pneumoconiosis</i>; complicated pneumoconiosis is also called <i>progressive massive fibrosis</i>. Silicosis generally affects the upper lung zones more heavily than the lower zones. Additionally, silicosis predisposes patients to development of <i>Mycobacterium</i> infection, presumably because it impairs alveolar macrophage function.</p>	

Coal Worker's Pneumoconiosis results from inhalation of coal dust. The characteristic lesion is the *coal macule*, which is a focal collection of coal dust & dust-laden macrophage with little inflammation &/or fibrosis (coal dust is much less fibrogenic than silica) with primary lesions initially localized to the respiratory bronchioles (like silicosis). Small associated regions of emphysema (*focal emphysema*) may be seen. Radiographic findings are similar to silicosis, with CWP also categorized as simple vs. complicated disease; in CWP, however, patients with simple ds are unlikely to be symptomatic.

Asbestosis results from exposure to fibrous silicate (asbestos), once used widely in construction as an insulator, fire-retardant, and component of brake linings in cars. Even though asbestos is no longer used, workers may still be exposed by remodeling or reinsulating buildings or pipes containing asbestos. Like silica, asbestos causes activation of macrophages and release of inflammatory cytokines & chemoattractants but unlike silica, asbestos does not seem to kill the activated macrophages. The mechanism of the potentially severe fibrotic reaction in asbestosis is likely related to macrophage-derived mediators like fibronectin, IGF-I, and PDGF, that promote fibroblast recruitment & replication. The earliest microscopic lesions occur around respiratory bronchioles, with an alveolitis that progresses into peribronchiolar fibrosis which subsequently becomes more generalized throughout the alveolar wall; fibrosis most heavily involves the lung bases and subpleural regions. The characteristic pathologic finding in asbestosis is the *ferruginous body*, a rod-shaped body with clubbed ends that appears yellow-brown in stained tissue and represents asbestos fibers that have been coated by macrophages with an iron-protein complex (not all such coated fibers are asbestos, however, and so ferruginous bodies may be seen in pts. without parenchymal lung disease). Chest radiography in asbestosis shows a reticular pattern that is generally more prominent at the lung bases and may be associated with cyst formation and honeycombing; there is also commonly evidence of pleural disease such as diffuse pleural thickening, localized plaques (which may be calcified), or pleural effusions (less frequent). Clinically, asbestosis is more likely to be associated with clubbing than are the other pneumoconioses. Asbestosis also increases a patient's risk for bronchogenic carcinoma and mesothelioma.

Berylliosis results from the inhalation of beryllium (used in the aerospace, nuclear weapons, and electronics industries as well as to make fluorescent light bulbs) and is characterized by granuloma formation within the lungs and hilar & mediastinal lymph nodes. The granulomatous pathology of berylliosis represents a cellular immune response to the foreign material: lymphocytes harvested from the blood or bronchoalveolar lavage fluid proliferate when exposed to beryllium salts *in vitro* (this is the *beryllium lymphocyte transformation test*), and this sensitization to beryllium may precede clinical symptoms in some patients. The pattern of cytokine release from proliferating lymphocytes suggests a T_{H1} phenotype; some studies also suggest that the presence of a glutamate residue in position 69 of the HLA-DPB1 molecule may confer genetic susceptibility to berylliosis. Clinically & radiographically, the disease resembles sarcoidosis (see # 9 sarcoidosis) and is characterized by granulomatous inflammation of multiple organ systems, especially the pulmonary parenchyma & intrathoracic lymph nodes.

Treatment	Notes
<p><i>Treatment of Pneumonconiosis:</i> None. Recognition & encouraging prevention of continued exposure are the MD's role.</p> <p><i>Treatment of Idiopathic Interstitial Pneumonias:</i> <i>DIP:</i> Corticosteroids + Quit Smoking <i>NSIP:</i> Corticosteroids (responds well) <i>AIP:</i> ?</p>	<ul style="list-style-type: none"> • Particles with diameters of 0.5 – 5.0 um are most likely to deposit in the respiratory bronchioles &/or alveoli. • Occasionally, parenchymal destruction may progress in the absence of continued exposure to the inciting agent. • The duration of exposure necessary for disease varies widely but is usually 10-20 years. • <i>Caplan's syndrome</i> is pneumoconiosis

6b. Diseases associated with other Environmental Exposures

<u>Clinical Presentation</u>	<u>Lab Presentation</u>
<p>Byssinosis → “Monday chest tightness” with ↓ in FEV₁ by 80%</p> <p>Grain Dust → cough, ↑ mucus, dyspnea/wheeze on exertion; ↓ FEV₁ & ↓ FEV₁/FVC</p>	
<p><u>Etiology and Pathogenesis</u></p> <p><i>Byssinosis</i> results from inhalation of dust from cotton, flax, or hemp. It is characterized by occasional then regular chest-tightness toward the end of the first day of the workweek (“Monday chest tightness”) associated with a drop in FEV₁ of up to 80% over the course of a Monday shift. In 10-25% of workers, the disease may be progressive, with chest tightness (thought to be due to histamine release) persisting throughout the workweek; after more than 10 years exposure, patients are likely to have an obstructive pattern on PFTs.</p> <p><i>Grain Dust Disease</i> results from inhalation of grain dust and results in clinical findings similar to smoking-induced COPD (cough, mucus hypersecretion, wheeze & dyspnea on exertion, ↓ FEV₁ & ↓ FEV₁/FVC).</p> <p>Symptoms and diseases associated with <i>Air Pollution</i> are the same as those associated with cigarette smoking.</p>	
<u>Treatment</u>	<u>Notes</u>
<p>Byssinosis → reduce exposure; bronchodilators to reverse bronchospasm;</p>	

7. Hypersensitivity Pneumonitis (aka *extrinsic allergic alveolitis*)

<p><u>Clinical Presentation</u></p> <p><i>Symptoms:</i> Acute → dyspnea / cough without wheezing / fever / infiltrates 4 - 6hrs after exposure</p> <p>Chronic → gradual onset SOB / cough / fatigue / loss of appetite and weight loss</p>	<p><u>Lab Presentation</u></p> <p><i>CXR:</i> Acute → patchy or diffuse infiltrates; Chronic → pattern becomes more nodular, eventually becoming the <i>reticulo-nodular</i> pattern that is characteristic of many chronic interstitial dses.</p> <p><i>CT:</i> “ground-glass” appearance in chronic HP</p> <p><i>Spirometry:</i> ↓ RV, ↓ FRC, ↓ TLC, ↓ VC; normal-to-high FEV₁/FVC, normal FEF_{25-75%}; ↓ diffusing capacity</p> <p><i>ABGs:</i> ↓ P_{O₂}, normal P_{CO₂}</p>
<p><u>Etiology and Pathogenesis</u></p> <p><i>Hypersensitivity pneumonitis</i> is a diffuse parenchymal lung disease where the immune response to an inhaled organic antigen induces interstitial pathology. It may occur with acute episodes 4-6 hours after exposure to the offending antigen or with a more insidious and chronic course. <i>Farmer’s lung</i> is pneumonitis due to antigens from microorganisms (thermophilic actinomycetes) that may be present in moldy hay. Other types of exposures include <i>air conditioner lung</i> (from microorganisms present in air conditioners or humidifiers) and <i>bird fancier’s lung</i> (from bird proteins). Only a small number of people who are exposed to these antigens contract pneumonitis, suggesting other factors (probably genetic) confer susceptibility. It is currently believed that the pathologic alveolitis is caused primarily by a type IV hypersensitivity reaction (T-lymphocyte mediated), though a type III reaction (immune-complex mediated) may also be involved. Pathologically, the alveolitis is composed primarily of CD8⁺ T-lymphocytes and includes sparse, poorly formed granulomas (unlike the well-defined granulomas characteristic of sarcoidosis) with a primarily peribronchiolar prominence (with obstruction of the small airways).</p> <p>(For a discussion of diffuse parenchymal lung disease in general, see # 6 Pneumoconiosis)</p>	
<p><u>Treatment</u></p> <p>Avoid exposure, though in some chronic cases damage may persist even after exposure is stopped.</p> <p>Corticosteroids may or may not help.</p>	<p><u>Notes</u></p> <ul style="list-style-type: none"> • A standard diagnostic test is to search for precipitating antibodies (called <i>precipitins</i>) to antigens that are known to induce HP. Sensitivity and specificity of this test are low, however, because an active immune response to a certain antigen does not necessarily mean that that particular antigen is the cause of the HP, and many cases of HP are caused by antigens that are not routinely included on the test panel.

8. Idiopathic Pulmonary Fibrosis

<p><u>Clinical Presentation</u></p> <p><i>Symptoms:</i> Dyspnea (progressively worse on exertion) Non-productive paroxysmal cough</p> <p><i>Physical Exam:</i> Rales/crackles Cyanosis Clubbing (50% of patients)</p>	<p><u>Lab Presentation</u></p> <p><i>CXR:</i> reticular or reticulo-nodular pattern that is generally bilateral & diffuse (though prominent at lung bases); no pleural effusions or hilar enlargement.</p> <p><i>CT:</i> scattered interstitial densities, especially in the subpleural regions.</p> <p><i>Spirometry:</i> ↓ RV, ↓ FRC, ↓ TLC, ↓ VC; normal-to-high FEV₁/FVC, normal FEF_{25-75%}; ↓ diffusing capacity</p> <p><i>ABGs:</i> ↓ P_{O₂}, normal P_{CO₂}, ↑ A-a gradient</p>
<p><u>Etiology and Pathogenesis</u></p> <p>(For a discussion of diffuse parenchymal lung disease in general, see # 6 Pneumoconiosis)</p> <p>IPF is characterized by progressive patchy interstitial fibrosis (the UIP pathologic pattern) and is thought to result from dysregulation of fibrosis in response to epithelial damage (i.e. wound healing). Injury to the epithelium is the inciting event, and normal proliferation & differentiation of type II cells (in response to damage to type I cells) does not happen at least in part due to disruption of the basement membrane. Macrophages activated by immune complexes or cytokines secrete IL-8 and leukotrienes which recruit neutrophils that in turn release mediators that dissolve local ECM. At the same time, damaged alveolar cells express a large number of pro-fibrotic cytokines (TGF-β1 & PDGF) and fibrotic foci develop at the site of alveolar epithelial injury. Clinical course is usually insidious, with signs and symptoms similar to those of other interstitial fibrotic diseases (dyspnea, rales/crackles over lung bases, PFTs in the restrictive pattern) along with clubbing of the digits. CT findings of scattered interstitial densities especially prominent in the subpleural regions are diagnostic. Many patients also have a positive test result for anti-nuclear antibodies (commonly seen in autoimmune processes).</p>	
<p><u>Treatment</u></p> <p><i>Corticosteroids</i> are frequently used, occasionally in combination with other cytotoxic & immunosuppressive agents (azathioprine or cyclophosphamide). - response is generally poor</p> <p>Give <i>Supplemental O₂</i> if needed.</p> <p><i>Lung transplant</i> for younger patients with severe disease.</p>	<p><u>Notes</u></p> <ul style="list-style-type: none"> • In the past it was believed that IPF was caused by exposure to an unknown antigen that would induce immune-complex formation & deposition in the lungs leading to fibrosis. • Most common age of onset is 50-70y, and the ds generally follows an insidious course. • Diagnosis of IPF requires no granulomas on biopsy along with UIP pathologic pattern (rather than DIP or NSIP). • From the time of diagnosis, mean survival is 2-5 years and prognosis is poor. • Transbronchial biopsy is not useful in making the diagnosis.

