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PULMONARY INFECTIONS AND THEIR COMPLICATIONS

Required reading: Robbins: Pathologic Basis of Disease, Chapter 16, pp. 717-726 and Chapter 9, pp. 347-353

I. **Incidence**

Pulmonary infections in the form of pneumonia account for 15-20% of all deaths in the United States. Most of these occur as "secondary pneumonia" in patients with other diseases (AIDS, cancer, alcoholism, etc), but many will present as a "primary pneumonia" in otherwise healthy children and adults.

II. **Routes of infection**

A. Pediatric

1. *Transplacental* - as part of a generalized infection, often acquired from the mother - includes cytomegalovirus, rubella, herpes, enterovirus and, less frequently, toxoplasmosis, syphilis, mycoplasma, listeria and m. tuberculosis.

2. *Intrauterine* - present at birth, usually related to ascending infection from the mother's vagina with prolonged rupture of membranes and aspiration of the infected amniotic fluid. Organisms include group B streptococcus and E. coli.

3. Pneumonia *acquired during birth* as the infant descends through the birth canal and comes in contact with (? aspirates)"vaginal" organisms. Infant develops symptoms during the first week of life from organisms such as group B streptococcus, h. influenzae, e. coli, herpes.

4. Pneumonia *acquired after birth* - organisms come from the environment (e.g. nursery equipment) and human contact (doctors, nurses, parents, sibs, etc.). Organisms include S. pneumoniae, Staphylococcus aureus, Respiratory syncytial virus, etc.

B. Adult

1. *Community-acquired* from infected contacts (family, coworkers, etc) or environment, often following a flu-like illness.. Streptococcus pneumoniae accounts for 60-70% of bacterial pneumonias with Legionella pneumonia providing up to 15% more cases. In endemic areas such as the Mississippi Valley (for histoplasmosis) and the San Joaquin Valley in California (for coccidiomycosis) 80-90% of the adult population have had infection by the appropriate organism, most of which were asymptomatic.

2. *Immunocompromised hosts* - patients with AIDS or on immunosuppressive therapy (e.g. for cancer) may develop Pneumocystis carinii pneumonia. Other organisms causing pneumonia in this population include cytomegalovirus, Mycobacterium avium-intracellulare, Cryptococcus neoformans and Legionella pneumonia.

3. *Nosocomial* or hospital-acquired pneumonia - patients in hospitals are exposed to virulent and often, unusual organisms including Staphylococcus aureus, gram negative bacilli, Aspergillus, Candida.

III. **Host defense mechanisms in the lung**

A. Nonimmune lung

1. Entrapment in the mucous blanket of the bronchi and bronchioles and removal via the mucociliary "elevator".

2. Phagocytosis by alveolar macrophages that can kill and degrade organisms and remove them from the air spaces by migrating onto the mucociliary "elevator".

3. Phagocytosis and killing by neutrophils recruited in the alveoli by macrophage factors.

4. Serum complement may enter the alveoli and be activated by the alternate pathway to provide opsonin C3b that enhances phagocytosis by neutrophils.

5. Organisms either singly or phagocytosed within macrophages may reach draining lymph nodes to initiate an immune response.

B. Immune lung

1. Secreted IgA can block attachment of the microorganism to epithelium in the upper respiratory tract.

2. Serum antibodies (IgM, IgG) present in the alveolar fluid of the lower respiratory tract activate complement by the classical pathway, yielding C3b.

3. Immune T cells control infections by viruses and other intracellular organisms.

IV. **Types and selected examples of pneumonia**

Case History: This 42 year-old white male was found unconscious under the Whitehurst Freeway. He had been living under the bridge for the past three months and was known to be a heavy drinker. On physical exam he was noted to have a fever (103) and a cough productive of rusty sputum. Breath sounds were noted to be markedly diminished over the lower portion of the ride side of his chest and he was shivering uncontrollably.

A. Acute bacterial pneumonia

1. ***Pneumococcal pneumonia*** (agent=S. pneumoniae) is the most common community-based bacterial pneumonia and occurs most frequently in infants and elders. Onset is abrupt with severe shaking chills accompanied by pleuritic chest pain and a cough productive of rusty colored purulent sputum. Patients at greatest risk are those with chronic obstructive pulmonary disease (COPD), alcoholism, intravenous drug abuse, and upper airway dysfunction.