Notes: Pulmonary Parenchymal Involvement in Connective Tissue Disease

I. General Information about the Disorders

1. Patients generally have non-pulmonary manifestations before pulmonary disease develops, but some patients may initially present with pulmonary symptoms.
2. Detailed physiologic & histologic studies show pulmonary involvement is more common in these diseases than is generally thought.
3. Histopathology of interstitial lung disease associated with connective tissue disease is usually UIP & often indistinguishable from IPF, but some diseases show an NSIP pattern.
4. Interstitial disease seen in connective tissue disorders primarily affects the lower lung zones.

II. *Rheumatoid Arthritis*

- Most common site of lung involvement is the pleura → pleurisy, pleural effusions, or both.
- Lung parenchyma may be involved, however, with one or more nodules in the interstitium.
- Rarely, pts. with RA may develop bronchiolitis or bronchiectasis (airway complications)

III. *Systemic Lupus Erythematosus*

- As with RA, the most frequent pulmonary manifestation is pleuritic pain or pleural effusion.
- The lung parenchyma may be involved by an *acute pneumonitis* in which infiltrates involve the alveolar spaces & alveolar walls, & less frequently by a *chronic interstitial disease* where extensive fibrosis usually does not occur.
- Shows ANAs (antibodies to dsDNA) in the serum which form immune complexes.
- Affects children more often than adults and women more often than men.

IV. *Progressive Systemic Sclerosis* or *Scleroderma*

- Of all the connective-tissue diseases, pulmonary complications are most serious in PSS.
- Likely to be associated with significant scarring (fibrosis) of the parenchyma.
- Typically occurs with presence of *autoantibodies to topoisomerase I* (Scl 70)
- May be complicated by disease of the small pulmonary blood vessels independent of alveolar fibrosis.

V. *Polymyositis-dermatomyositis*

- Associated interstitial disease is infrequent and without particular distinguishing features.
- Patients may have respiratory problems resulting from inspiratory muscle weakness.

VI. *Sjogren's syndrome*

- Pulmonary involvement is primarily a lymphocytic infiltrate within the alveolar walls, rather than UIP or NSIP.
- Other lymphocytic complications can develop in the lung such as pseudo-lymphoma & lymphoma.

10. Bronchiolitis Obliterans with Organizing Pneumonia (BOOP)

<p><u>Clinical Presentation</u></p> <p><i>Symptoms:</i> Cough / Dyspnea / Fever / Malaise</p>	<p><u>Lab Presentation</u></p> <p><i>CXR:</i> patchy infiltrates with an alveolar (rather than interstitial) pattern.</p> <p><i>Histology:</i> fibromyxoid plugs in distal bronchioles & alveoli; may be associated with endogenous lipoid pneumonia</p>
<p><u>Etiology and Pathogenesis</u></p> <p>BOOP is characterized by connective tissue plugging of the small airways accompanied by mononuclear cell infiltration of the surrounding pulmonary parenchyma. This histologic picture may be associated with with connective tissue disease, toxic fume inhalation, or infection; when no cause is found, the term <i>cryptogenic organizing pneumonia</i> is used. BOOP often has a subacute presentation (over weeks to months) with systemic as well as respiratory symptoms. The CXR finding of patchy infiltrates with an alveolar (rather than interstitial) pattern mimics that of community-acquired pneumonia.</p>	
<p><u>Treatment</u></p> <p><i>Corticosteroids</i></p> <ul style="list-style-type: none"> - reponds dramatically over days-to-weeks. - therapy is usually prolonged to prevent relapse. 	<p><u>Notes</u></p>

11. Wegener's Granulomatosis

<p><u>Clinical Presentation</u></p> <p>Cough Hemoptysis Pleuritis</p> <p>Renal Disease</p>	<p><u>Lab Presentation</u></p> <p><i>CXR</i>: one or more cavitory nodules (often large); infiltrates</p> <p><i>Immunofluorescence</i>: c-ANCAs present in serum</p> <p><i>Histology</i>: palisading histiocytes; RBCs in alveolar spaces hemosiderin in macrophages; disruption of the elastic lamina; necrotizing granulomatous vasculitis</p>
<p><u>Etiology and Pathogenesis</u></p> <p><i>Wegener's Granulomatosis</i> is characterized by granulomatous vasculitis in the lung and URT with glomerulonephritis in the kidney. Patients typically have serum antibodies against <i>proteinase 3</i>, a serine protease present in the azurophilic granules of neutrophils – immunofluorescence reveals a characteristic presence of antineutrophil cytoplasmic antibodies (ANCA) specifically with a cytoplasmic staining pattern (c-ANCA). Whereas WG was once considered an aggressively fatal disease (mean survival of 5mos), most patients achieve complete & long-term remissions with cyclophosphamide/prednisone treatment.</p>	
<p><u>Treatment</u></p> <p>Standard of Care: <i>Cyclophosphamide</i> with addition of <i>prednisone</i> for the initial period of therapy.</p> <p>Experimental Therapy: Trimethoprim-sulfamethoxazole may work as treatment or to prevent relapse after immunosuppressive therapy.</p>	<p><u>Notes</u></p>

11b. Goodpasture's Syndrome

<p><u>Clinical Presentation</u></p> <p>Pulmonary hemorrhage</p> <p>Glomerulonephritis</p>	<p><u>Lab Presentation</u></p> <p>Serum anti-GBM antibodies present (usually IgG).</p> <p><i>Histology:</i> RBCs in alveolar spaces hemosiderin in macrophages; necrosis of the alveolar walls</p>
<p><u>Etiology and Pathogenesis</u></p> <p><i>Goodpasture's Syndrome</i> is characterized by recurrent episodes of pulmonary hemorrhage (with subsequent fibrosis) and glomerulonephritis from linear deposits of antibody along the glomerular basement membrane. Patients have circulating antibodies against a component of type IV collagen in their own glomerular basement membrane (anti-GBM antibodies) which may cross-react with the basement membrane in the alveolar walls (Type II hypersensitivity). Onset of the disease may follow influenza infection or exposure to a toxic hydrocarbon – there may also be additional anti-self antibodies generated in response to basement membrane injury and exposure of previously protected basement-membrane antigens. Therapy is based on reducing the burden of anti-GBM antibodies presented to the lung and kidney: plasmapheresis to remove Ab and immunosuppressives to reduce Ab production.</p>	
<p><u>Treatment</u></p> <ol style="list-style-type: none"> 1. <i>Plasmapheresis</i> 2. <i>Cyclophosphamide + prednisone</i> 	<p><u>Notes</u></p> <p>Primarily affects young adults (men more so than women).</p>

12. Pleural Effusion

<p>Clinical Presentation</p> <p><i>Symptoms:</i> Pleuritic chest pain (especially in inflammatory processes) Fever (especially in inflammatory processes) Dyspnea (major effusions)</p> <p><i>Physical Exam:</i> Dullness to Percussion Decreased Breath Sounds Pleural Friction Rub</p>	<p>Lab Presentation</p> <p><i>CXR:</i> blunting of the costophrenic angle; meniscus seen at the lung bases (larger effusions); elevation or flattening of the hemidiaphragm.</p> <p><i>Ultrasound:</i> may reveal very small effusions.</p> <p><i>Thoracentesis:</i> reveals composition of pleural fluid.</p> <p><i>PFTs:</i> usually normal; large effusions may show restrictive pattern.</p>
<p>Etiology and Pathogenesis</p> <p><i>Pleural Effusion</i> is fluid in the pleural space greater than the 10mL normally needed to lubricate the pleura. Effusions can be caused by increased permeability of the pleural surface &/or increased hydrostatic pressure or decreased colloid osmotic pressure in the pleural capillaries. Increased permeability of the pleural surface is associated with <i>exudative pleural fluid</i> (fluid with a high protein content, due to increased permeability of the pleural capillaries & pleural surface to proteins); increased hydrostatic pressure or decreased osmotic pressure within the capillaries is characterized by a <i>transudative pleural fluid</i> (fluid with low protein content). Transudative pleural effusions are most commonly associated with left-heart failure (pulmonary venous hypertension) but can also be caused by nephrotic syndrome (hypoproteinemia due to loss of serum protein in urine) and subdiaphragmatic disease (cirrhosis, pancreatitis, subphrenic abscess, with movement of ascitic fluid up through diaphragmatic defects into the pleura). Exudative pleural effusions are generally associated with malignancies growing on the pleural surface &/or blocking lymphatic outflow from the pleural space and inflammatory diseases such as infection and pulmonary embolus. Transudates & serous exudates are usually reabsorbed without residual effects; fibrinous, hemorrhagic, and suppurative exudates may cause adhesions, thickening, &/or calcifications. Clinically, inflammatory pleural effusions are associated with fever, pleuritic pain, and friction rub on auscultation; mild-to-moderate non-inflammatory effusions in an otherwise normal lung are usually asymptomatic, though major effusions may cause dyspnea. CXR will commonly show blunting of the costophrenic angle resulting from fluid accumulating in the lung base upon sitting/standing; chronic inflammation may cause fibrosis (loculations) that restricts fluid movement in the pleural space and can be revealed on the lateral decubitus film.</p>	
<p>Treatment</p> <p><i>Drain Fluid</i> when there is a high likelihood that the effusion will eventuate extensive fibrosis/loculation of the pleural space (e.g. with empyema or hemothorax).</p> <ul style="list-style-type: none"> • <i>Thrombolytics</i> can be given if the effusion is loculated or does not drain despite fluid seen on CXR. • Contraindications to draining the effusion: <ol style="list-style-type: none"> 1. uncooperative patient 2. bleeding diathesis; anticoagulation 3. mechanical ventilation 4. small amounts of fluid or non free-flowing fluid - get lateral decubitus CXR to check free flow <p>Recurrent large effusions may be treated by <i>pleurodesis</i>: injecting an irritating agent (talc or tetracycline derivative) into the pleural space after the pleural fluid is drained; this induces pleural adhesions that resist the development of effusions.</p> <p>Chylothorax may be treated with a <i>pleuripertoneal shunt</i>.</p>	<p>Notes</p> <ul style="list-style-type: none"> • A pleural effusion associated with pneumonia extending to the pleural surface is known as a <i>parapneumonic effusion</i>; when the effusion itself harbors organisms or when it has appearance of pus, it is known as an <i>empyema</i>. • Definition of <i>Exudative Effusion</i> (one or more of the following) <ol style="list-style-type: none"> 1. Pleural fluid / serum protein ratio > 0.5 2. Pleural fluid / serum LDH ratio > 0.6 3. Pleural fluid LDH > 2/3 normal serum LDH <ul style="list-style-type: none"> > 50% lymphocytes → cancer or TB > 5% mesothelial cells → not TB > 10% eosinophils → blood/air, drug reaction, asbestosis > 10% basophils → leukemia > 50% neutrophils → acute bacterial infection glucose < 60 mg/dl → rheumatoid, empyema, esophageal rupture, malignancy • <i>TB effusion</i>: 90-95% lymphocytes, protein > 4.0g, no mesothelial cells, adenosine deaminase > 40 U/L.

13. Pneumothorax

<p><u>Clinical Presentation</u></p> <p><i>Symptoms:</i> Dyspnea Chest Pain (may be asymptomatic) Severe Acute Distress (tension pneumothorax)</p> <p><i>Physical Exam:</i> ↓ Breath Sounds Hyper-resonance ↓ Tactile Fremitus Trachial deviation (tension pneumothorax) ↓ BP (tension pneumothorax)</p>	<p><u>Lab Presentation</u></p> <p><i>CXR:</i> shows visceral pleura displaced from chest wall with absence of vascular markings in the involved area.</p> <ul style="list-style-type: none"> - small PT → displaced pleura only at apex - collapsed lung → ↑ lung-tissue density - tension PT → mediastinal shift
<p><u>Etiology and Pathogenesis</u></p> <p><i>Pneumothorax</i> is the presence of air in the pleural space; it may result from breaks in the parietal pleura (trauma, needle or catheter insertion) or visceral pleura (rupture of subpleural air pocket or necrosis of adjacent lung tissue by pneumonia or neoplasm). Because the pressure within the subpleural space is sub-atmospheric, any opening in the pleura will result in air entering down its pressure gradient. Pneumothorax patients who do not have a defined abnormality of the lungs are said to have <i>primary spontaneous pneumothorax</i>; in this case there are usually subpleural air-pockets present (especially at the lung apex). Patients who receive positive pressure ventilation are also subject to development of a pneumothorax resulting from forced rupture of an alveolar wall and airflow which tracks through the interstitial space and subpleural surface – More commonly, however, air entering a ruptured alveolar wall tracks upward to the mediastinum along airways and vessels, producing a <i>pneumomediastinum</i>, which may then cause a pneumothorax as air ruptures through the mediastinal pleura. Because the lung is enclosed by a rigid chest wall, accumulation of pleural air can result in lung collapse. Air in the pleural space is generally at atmospheric or sub-atmospheric pressure; when the pleural air is at positive pressure (relative to atmospheric pressure), a <i>tension pneumothorax</i> is present – Tension pneumothorax is thought to arise when air can enter the pleura during inspiration but can not exit during expiration (as collapse of the airways closes the hole in the pleura). This is a medical emergency and can result in total cardiovascular collapse due to reduced venous return &/or inadequate gas exchange. For most cases of pneumothorax, however, pleural air will be spontaneously reabsorbed into the bloodstream as gas pressures in the pleura are significantly higher than those in the surrounding capillaries & venules – pure O₂ can speed this process as O₂ replaces N₂ in arterial blood, which allows N₂ (the most abundant gas in air) to be expired and decreases N₂ pressure in the blood allowing more gas from the pneumothorax to be reabsorbed (& since the tissues use O₂, even with supplemental O₂ there is still higher oxygen pressure in the pleura than the bloodstream).</p>	
<p><u>Treatment</u></p> <p>For a small pneumothorax causing few symptoms, wait for resolution with or without giving supplemental 100% O₂.</p> <p>For a large pneumothorax with significant clinical sequelae, remove air from the pleural space by inserting a needle, catheter, or large-bore tube into the pleural space.</p> <ul style="list-style-type: none"> - do this immediately for tension pneumothorax - response is usually rapid <p>For recurrent spontaneous pneumothorax, you can obliterate the pleural space with irritating agents or surgery.</p>	<p><u>Notes</u></p> <ul style="list-style-type: none"> • The usual PT patient: young adult, tall & thin male smoker. • In immunocompromised pts, <i>Pneumocystis carinii</i> can cause pneumothorax, presumably due to necrosis or cyst formation adjacent to the involved pleura. • <i>Tension pneumothorax</i> is especially a problem in pts. on mechanical ventilation. • In small pneumothoraces, pleural air accumulates at the apex of the lung. • In <i>hydropneumothorax</i> (air + fluid in the pleural space), CXR shows a perfectly horizontal border of the area of radio-opacity on the involved side, corresponding to fluid distributing to the lowest area of the lung and air to the upper areas.

14. Lung Cancer

Clinical Presentation	Lab Presentation
<p><i>Symptoms Relating to Primary Lung Lesion:</i> Cough / Hemoptysis Obstructive Pneumonia & Dyspnea (for large-airways tumors) Pleuritic Pain, Effusion, & Dyspnea (with pleural involvement) Pericardial Effusion/ Dysphagia (involvement of local structures) Horner's with Arm pain & weakness (apical tumors)</p> <p><i>Symptoms Relating to Nodal Metastases:</i> Diaphragmatic Paralysis (phrenic nerve) Vocal Cord Paralysis (recurrent laryngeal nerve) Facial & Upper Extremity Edema (SVC obstruction)</p> <p><i>Symptoms relating to distant mets vary with the organ involved.</i></p> <p><i>Paraneoplastic Syndromes:</i> ↑ ↑ ADH or ↑ ↑ ACTH (small cell carcinoma) Neurologic syndromes Clubbing & Hypertrophic Osteoarthropathy (NSCLC) Anorexia & Weight Loss</p>	<p><i>CXR:</i> reveals nodule or mass & pleural involvement - large cell or adenocarcinoma → peripheral lesions - squamous or small cell → central lesions - mesothelioma → diffuse pleural involvement</p> <p><i>Histology:</i> Squamous cell CA → keratin pearls, desmosomes Small cell CA → irregular, darkly stained nuclei, sparse cytoplasm. Adenocarcinoma → ↑ glands, ↑ mucin secretion Large cell CA → (not anything else) Mesothelioma → long microvilli in EM; stains + for keratin epithelioid histology mimics adenocarcinoma</p> <p><i>Blood Tests:</i> Squamous cell CA → hypercalcemia Small cell CA → ↑ ↑ ADH &/or ↑ ↑ ACTH Bronchial Carcinoid Tumor → ↑ serotonin (< 5% of cases)</p>

Etiology and Pathogenesis

Smoking is the primary risk factor for developing lung cancer: nitrosamines, benzo[a]pyrene, and other polycyclic hydrocarbons are the likely carcinogenic toxins – filters appear to slightly reduce but not eliminate the risk associated with smoking. Though the development of lung CA appears to require several years of exposure, histological changes such as loss of bronchial cilia, hyperplasia of bronchial epithelial cells, and nuclear abnormalities (most of which are reversible) occur well before disease is evident. *Occupational exposures*, such as asbestos, arsenic, haloethanes, polycyclic hydrocarbons, and ionizing radiation can also cause lung CA – Absbestos exposure and smoking have a multiplicative effect on risk; the increased risk associated with asbestos exposure alone is 2-5 fold and that associated with smoking alone is 10-fold, but the increased risk associated with both together is 20-50-fold. *Genetic factors* such as increased levels of the cyP-450 enzyme *aryl hydrocarbon hydroxylase* (which converts hydrocarbons to carcinogenic metabolites) and the cyP-450 isozyme that degrades the antihypertensive drug *debrisoquine* have been implicated in increasing risk. Alterations in *tumor suppressor genes* (Rb, p53, cluster on chromosome 3p) or *proto-oncogenes* (ras, myc) may be necessary for developing CA – because both copies of a tumor suppressor must be deficient for an altered phenotype to be realized, these phenotypes are inherited in a recessive pattern; because one altered copy of a proto-oncogene may result in a cancerous phenotype, the associated phenotypes are inherited in a dominant pattern. *Parenchymal scarring* resulting from prior disease can serve as a locus for CA, most often *bronchioloalveolar carcinoma*, though it may not be possible to tell whether the fibrosis came before or after tumor formation. *Radon gas exposure* (from decay of radium in the ground under people's houses) and *low intake of beta-carotene* have also be suggested to increase risk, though one study showed an increased incidence in patients who took supplemental beta-carotene.

Based on the common finding of cellular heterogeneity in tumors, it is thought that all types of lung CA arise from pulmonary undifferentiated stem cells, which then may or may not partially differentiate over the course of their malignant transformation to produce histological patterns associated with specific disease processes. Cough and hemoptysis result from local tissue destruction & inflammation, and in many cases the primary tumor or a metastasis may compress important mediastinal structures (e.g. brachial plexus, phrenic nerve, recurrent laryngeal nerve, SVC) resulting in neuropathic symptoms &/or facial/upper extremity edema.

Small Cell Carcinoma (20% of bronchogenic carcinomas) generally originate in the bronchial wall proximally. In the past they were thought to arise from K-cells (neurosecretory cells in the epithelium), but recent work suggests they arise from pluripotent stem cells (like the other lung tumors). Histologically, the malignant cells have irregular, darkly stained nuclei and sparse cytoplasm. Local growth of tumors initially follows a submucosal pattern, but the tumors quickly invade lymphatics; hilar and mediastinal nodes are involved early in the course of the disease and may be the most prominent aspect of the disease. Metastatic spread to distant sites is a common early complication, and distant disease is often present at the time of clinical presentation; as a result of this, small cell carcinoma has the worst prognosis. Almost all small cell carcinomas demonstrate deletions in chromosome 3p; myc and Rb mutations are also common. Small cell carcinomas may also secrete the hormones ACTH & ADH; paraneoplastic syndromes include SIADH, Cushing's, Lambert-Eaton, peripheral neuropathy, and cerebellar degeneration. Brain and bone scans must be done in all patients

Squamous Cell Carcinoma (1/3 of all bronchogenic carcinomas) originates from the epithelial layer of the bronchial wall after a series of histological changes: initially, there is metaplasia of the normal bronchial columnar epithelium followed by progressive heterogeneity ending in carcinoma in situ which may develop into invasive CA. Specific histological features include keratin pearls and desmosomes. Squamous cell carcinomas tend to be located in the large or proximal airways (most often at the subsegmental, segmental, or lobar level) and may obstruct the airways leading to lung collapse &/or pneumonia distal to the obstruction. A cavity may also develop within the tumor (this is more common in squamous cell carcinoma than other bronchogenic carcinoma). Spread of squamous cell carcinoma beyond the airway usually involves direct extension into the pulmonary parenchyma or invasion of the local lymphatics with spread to the hilar or mediastinal lymph nodes – these tumors tend to remain within the thorax. Squamous cell carcinomas may also secrete a peptide with parathyroid-hormone-like activity and cause hypercalcemia. Overall prognosis for patients with squamous cell carcinoma is best of the lung CAs.

Adenocarcinoma (more than 1/3 of bronchogenic carcinomas, most common CA of non-smokers) most often occur in the lung periphery and probably arise at the level of the bronchioles or alveolar walls; these tumors sometimes appear at a site of parenchymal scarring. The characteristic findings are tendency to form glands and in many cases to secrete mucus. In the bronchioloalveolar (BAC) subcategory the malignant cells seem to grow and spread along the alveolar walls – BAC more often occurs in women, is not associated with smoking, may be unifocal or multifocal (& confused with mets), shows a lepidic growth pattern and presents as cough with frothy sputum. The usual presentation of adenocarcinoma is a peripheral lung nodule or mass; occasionally, it can arise within a large bronchus and may present as bronchial constriction (like squamous cell CA); the BAC subcategory can manifest as a nodule, mass lesion, localized infiltrate simulating a pneumonia, or widespread parenchymal disease. Though adenocarcinoma may spread locally to adjacent regions of lung or to pleura, is also has a propensity for nodal involvement and distant metastatic spread. Prognosis is intermediate between those of squamous and small cell carcinomas.

Large Cell Carcinoma (15-20% of bronchogenic carcinomas) is difficult to define because histologically it is a diagnosis of exclusion. Its behavior is similar to adenocarcinoma, often appearing in the periphery of the lung as mass lesions (although they are often larger than adenocarcinomas) and having a similar course and prognosis.

Bronchial Carcinoid Tumors (5% of primary lung tumors) are low-grade malignancies that arise from either K-cells or pluripotent stem cells in the walls of relatively central airways. Most have an excellent prognosis and are cured by surgical removal, though some show histological features consistent with increased malignancy (similar to small cell carcinoma) – these have a worse prognosis and are much more likely to have distant metastases. Two features distinguish BCTs from the other lung cancers: smoking does not appear to increase risk, and tumors are often found in young adults rather than older pts. Hemoptysis and pneumonia distal to an airway obstruction are the common presenting features, though ectopic production of serotonin may be found in < 5% of BCTs.

Malignant Mesothelioma primarily involves the pleura rather than the airways or pulmonary parenchyma. Smoking is not a risk factor but known asbestos exposure (often 30-40 years earlier) is, though heavy exposure does not seem to be necessary – MM has been known to develop in the wives of asbestos workers, presumably due to inhalation of asbestos while cleaning their husband's clothes. Major symptoms are chest pain, dyspnea, and cough, and signs are pleural effusion with irregular or lobulated thickening of the pleura. Diagnosis requires biopsy of the pleura, and because the tumor does not directly communicate with the airways it is unlikely that malignant cells will be found in the sputum. Prognosis is poor, as the tumor eventually entraps the lung and spreads to mediastinal structures, often leading to respiratory failure; no good tx is available, and fewer than 10% of pts. survive 3 yrs. Extrapleural pneumonectomy (removal of ipsilateral lung along with visceral & parietal pleura), immunotherapy, and use of biological response modifiers (IFNs and IL-2) are under investigation as possible therapies.

Hamartomas are benign tumors that present grossly as peripheral, lobulated, cartilagenous solitary nodules; histologically they show normal fibrotic tissue in excess & disarray – hamartomas are not seen in newborns.

Treatment	Notes
<ol style="list-style-type: none"> 1. Surgery for localized tumors. <ul style="list-style-type: none"> - may use pre/post chemotx - do not use when tumor extends into pleura or mediastinum - do not use if contralateral lymph nodes are involved. - do not use in patients with distant metastases. 2. Chemotherapy with radiation for small cell carcinoma (unless the tumor is a solitary nodule without evidence of nodal or distant involvement – rare). <ul style="list-style-type: none"> - chemotx alone for extensive disease; palliative for mets 3. Chemotherapy &/or Radiation for unresectable non-small cell carcinomas 4. Palliative therapy to restore patency of an obstructed airway <ul style="list-style-type: none"> - bronchoscopic LASER, cryotherapy, or electrocautery - placement of an endobronchial stent. 	<p>Epidemiology</p> <ul style="list-style-type: none"> • 170,000 new cases & 150,000 deaths in USA per year. • 25% of American adults still smoke. • 25-30% of cancer deaths & 5% of all deaths in USA. • Cigarette smoking is responsible for 85% of lung CAs. • Risk ↓ s after quitting smoking but does not return to the level in non-smokers (even after 10-15 years). • 5yr survival is 14%. <p>• Ras mutation occurs in 35% of adenocarcinomas.</p> <p>• There is a much lower risk associated with pipe or cigar smoking relative to cigarette smoking, presumably because pipe and cigar smoke are not inhaled.</p> <p>• Staging of Non-Small Cell CA (criteria): I: T1-2, N0, M0 II: T1-2, N1, M0 T3, N0, M0</p>

15. Pneumonia

Clinical Presentation	Lab Presentation
<p><i>Symptoms:</i> Fever / Cough / Dyspnea / Pleuritic Pain</p> <p><i>Physical Exam:</i> Tachycardia / Tachypnea Dullness to Percussion (over consolidated area) Rales &/or Crackles</p>	<p><i>CXR:</i> reveals consolidations &/or infiltrates</p> <p><i>ABGs:</i> ↓ PaO₂, ↓ to normal PaCO₂,</p> <p><i>Histology:</i> Strep. pneumoniae infection is associated with “red hepatization” (PMNs & RBCs) early and “grey hepatization” (macrophages & fibrinous exudates) later in infection.</p>
Etiology and Pathogenesis	
<p><i>Pneumonia</i> is infection of the pulmonary parenchyma. Infectious organisms enter the respiratory tract primarily by inhalation (airborne pathogens) or aspiration (enteric pathogens); though everyone aspirates a small amount of gastric fluid, lung defense mechanisms are usually adequate to prevent productive infection – immunosuppressed patients or those unable to protect their airway from secretions by cough and glottic closure are more vulnerable to aspiration pneumonia. Pathogens (especially <i>Staphylococcus</i>) may also reach the pulmonary parenchyma through the bloodstream via dissemination from distant sites or direct injection. Bacterial etiologies include: 1) <i>Streptococcus pneumoniae</i> commonly acquired in the community and frequently following a viral URTI, 2) <i>Staphylococcus aureus</i> as a secondary complication of influenza, in immunocompromised hospital patients whose oropharynx is colonized, and as a complication of bloodstream sepsis, 3) <i>Gram-negative organisms</i> such as <i>Haemophilus influenzae</i> (causes pneumonia in children & adults with COPD), <i>Klebsiella pneumoniae</i> (normal resident of the GI tract & often causing pneumonia in alcoholics), and <i>Pseudomonas aeruginosa</i> (especially in hospitalized patients who have been treated with antibiotics), 4) <i>Oropharyngeal anaerobes</i> in those who are immunocompromised &/or prone to aspiration (i.e., with impaired consciousness or difficulty swallowing) – in prolonged hospitalization or antibiotic treatment, the oropharyngeal flora may become more populated with <i>S.aureus</i> and aerobic gram-negative bacilli, which may then be aspirated and cause pneumonia. <i>Legionella pneumophila</i> and <i>Chlamydia pneumoniae</i> also cause pneumonia; legionella is associated with diarrhea & abdominal pain. Viruses are common causes of URTIs but are rare causes of pneumonia (except in children); in adults, influenza virus is the most common viral pneumonia, with adenoviral pneumonia seen in military recruits and hantaviral pneumonia (along with fever, hemorrhage, and acute renal failure) occurring in the developing world. <i>Mycoplasma</i> accounts for 10-20% of pneumonia cases (most commonly in young adults) and is associated with a mononuclear infiltrate and patchy consolidation usually of the lower lobe.</p> <p>The pathologic process common to all pneumonias is inflammation of the distal pulmonary parenchyma with an influx of neutrophils, edema fluid, RBCs, mononuclear cells and fibrin seen in variable amounts. <i>Lobar pneumonia</i> is believed to spread from alveolus to alveolus and acinus to acinus via the intra-alveolar pores of Kohn; it is often associated with <i>S.pneumoniae</i> and <i>Klebsiella</i> infections. <i>Bronchopneumonia</i> shows a more patchy distribution on CXR and spreads via the airways; it is often associated with staphylococci and a variety of gram-negative bacilli. <i>Interstitial pneumonia</i> is characterized by inflammation within the interstitial walls rather than in the alveolar spaces; viral pneumonias often begin as interstitial then may progress into the alveolar space. Pneumococcal pneumonia is associated with eventual restoration of the injured lung tissue, whereas staphylococcal and anaerobic pneumonias may result in tissue necrosis, abscess formation, and scarring of the parenchyma. Functionally, pneumonia produces shunting and V/Q mismatch with hypoxemia; minute ventilation usually increases to result in hypocapnia. In bacterial pneumonia, cough is often productive (possibly of purulent sputum); cough is usually non-productive in viral and mycoplasma pneumonia. In most bacterial pneumonias, large numbers of neutrophils are seen in the sputum, whereas mycoplasma and viral pneumonias show fewer neutrophils and more mononuclear inflammatory cells. Anaerobic aspiration pneumonias show a mixed population of bacterial of many different morphologies.</p> <p>Intrathoracic complications of pneumonia include: 1) <i>lung abscess</i> primarily from bacteria that cause significant tissue necrosis (anaerobes, staphylococcus, enteric gram-negative rods) and 2) <i>empyema</i> when a pneumonia extends to the pleural surface. Abscesses and empyemas must be drained by thoracentesis. Abscess formation is most commonly associated with alcoholism (i.e. ↓ cough reflex & ↑ oral anaerobes) and presents with foul-smelling breath and sputum.</p>	

<p>Pathogen-specific risk factors: Aerobic gram-negative bacilli → alcoholism, nursing home residency, cardiac disease</p> <p>Anaerobes → loss-of-consciousness, swallowing dysfunction, poor dental hygiene, airway obstruction</p> <p>Haemophilus influenzae → COPD, smoker</p> <p>Klebsiella pneumoniae → alcoholism</p> <p>Staphylococcus aureus → post-flu, nursing home, bronchiectasis, IVDA</p> <p>Pseudomonas aeruginosa → bronchiectasis/CF, recent broad-spectrum antibiotics, malnutrition, steroids</p> <p>DRSA → age > 65, β-lactam treatment within last 3mos, exposure to child in daycare, co-morbidities</p> <p>Viral Pneumonias: CMV → interstitial with large “megalic” cells (enlarged nucleus with large, single basophilic inclusion)</p> <p>Measels → involves airways & parenchyma; multinucleate giant cells with nuclear viral inclusions</p> <p>Varicella → interstitial mononuclear cell pneumonia with nuclear viral inclusions; may → focal necrosis</p> <p>Herpes Simplex → necrotizing tracheobronchitis with DAD pathology & viral inclusions</p> <p>Adenovirus (especially in kids)</p> <p>RSV</p>	
<p><u>Treatment</u></p> <p>Antibiotic Therapy</p> <ol style="list-style-type: none"> 1. <i>S.pneumoniae</i> → penG, macrolide, quinolone, vancomycin 2. <i>Stapylococcus</i> → oxacillin, nafcillin, vancomycin 3. <i>H.influenzae</i> → 2nd or 3rd generation cephalosporin or trimethoprim-sulfamethoxazole 4. <i>Gram-negative rods</i> → 3rd generation cephalosporin, aminoglycoside, quinolone 5. <i>Anaerobes</i> → penicillin, clindamycin 6. <i>Mycoplasma</i> → macrolide, quinolone 7. <i>Legionella</i> → macrolide, quinolone 8. <i>Chlamydia pneumoniae</i> → tetracycline, macrolide <p>Antiviral Therapy</p> <ol style="list-style-type: none"> 1. <i>Influenza A</i> → amantadine, rimantidine <i>Influenza A & B</i> → zanamivir, oseltamivir (NA inhibitors) <p>Supportive Therapy</p> <ol style="list-style-type: none"> 1. Chest Physical Therapy 2. Supplemental O₂ for pts. with hypoxemia <p>Treatment based on clinical setting:</p> <ol style="list-style-type: none"> 1) <i>Community Acquired Pneumonia</i> <ul style="list-style-type: none"> No coexisting disease & no hospitalization → azithromycin Coexisting disease & no hospitalization → quinolone or β-lactam + macrolide Hospitalization needed → IV β-lactam + IV or oral macrolide or IV quinolone ICU needed → IV β-lactam + IV azithromycin or IV quinolone 2) <i>Nosocomial Pneumonia</i> <ul style="list-style-type: none"> Resistant gram-negatives & MRSA → consider vancomycin Pseudomonas risk → give cipro + β-lactam 	<p><u>Notes</u></p> <p>Epidemiology</p> <ul style="list-style-type: none"> • 10% of hospital admissions. • > 5 million cases per year. • > 80,000 deaths per year. • The virulence of <i>S.pneumoniae</i> depends on its polysaccharide capsule. <p>Organisms to cover with therapy:</p> <p><i>S.pneumo</i>, <i>H.influenzae</i>, <i>Mycoplasma</i>, <i>Chlamydia</i>, Viruses add DRSA & Anaerobic gram-negatives</p> <p>add Legionella</p> <p>add Staph.aureus & MRSA</p>

16. Tuberculosis

<p><u>Clinical Presentation</u></p> <p><i>Symptoms:</i> Weight loss / Wasting / LOA Fatigue / Fever / Night sweats Cough Hemoptysis</p> <p><i>Physical Exam:</i> Rales (may be found over involved area) Pleural effusion (see # 12) may be present.</p>	<p><u>Lab Presentation</u></p> <p>PPD+ skin test - test may show false negative if pt. is immunocompromised - false positive if pt. is infected with atypical mycobacteria - PPD+ means infection, not necessarily active disease.</p> <p><i>Sputum or Biopsy:</i> organisms seen on acid-fast stain</p> <p><i>Histology:</i> Granulomas with caseous necrosis, multinucleate giant cells, and epithelioid histiocytes.</p> <p><i>CXR:</i> may show nodule(s), infiltrates, &/or cavitations; may show hilar node enlargement &/or pleural effusion - primary TB → lower lobe infiltrate - reactivation TB → upper lobe infiltrate</p> <p>BACTEC+ (releases CO₂ when given palmitic acid)</p> <p>PCR & DNA probes for rRNA may be used to distinguish <i>M. tuberculosis</i> from other mycobacteria</p>
<p><u>Etiology & Pathogenesis</u></p> <p><i>Mycobacterium Tuberculosis</i> is an aerobic rod-shaped bacterium that shows up in acid-fast staining. Transmission occurs via direct inhalation aerosolized droplets (1 – 5µm in diameter) that are released when an infected person speaks, coughs, or laughs; TB is not transmitted by fomites (i.e. articles of clothing, eating utensils, ect.). <i>Primary infection</i> develops where the mycobacteria reaches the distal lung parenchyma – alveolar macrophages represent the body’s initial defense which is usually effective in containing the infection even though organisms spread via lymphatics to the draining lymph nodes and by the blood stream to distant sites. Continued control is possible as a robust cell-mediated immune response (delayed hypersensitivity) develops within weeks of initial exposure. 95% of patients are unaware of primary infection and show only a positive delayed hypersensitivity (i.e. + PPD test) as evidence of infection. Though the initial immune response is usually successful at containing TB, it does not eliminate all the mycobacteria; some become dormant or latent and proliferate in equilibrium with immune-mediated killing. <i>Reactivation tuberculosis</i> happens when the immune response no longer controls infection and mycobacteria can proliferate vigorously. <i>Miliary tuberculosis</i> refers to disseminated disease resulting from hematogenous spread of mycobacteria to many organ systems (the pleura, pericardium, kidney, peritoneum, adrenal glands, and CNS may be affected); miliary TB can happen in primary or reactivation TB though it is more likely in the latter. 10% of untreated infected individuals with a normal immune response will develop active disease in their lifetime, with half of these developing active TB in the first two years after infection; development of active TB is much more likely in immunocompromised patients (especially those who are HIV⁺ → TB may develop as an early opportunistic infection; it is also more likely to be disseminated in patients with more severe immuno-suppression and may be paradoxically made worse if the patients overall immune status is improved with HAART). The pathology of primary infection is characterized by the presence of organisms and a non-specific inflammatory response in the involved area of the lung parenchyma. When delayed hypersensitivity develops, granulomas bordered by epithelioid histiocytes and enclosing areas of caseous necrosis and multinucleate giant cells are seen. Cavitation, fibrosis, and calcifications may also be present. Within the lung, characteristic locations for reactivation TB are the apices and apical regions of the lower lobes (where P_{O2} is high); these areas likely represent locations of favorable TB spread rather than the sites of primary infection. The chronic destructive process in the lungs eventually causes progressive parenchymal scarring, but lung function is generally well-preserved, presumably because TB is often limited to areas of the lung (apical regions) that are less involved in normal gas-exchange and because V/Q mismatch occurs less often since ventilation and perfusion are both similarly impaired in affected regions – ABGs & PFTs are often unchanged.</p>	
<p><u>Treatment</u></p> <p>For pts. with active disease:</p> <ul style="list-style-type: none"> • Isoniazid + rifampin for 6mos, with pyrazinamide for the 1st two months and ethambutol until the organism’s sensitivity/resistance is known. <p>For newly PPD+ pts. without active ds, PPD+ pts. who are newly immunocompromised, household contacts of TB pts, and pts. with CXR findings of prior TB but no prior treatment:</p> <ul style="list-style-type: none"> • Isoniazid alone for 9mos. 	<p><u>Notes</u></p> <ul style="list-style-type: none"> • Acid-fast staining & BACTEC tests will be positive for any mycobacteria, not just for TB. • Definitive diagnosis depends on culturing the organism (as does demonstration of susceptibility to antibiotic therapy); organisms may require 6 weeks to grow in culture for a + ID. • Acid-fast stains include: Ziehl-Neelsen, Kinyoun, auramine-rhodamine staining.

17. Fungal and Pneumocystis Infections

Clinical Presentation	Lab Presentation
<p>Histoplasmosis: Cough / Fever / Malaise / Myalgia / Weight loss</p> <p>Coccidioidomycosis: Cough / Fever / HA / Chest pain / Erythema nodosum</p> <p>Blastomycosis: Cough / Fever / Purulent sputum production</p> <p>Aspergillosis: Allergic → wheezing / dyspnea / low-grade fever / cough Aspergilloma → asymptomatic or hemoptysis Invasive → severe illness: fever / cough / dyspnea / chest pain</p> <p>Pneumocystis: Dyspnea / Fever / Hypoxemia</p>	<p><i>CXR:</i> <i>Histoplasmosis:</i> Acute primary → infiltrate maybe with hilar adenopathy Disseminated → widespread pulmonary involvement Chronic pulmonary → resembles findings in TB (see #16) <i>Coccidioidomycosis</i> → infiltrates, nodules, hilar adenopathy, possible pleural effusions. <i>Blastomycosis</i> → resembles bacterial pneumonia or lung CA <i>Aspergillosis</i> Allergic → infiltrates, bronchiectasis Aspergilloma → mass surrounded by lucent rim Invasive → localized or diffuse infiltrates <i>Pneumocystis</i> → bilateral infiltrates</p> <p><i>Histology: (methenamine silver staining)</i> Histoplasmosis → tiny yeast Coccidioidomycosis → large spherules with many endospores</p>

Etiology and Pathogenesis

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*, found in the US primarily in the Mississippi and Ohio river valleys. *Histoplasma* flourishes in soil that has been contaminated by bird droppings, and transmission happens when this soil is disturbed (i.e. with bulldozing) and patients inhale the infectious spores – after inhalation and when the spores reach body temperature, they undergo a conversion to the yeast phase; an inflammatory response ensues that is characterized primarily by the recruitment of macrophages. Organisms also often spread to regional lymph nodes and to the spleen via the blood stream. Within 3 weeks, cell-mediated immunity (delayed hypersensitivity) against *histoplasma* is seen and the inflammatory response becomes granulomatous; central areas of caseation may occur (similar to TB). When the primary lesions heal, fibrotic &/or calcific pulmonary nodules may be visible on CXR. In young children or the immunosuppressed, dissemination may occur and the patient is said to have *progressive disseminated histoplasmosis*; in pts. with emphysema or significant underlying airways disease, *chronic pulmonary histoplasmosis* may occur, characterized by inflammatory destruction of the lung parenchyma and cavity formation. Diagnosis depends on culture, identification of *histoplasma* in tissue, detection of *Histoplasma* antigen in the urine, or detection of an immune response by serology.

Coccidioidomycosis is caused by the dimorphic fungus *Coccidioides immitis*, endemic to the western and southwestern US and present in tissue as round, thick-walled spherules that contain multiple endospores. Like *histoplasma*, *coccidioides* elicits a delayed hypersensitivity immune response which leads to the formation of granulomas. Dissemination occurs in immunosuppressed, pregnant, and Filipino or African-American patients – immunosuppressed patients may also develop fulminant disease due to the release of endospores in the lung. Also like *histoplasma*, primary infection may be sub-clinical or present with manifestations of hypersensitivity to the organism, and chronic disease resembles TB. Skin manifestations such as *erythema nodosum* (tender, red nodules on the anterior surface of the lower legs) are common and represent a type of hypersensitivity.

Blastomycosis is caused by the soil-dwelling fungus *Blastomyces dermatitidis*, which is endemic to the midwestern & southwestern US (often seen in outdoorsmen). The primary inflammatory response is recruitment of neutrophils followed by T-lymphocytes and macrophages, and the eventual pathological pattern is a combination of granulomatous and pyogenic inflammation. The organism can disseminate, especially to skin, but it usually is confined to the lungs. Acute infection often resembles bacterial pneumonia. Diagnosis is made by demonstrating characteristic yeast-forms in sputum or tissue or by sputum culture.

Aspergillosis is caused by the monomorphic (occurring in soil & tissue as branching hyphae) and widely-distributed fungus *Aspergillus*. *Allergic bronchopulmonary aspergillosis* is a hypersensitivity reaction to airways colonization that occurs almost exclusively in asthmatics. Type I (immediate, IgE-mediated) & Type III (immune-complex, IgG-mediated) immune responses are involved. *Aspergillus* can frequently be cultured from the sputum, and bronchiectasis behind proximal mucus-plugged airways is possible. Diagnosis is made by skin tests for type I & III immune reactions and by serology; treatment is steroids. *Aspergilloma* is a saprophytic colonization of a pre-existing cavity by a mycetoma (“fungus-ball”). *Invasive aspergillosis* is the most life-threatening manifestation of *aspergillus* infection – it involves invasion of the lung parenchyma & vasculature (which may lead to infarction) and is seen in patients with significant immunosuppression (especially neutropenia); marijuana smokers are at increased risk for invasive *aspergillosis*. *Chronic necrotizing pulmonary aspergillosis* involves a sub-acute & chronic invasion and destruction of the pulmonary parenchyma by *aspergillus*, often complicated by cavity formation and secondary development of a mycetoma and often occurring in patients with underlying lung disease or who are immunocompromised.

Pneumocystis carinii infection is cause of pneumonia in immunocompromised patients (especially those with AIDS). It is widely distributed in nature and can normally be found in the lungs; it does not normally cause disease in patients with adequate cellular immunity. Pneumocystis cysts are seen on light-microcopy (with methenamine silver staining) as round or cup-shaped structures in the alveolar lumen. The tissue response to pneumocystis includes infiltration of mononuclear cells within the pulmonary interstitium and exudation of foamy fluid (with cysts) into the alveolar spaces. Diagnosis is via demonstrating the presence of the organism in tissue, bronchiolar lavage fluid, or sputum (induced by having pt. inhale a hypertonic saline solution), or by monoclonal Ab or PCR techniques – no serologic or skin test is available. *P. carinii* pneumonia develops at least once during the illness of 75% of AIDS patients; high-risk happens when the pts. CD4⁺ counts drop below 200 cells/mm³. The CXR often shows diffuse haziness in which it is difficult to distinguish an interstitial from alveolar pattern (e.g. the “ground-glass” appearance). Trimethoprim-dapsone is generally used to treat PCP in AIDS patients, since they often have allergic reactions to sulfonamides – Atovaquone or clindamycin-primaquine may also be used. Corticosteroids may help in averting respiratory failure. PCP prophylaxis in AIDS patients is recommended when CD4⁺ counts are < 200 cells/mm³ and may consist of low dose oral trimethoprim-sulfamethoxazole, dapsone alone or with pyrimethamine, or once-a-month inhaled pentamidine (often associated with atypical presentation in the patients who develop PCP despite prophylaxis – pulmonary infiltrates are limited to the upper lung zones rather than being diffuse).

Cryptococcus is associated with pigeon droppings and causes disease only in the immunocompromised; the lungs are the portal of entry with the CNS (meningitis) the most common site of infection. It may cause a solid mass (cryptococcoma) that mimics lung cancer. *Mucormycosis* can be caused by several fungi that show up in tissue as non-septate hyphae; it often occurs in diabetics and causes rhinocerebral and pulmonary disease.

Treatment	Notes
<p>Histoplasmosis:</p> <ul style="list-style-type: none"> Acute primary → generally self-limited; no tx necessary Disseminated → amphotericin B followed by itraconazole Chronic pulmonary → itraconazole alone or preceding amphotericin B <p>Coccidioidomycosis:</p> <ul style="list-style-type: none"> Acute & low-risk → none Acute & high-risk → fluconazole Disseminated → amphotericin B; add fluconazole for maintenance in immunosuppressed pts. Chronic pulmonary → amphotericin B + fluconazole <p>Blastomycosis:</p> <ul style="list-style-type: none"> Less severe cases → itraconazole More severe cases → amphotericin B <p>Aspergillosis:</p> <ul style="list-style-type: none"> Allergic bronchopulmonary → corticosteroids Aspergilloma → none; surgery if severe Invasive → amphotericin B followed by itraconazole Chronic necrotizing → amphotericin B or itraconazole <p>Pneumocystis:</p> <ul style="list-style-type: none"> Non-AIDS pts. → trimethoprim-sulfamethoxazole AIDS pts. → trimethoprim-dapsone or pentamidine; corticosteroids for PaO₂ < 70 or A-a > 35 Tranplant pts. and children receiving chemotx for leukemia → low-dose prophylactic trimethoprim-sulfamethoxazole Pts that do not respond to other regimen → pentamidine 	

18. Pulmonary Embolism

<p>Clinical Presentation</p> <p><i>Symptoms:</i> Dyspnea Pleuritic Chest Pain Hemoptysis Syncope (in obstruction of > 2 lobes)</p> <p><i>Physical Exam:</i> Tachycardia / Tachypnea Localized Rales or Wheezing Pleuritic Chest Pain ↓ Breath Sounds & Dullness to Percussion (pleural effusion) Loud P₂ / Audible S₄ / ↑↑ JVD / RV-heave (right-heart failure) 50% of patients show signs of DVT</p>	<p>Lab Presentation</p> <p><i>CXR:</i> most often normal; may show “Hampton’s hump”; may show atelectasis or elevation of a hemidiaphragm; may show pulmonary artery enlargement (in proximal PE); may show abrupt termination of a pulmonary vessel. - small pleural effusions in acute PE</p> <p><i>V/Q scan &/or contrast CT angiography:</i> reveals area(s) of decreased perfusion</p> <p><i>ABGs:</i> ↓ P_{O2}, ↓ P_{CO2}, ↑ pH, ↑ A-a difference</p> <p><i>Blood Tests:</i> ↑ D-dimer levels (> 500 ng/ml)</p>
<p>Etiology and Pathogenesis</p> <p><i>Pulmonary Embolism</i> refers to movement of a blood clot from the systemic circulation (most often from the deep veins of the legs) through the right heart and lodging in a branch of the pulmonary arteries (tumor cells or fragments, fat, amniotic fluid, or air can also produce an embolus). 50% of patients with pulmonary emboli have previous clinical evidence of venous thrombosis in the lower extremities or elsewhere. The risk of PE is increased by anything that increased the chance of deep venous thrombus formation. Major consequences of PE include: <i>pulmonary infarction</i> (with necrosis) if little or no O₂ reaches the area distal to the embolism, <i>hemorrhage and edema</i> in the tissue supplied by the occluded artery and subsequent collapse of lung parenchyma (<i>congestive atelectasis</i>). These processes often extend to the pleural surface, and pleural involvement may be seen on CXR; scarring often follows tissue infarction, whereas there may be no pathologic sequelae of congestive atelectasis alone. In many cases, neither of these pathologic changes occurs, presumably because of incomplete occlusion & sufficient O₂ delivery, and the thrombus undergoes lysis and is reabsorbed – whether or not dissolution occurs is important in the pathologic consequences of PE; clots that do not fragment or lyse undergo eventual organization & recanalization to form “webs” within the arterial lumen. Arterial occlusion in PE initially causes V/Q mismatch in the alveolar region supplied by the occluded artery, resulting in hypoxemia and hypocapnia (as minute ventilation is increased in response to hypoxemia); if minute ventilation is fixed (e.g. in mechanical ventilation) then hypercapnia can result. If 50-70% of the vascular bed becomes occluded, the pulmonary vascular resistance increases (potentiated by the release of bronchoconstrictive mediators from platelets that adhere to the thrombus) – Pulmonary vascular resistance may increase to the point where right-heart failure ensues, which may result in syncope or hypotensive shock (which manifests on exam as ↑↑ JVD). Constriction of small airways in regions of the lung uninvolved with emboli is likely due to the effect of bronchoconstrictive mediators and creates areas of V/Q mismatch that may be a major cause of hypoxemia in PE. Vascular compromise also results in decreased surfactant secretion (rendering the alveoli more likely to collapse) and hypocapnia causes secondary bronchoconstriction – both of these mechanisms may potentiate the atelectasis in PE. If pleuritic chest pain is present, the patient may try to breathe shallowly in order to diminish pleural rub. <i>Hampton’s hump</i> refers to a finding on CXR of a wedge-shaped area of opacified necrosis extending to the pleura.</p>	
<p>Treatment</p> <ol style="list-style-type: none"> <i>Anticoagulant therapy</i> (IV heparin followed by 3-6mos of oral coumadin) to prevent formation of new thrombi &/or propagation of old thrombi. May add <i>fibrinolytic therapy</i> (streptokinase, urokinase, or tPA) given IV prior to the IV-heparin. <ul style="list-style-type: none"> - used in pts. with massive PE or RV dysfunction - not shown to improve survival DVT Prophylaxis <ol style="list-style-type: none"> external compression of the lower extremities with an intermittently inflating pneumatic device sub-q LMW-heparin <p>For patients with contraindications to anticoagulation &/or in whom a 2nd PE would most likely be fatal, surgical implantation of a filtering device in the IVC is an option.</p>	<p>Notes</p> <ul style="list-style-type: none"> Remember Virchow’s Triad: <ol style="list-style-type: none"> Venous Stasis Endothelial Injury Hypercoagulable State V/Q scans have low specificity for PE because decreased perfusion is also seen in multiple parenchymal diseases; V/Q scans have a very high sensitivity, however. High D-dimer levels are also sensitive but not very specific. The diagnostic “gold standard” is pulmonary angiography. Death beyond a few hours post-embolism is due to recurrence of PE and thus should be preventable.

19. Pulmonary Hypertension

<p>Clinical Presentation</p> <p><i>Symptoms:</i> Dyspnea, especially on exertion Substernal Chest Pain (angina from RV-ischemia) Fatigue Syncope Hemoptysis</p> <p><i>Physical Exam:</i> ↑ JVD Loud P₂ RV-Heave Audible S₃ Audible S₄ & Peripheral Edema (in RV-failure)</p>	<p>Lab Presentation</p> <p><i>CXR:</i> ↑ size of central arteries with rapid tapering (most apparent as bulging of anterior cardiac border); may show blood flow redistribution to the upper lung zones and edema (in LV-failure & intracardiac shunt)</p> <p><i>PFTs:</i> ↓ diffusing capacity; may show restrictive or obstructive pattern of underlying disease</p> <p><i>V/Q scan:</i> rules out PE as cause of pulmonary HTN</p> <p><i>ABGs:</i> may show hypoxemia (possible cause of HTN)</p> <p><i>Histology:</i> medial hypertrophy, intimal proliferation/fibrosis, plexiform lesions</p>
<p>Etiology and Pathogenesis</p> <p><i>Pulmonary hypertension</i> is defined as pulmonary arterial systolic pressure above 40torr or a mean pressure above 25torr at rest or 30torr with exercise, although in some cases an elevation in pulmonary venous pressure is an important forerunner of arterial HTN. Causes of pulmonary HTN include: 1) acute PE occluding more than 50% of the pulmonary vasculature or chronic recurrent PE, 2) thickening of the arterial and arteriolar walls (in <i>primary pulmonary hypertension</i>, scleroderma, portal HTN, HIV infection, exogenous toxins), 3) loss of vessels from scarring or destruction affecting the alveolar walls (emphysema, interstitial lung disease) – pulmonary BP in this case is usually normal at rest but increased with exercise, as the lung cannot recruit new vessels to handle the increased CO, 4) vasoconstriction in response to hypoxia and acidosis – in many causes of cor pulmonale (especially in type B COPD) hypoxia is the major factor leading to pulmonary HTN and is also treatable, 5) increased pulmonary vascular flow (as in left-to-right shunts), and 6) elevated pressure in the left atrium creating a “backpressure” (as in mitral stenosis or left-ventricular failure). The most prominent abnormalities are frequently seen in the pulmonary vessels whose diameter is less than 1mm – the muscular arteries (0.1-1.0mm) undergo medial hypertrophy and intimal hyperplasia, whereas the arterioles (less than 0.1mm in diameter) which do not usually have a significant muscular component undergo muscularization of their walls as well as intimal hyperplasia. Ultimately, the vessel lumen may be obliterated and the total number of small vessels decreased; in some cases (especially when the HTN is due to primary pulmonary vascular disease or intracardiac shunts), the small arterioles may show <i>plexiform changes</i>, appearing as a plexus of small slit-like vascular channels. When pulmonary HTN becomes marked, the larger (elastic) pulmonary arteries become more like the elastic arteries of the systemic circulation, with medial thickening and development of atherosclerotic plaques. Endothelial damage and sluggish flow through parts of the vasculature may result in <i>in situ thrombosis</i> (which worsens the HTN by obstructing more blood flow). Cardiac consequences include initial concentric hypertrophy of the right ventricle, followed by dilation if the RV fails – this is seen on exam as an increased systemic venous pressure (↑ JVD, hepatomegaly, peripheral edema). If pulmonary HTN is due to vascular change at the level of the arteries or arterioles (as in <i>cor pulmonale</i>) the arterial pressures rise in systole & diastole whereas the pulmonary capillary pressure remains normal; if the HTN is due to pulmonary venous & capillary HTN (as in mitral stenosis or LV-failure), then of course the capillary pressure is also elevated</p>	
<p>Treatment</p> <p><i>Supplemental O₂</i>: to reduce hypoxia-induced vasoconstriction.</p> <p><i>Calcium-channel blockers</i> have been used to varying effect - efficacy limited by greater effect on systemic vasculature - do not reduce fibrotic remodeling</p> <p>Experimental Therapies: <i>Anticoagulation</i> prolongs survival.</p> <p><i>Prostacyclin</i> by continuous infusion → ↑ survival, ↑ exercise, better hemodynamics</p> <p><i>Bosentan</i> (an endothelin receptor antagonist)</p> <p><i>Transplant</i></p>	<p>Notes</p> <p>Prevalence of pulmonary HTN: Sporadic primary PH (5%): idiopathic, young adults Familial primary PH (5%): autosomal dominant Secondary PH: 90%</p>

19. Pulmonary HTN (cont.)

Specific Disorders Associated with Pulmonary HTN

Primary Pulmonary Hypertension usually occurs sporadically in women aged 20-40 associated with Reynaud's phenomenon, potentially due to an imbalance between vasodilatory & vasoconstrictor influences on the pulmonary vasculature (i.e. increased endothelin &/or thromboxane release from the endothelium or impairment/deficiency of K-channels in the smooth muscle, as well as ↓ prostaglandins & ↓ eNOS) – because vasoconstrictors act as growth factors, increased levels of these mediators may be involved in the long-term remodeling that accompanies pulmonary HTN. Familial and non-familial forms may be related to a mutant BMPR-2 (bone morphogenic protein receptor II) that results in loss of inhibition of smooth muscle cell growth. Prognosis is generally poor, with most patients dying of cor pulmonale within several years of diagnosis. Treatment is usually with vasodilators (nifedipine or diltiazem), though pulmonary efficacy is limited by the greater hypotensive effect on the systemic vasculature – results of treatment have been inconsistent also because the pathology involves remodeling of the vasculature as well as vasoconstriction. Recent treatment with IV prostacyclin (PGI₂) has been associated with clinical & hemodynamic improvement as well as improved survival and seeming decreases in remodeling; early results with an endothelin receptor antagonist have also been encouraging. Anticoagulation (warfarin) may also improve survival by preventing in situ thrombosis in the pulmonary vasculature. Inhalation NO is an effective pulmonary-selective vasodilator, but it is impractical for long-term use.

Chronic Pulmonary Thromboembolism presents commonly as pulmonary HTN rather than as acute PE. In patients with large proximal thromboemboli surgical removal may be an effective treatment. In patients with extensive occlusion of the smaller vessels (likely resulting from hypercoagulability of the microvasculature due to endothelial damage), therapy involves anticoagulation and possibly vasodilators.

Pulmonary Hypertension Secondary to Airway or Parenchymal Lung Disease. Type B COPD-induced hypoxia is a common cause of pulmonary HTN (exacerbated in this case by respiratory acidosis and secondary polycythemia); interstitial lung diseases cause pulmonary HTN by the fibrotic destruction of the vascular bed as well as hypoxia. Maintaining arterial O₂ levels of > 60mmHg by use of supplemental O₂ can eliminate the hypoxia-induced vasoconstriction.

Pulmonary Venous Hypertension (from mitral stenosis or LV-failure) may cause pulmonary arterial hypertension. Pathologically, engorged veins are associated with chronic extravasation of RBCs into the interstitium where they are taken up by macrophages that then have a high level of hemosiderin (iron-containing Hb breakdown product) in their cytosol – Alveolar walls show a fibrotic response to extravasated RBCs, resulting in interstitial disease which worsens the pulmonary HTN. Radiographic evidence of pulmonary venous hypertension includes: redistribution of blood to the upper lung zones, interstitial & alveolar edema, and Kerley's B lines (small horizontal lines extending to the pleura at both lung bases and corresponding to thickening of or fluid in the lymphatics of the interlobular septa as a consequence of interlobular edema). Treatment depends on correcting the heart disease which causes the elevated pulmonary venous pressure.

20. Sleep Apnea Syndrome

<p><u>Clinical Presentation</u></p> <p><i>Symptoms:</i> Loud snoring & violent movements during sleep Headache Daytime hypersomnolence</p> <p><i>Physical Exam:</i> Hypertension / Tachycardia</p>	<p><u>Lab Presentation</u></p>
<p><u>Etiology and Pathogenesis</u></p> <p><i>Sleep apnea syndrome</i> is characterized by repetitive periods of apnea > 10sec during sleep. SAS is commonly divided into three types: 1) <i>obstructive sleep apnea</i> – where the drive to breath and contraction of the inspiratory musculature are still present during apneic episodes, but transient obstruction of the upper airway prevents inspiratory airflow, 2) <i>central sleep apnea</i> – where there is no drive to breath during the apneic episode, and 3) <i>mixed sleep apnea</i> – where patients have elements of both central and obstructive sleep apnea (most often the episodes begin with central apnea then obstruction is present when respiratory drive returns). Loud snoring &/or violent movements during sleep and daytime headaches & hypersomnolence (sleepiness) are common manifestations. During apneic episodes, an increased SNS outflow may cause cardiac arrhythmias & conduction abnormalities; prolonged hypoxia may also cause pulmonary hypertension (cor pulmonale may develop as a result of this and may be the presenting problem). In patients with obstructive sleep apnea, an excess of soft tissue (often due to obesity) blocks the pharynx during inspiration (especially during REM sleep, as generalized loss of muscle tone allows soft-tissue collapse into the pharynx) – airflow resumes again as hypoxia induces ↑ SNS activity & an arousal (of which the patient may not be aware), but as soon as the patient falls asleep again an apneic episode may recur. Patients at risk for sleep apnea include those who are obese and those with micrognathia (small jaws), a large tongue, or large tonsils.</p>	
<p><u>Treatment</u></p> <p>Treatment of Central Sleep Apnea:</p> <ol style="list-style-type: none"> 1. respiratory stimulants 2. phrenic nerve stimulation via implanted pacemaker <p>Medical Treatment of Obstructive Sleep Apnea:</p> <ol style="list-style-type: none"> 1. <i>Weight loss</i> in obese patients. 2. <i>Nasal CPAP</i> to open airway & deliver O₂ during sleep 3. <i>Oral appliance</i> to keep airway open during sleep. <p>Surgical Treatment of Obstructive Sleep Apnea:</p> <ol style="list-style-type: none"> 1. <i>Uvulopalatopharyngoplasty</i> – removal of extraneous soft tissue in the upper airway. 2. <i>Tracheostomy</i> <p>Avoid use of respiratory depressants in patients with either type of sleep apnea.</p>	<p><u>Notes</u></p> <p>Epidemiology</p> <ul style="list-style-type: none"> ● prevalence of 2 - 4% in middle-aged adults ● men are more commonly affected than women, and women who are affected are most often post-menopausal ● The <i>genioglossus</i> muscle is particularly important in opening the pharynx during inspiration. ● Benefits of treatment: <ol style="list-style-type: none"> 1. ↓ risk of seizure in epileptics 2. ↓ BP (by an average of 3.3mmHg) 3. better outcomes following stroke

21. Acute Respiratory Distress Syndrome

Clinical Presentation	Lab Presentation
<p><i>Symptoms:</i> Rapid, shallow breathing (↓ lung compliance) Dyspnea</p> <p><i>Physical Exam:</i> Rales Dullness to Percussion (pulmonary edema) Shock → ↓ BP</p>	<p><i>ABGs:</i> ↓ P_{O₂}, normal or ↓ P_{CO₂}, ↑ A-a difference PaO₂/FIO₂ ≤ 300: Acute Lung Injury PaO₂/FIO₂ ≤ 200: ARDS</p> <p><i>CXR:</i> bilateral infiltrates → interstitial & alveolar edema - Air bronchograms represent alveolar edema</p> <p><i>Histology:</i> DAD (see below) with microatelectasis</p>
<p>Etiology and Pathogenesis</p> <p>ARDS is characterized by increased permeability of the endothelium and alveolar epithelium to fluid and protein resulting in interstitial and alveolar edema with fluid of high protein content (similar to that of serum). Possible causes of ARDS include: 1) <i>inhalation of injurious agents</i> – liquid of pH < 2.5 causes a “chemical burn” of the lung parenchyma, salt water draws fluid from capillaries down its osmotic gradient into the alveolar space, fresh water inactivates surfactant and enters cells down the osmotic gradient to cause cellular edema, inhaled hydrocarbons inactivate surfactant, NO₂ and some components of smoke are acutely toxic, high concentrations of O₂ may cause oxidative damage, and infective agents (esp. <i>Pneumocystis carinii</i> & viruses) may also damage parenchymal cells, 2) <i>injury to the pulmonary circulation</i> as in trauma, sepsis, DIC, fat or amniotic fluid embolism, narcotic administration, release of pancreatic enzymes into the circulation (pancreatitis), and ↑↑ SNS outflow causing pulmonary HTN after seizures or intracerebral hemorrhage (i.e. <i>neurogenic pulmonary edema</i>). Damage to the type I epithelial cells from inflammatory mediators released from neutrophils, macrophages, and platelets is likely involved – Less than 30min after the initial insult, alveolar macrophages secrete IL-8 (chemotactic for neutrophils), after which neutrophils invade the interstitium & alveolar spaces and mediate inflammatory destruction. Pathologic findings in ARDS (collectively called <i>diffuse alveolar damage</i>) occur in three stages: In the <i>exudative phase</i> (days 0-7), there is: 1) damage to alveolar type I epithelial cells with interstitial and alveolar fluid present, 2) areas of alveolar collapse (via inactivation of surfactant by protein-rich alveolar exudates and damage to type II epithelial cells), 3) inflammatory infiltration (mostly neutrophils and macrophages) of the interstitium & alveolar space along with fibrin/cellular debris located in & around the alveolar wall, and 4) presence of <i>hyaline membranes</i> (protein-rich alveolar fluid plus debris from necrotic epithelial cells) in the alveolar spaces. The <i>proliferative phase</i> (weeks 2-3) is characterized by hyperplasia of the type II epithelial cells, septal fibrosis & inflammation, and reabsorption of the hyaline membranes. A <i>fibrotic phase</i> is said to be present if interstitial fibrosis continues and irreversibly impairs lung function.</p> <p>Clinical consequences of ARDS include: 1) shunting &/or V/Q mismatch in regions of flooded alveoli resulting in hypoxemia, (typically PaCO₂ is normal due to increased minute ventilation), 2) impaired function &/or production of surfactant resulting in alveolar collapse, 3) increased pulmonary vascular resistance caused by hypoxia, microthrombi, &/or fibrotic changes in the vessel walls and leading to more areas of V/Q mismatch, 4) decreased lung compliance resulting in decreased FRC and necessitating rapid, shallow breathing that is inefficient and likely causes the characteristic feeling of dyspnea associated with ARDS. After the initial insult, whatever it may be, there is generally a lag of several hours to a day or more before symptoms occur – Initial presentation is usually dyspnea & tachypnea with an abnormal A-a difference and normal PaCO₂; as fluid and protein continue to leak into the interstitial and alveolar spaces, symptoms may worsen, rales may appear on examination, and CXR may reveal the edema.</p>	
<p>Treatment</p>	<p>Notes</p>
<p>1. Treat the underlying disorder.</p> <p>2. Interrupt the increased capillary permeability. - no successful agents so far to do this - maybe steroids; maybe cytokine-inhibitors</p> <p>3. Support gas-exchange until lung function improves. - intubation & mechanical ventilation</p> <p>Experimental Therapies</p> <ul style="list-style-type: none"> • <i>Inhaled NO</i> to dilate the airways which are well-ventilated leading to better V/Q matching. - not shown to improve survival • <i>Recombinant aPC</i>, which has antithrombotic and anti-inflammatory effects, has been shown to improve survival in patients with sepsis 	<ul style="list-style-type: none"> • <i>Cardiogenic pulmonary edema</i> is interstitial & alveolar edema that is caused by increased hydrostatic pressure in the pulmonary capillaries (as in mitral stenosis or LV-failure). - This is <i>not</i> considered ARDS. • The distribution of alveolar damage in ARDS is heterogenous across the lung, with some areas destroyed and others relatively unscathed. • High mortality in ARDS (30 – 50%) is mostly due to underlying disease rather than the respiratory failure. - Lung function returns for most patients in 6-12mos if the acute insult is survived and fibrosis does not continue. • Increased capacity for pulmonary fluid uptake → ↓ mortality

Management of Respiratory Failure

Maintenance of CO₂ Elimination. Patients with COPD, chest wall ds, & neuromuscular ds are subject to chronic hypercapnia; acute hypercapnia is seen in respiratory-drive depression by narcotics (i.e. in an accidental or purposeful overdose) and in *status asthmaticus*. Mechanical ventilation to eliminate CO₂ is often necessary if blood pH is < 7.25 – 7.30, if significant mental status changes have ensued, if vital capacity is less than 10mL/kg body weight, or if maximal inspiratory pressure is < 25cmH₂O negative pressure.

Maintenance of Oxygenation. When V/Q mismatch &/or hypoventilation is responsible for hypoxemia, supplemental O₂ is commonly very effective even at low doses (40%) to bring the PaO₂ up to 60mmHg. Patients with chronic hypercapnia may show substantial increases in PaCO₂ with supplemental O₂, and in this case they may need mechanical ventilation to eliminate excess CO₂. When shunting in addition to V/Q mismatch is involved in the hypoxemia (as often happens in ARDS), supplemental O₂ at 60-100% may be ineffective at raising PaO₂ significantly – these patients may require mechanical ventilation for oxygenation. Beneficial effects of assisted ventilation in ARDS include: 1) more reliable administration of O₂, 2) reduced work of breathing resulting in larger tidal volumes, 3) positive end-expiratory pressure may be maintained in order to keep collapsible airways open (i.e. to ↑ FRC) and reduce shunting – decreased shunting makes the patient much more responsive to supplemental O₂ which can then be given at a lower concentration (& high-concentration O₂ toxicity can be avoided).

Reducing Work of Breathing. Work of breathing is increased in conditions that cause hyperinflation (which puts the diaphragm at a mechanical disadvantage) and in neuromuscular disease. Mechanical ventilation may be necessary to remove dyspnea and assure adequate pressures for sufficient gas-exchange; large amounts of blood-flow consumed by an overworked respiratory musculature can also be shifted to perfusion of other organs.

Mechanical Ventilation. *Volume cycling* refers to ventilation wherein inspiration is ended (and passive expiration is allowed to begin) after a specific tidal volume has been delivered by the machine; in *pressure-limited ventilation*, inspiration is ended when a specific positive airway pressure is reached. Ventilatory patterns associated with volume cycling include: 1) *controlled ventilation*, where ventilation is supplied only by the ventilator at a respiratory rate, tidal volume, & inspired O₂ concentration set by the MD (can be quite uncomfortable for a conscious patient), 2) *assist-control ventilation*, where the ventilator senses when the patient initiates inspiration and delivers a specified tidal volume (respiratory rate is controlled by the patient but tidal volume by the machine); if the patient fails to initiate respiration for a certain time (set by the MD), the machine will deliver a breath, and 3) *intermittent mandatory ventilation*, where the machine delivers a preset number of breaths at a specified tidal volume and inspired O₂ concentration, and in between the machine-breaths the patient breathes spontaneously from a source providing the same O₂ concentration (in *synchronized IMV*, the machine-delivered breaths are timed to coincide with and assist a patient-initiated breath. Clinically, both assist-control and synchronized IMV are very useful and effective. Two types of pressure-limited ventilation are used: in *pressure support ventilation* the ventilator senses when the patient initiates a breath and supplies a certain amount of positive pressure to the airways then stops when the inspiratory flow rate falls below a specified level (breathing stops if pt. stops initiating respiration); in *pressure-controlled ventilation*, the initiation of breathing, duration of inspiration & duration of expiration are set by the MD; it is used most often in patients with ARDS in whom problems with oxygenation & decreased lung compliance are particularly severe. An important option available for the intubated patient with hypoxemic respiratory failure is the use of *positive end-expiratory pressure* (PEEP) to keep airways open throughout the respiratory cycle (and prevent alveolar collapse and subsequent V/Q mismatch). A variation on PEEP that works on the same principle is *continuous positive airway pressure* (CPAP), where the patient inspires spontaneously but expires through tubing connected to a PEEP valve. *Protective open lung strategy* (PEEP with avoidance of excessive inspiratory inflation pressure and with tidal volumes as low as 6mL/kg) is commonly used in ARDS. When oxygenation is especially difficult, inspiration may be prolonged relative to expiration; this technique is called *inverse ratio ventilation* (IRV) since in many cases inspiration is made to last longer than expiration. Mild hypercapnia may be permitted so as to not incur the risks associated with high-pressure ventilation. Mechanical ventilation may be discontinued when the ratio of the patient's respiratory rate divided by the tidal volume (the *rapid shallow breathing index*) is less than 100, and weaning can be done with SIMV or PSV with gradually less aid from the machine, or after a successful trial of spontaneous breathing (2 hours without mechanical ventilation). Complications of mechanical ventilation include: ventilator-associated pneumonia (often gram-negative bacilli & *Staphylococcus aureus*), barotrauma/volutrauma, pneumothorax, impairment of cardiovascular function (positive inspiratory pressure during inspiration impedes venous return and increases pulmonary vascular resistance).

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<u>Treatment</u>	<u>Notes</u>