2. Pneumococcal pneumonia occurs primarily as a lobar pneumonia (segmental to complete involvement of a single lobe) but may also present as a bronchopneumonia (patchy involvement of one or more lobes).

3. Stages
Acute congestion - bacterial proliferation, fluid exudation, neutrophils, RBCs produce "rusty" sputum.
Red hepatization - consolidation by cellular exudate with RBCs, neutrophils and fibrin.
Gray hepatization - fibrinous exudate depleted of RBCs.
Resolution - exudate digested and resorbed or expectorated.

4. Complications include **pleural involvement** with loculation and accumulation of pus, **bacteremia** (which may lead to meningitis and endocarditis), **abscess formation**, **necrotizing pneumonia** and "chronic" **fibrosing pneumonia.**

B. "Atypical" pneumonia

Case History: This 24 year old USUHS medical student had had a persistent nonproductive cough and low grade fever since he participated in

a week long spring break in Ft. Lauderdale, FL six weeks ago. While not sick enough to miss classes he complained of a headache and generalized malaise. Chest x-ray displayed a patchy consolidation in the upper portion of his left lung. He had also noted a maculopapular rash over his arms and legs approximately three weeks ago that had persisted for 10 days.

1. ***Mycoplasma pneumonia*** is an aerosol-spread, acute, self limiting lower respiratory tract infection affecting mostly small groups of children and young adults who have frequent close contact (e.g. families , military units, etc.). Symptoms including fever, headache, malaise and a nonproductive cough are usually mild and have given this infection the appellation "walking pneumonia". The lungs display patchy consolidation of a single segment, with a mononuclear infiltrate of the mucosa and an alveolar interstitial infiltrate of lymphocytes and occasional plasma cells. Erythematous, maculopapular, or vesicular eruptions of the skin that persist for 1-2 weeks may be seen in about 10% of cases.

Case History: This 4-month old female was noted to have a cough, fever (39.5C) and moderate to severe dyspnea. Her two-year-old brother had similar, though milder, symptoms along with two episodes of vomiting. Chest x-ray displayed streak like areas of consolidation (interstitial infiltrates) along with areas of increased lucency (hyperinflation). The infant was hospitalized because of mild cyanosis and hypoxia.

2. ***Respiratory syncytial virus (RSV) pneumonia*** is the most important respiratory pathogen of infancy and early childhood and accounts for 60-90% of cases of pediatric bronchitis and up to 40% of pneumonias in young children, mainly those under two years of age. In recent years, RSV has been seen with increasing frequency in elderly patients, particularly those in nursing homes. Symptoms in both age groups include fever, cough, rhinitis, pharyngitis , dyspnea and vomiting. Imaging displays a diffuse interstitial pneumonitis with hyperinflation. Microscopically, lymphocytes surround and infiltrate bronchiolar walls progressing to mucosal necrosis and bronchiolar luminal narrowing. Necrotic epithelium, some in characteristic clumps of multinucleated (syncytial) giant cells sloughs into the lumen and impedes airflow, producing the distal air-trapping noted on chest x-ray. Pneumonia consists of an interstitial infiltrate of lymphocytes and macrophages.

C. Chronic pneumonia

1. **Tuberculosis** is a chronic, communicable disease caused principally by M. tuberculosis hominis that affects the lung primarily, but may infect most any organ of the body.

Primary tuberculosis is the infection of a person who has not had prior contact with the tubercle bacillus. Inhaled bacilli are deposited in the alveoli where they are phagocytosed by and subsequently proliferate in macrophages, which in turn die and release more organisms, producing a ***localized pneumonia***. Organisms are also carried to ***regional lymph nodes*** and from there may be disseminated throughout the body. Hypersensitivity and cell-mediated immunologic responses are initiated by the bacilli-containing macrophages and act to contain this initial infection over a period of 3-6 weeks through a vigorous ***granulomatous reaction*** often with characteristic cheese-like ***(caseous) necrosis***. The primary focus in the

lung and the involved hilar or mediastinal lymph nodes comprise the ***Gohn complex***.
In over 90% of normal adults, the primary infection follows a ***self-limited course***. In immunocompromised patients and often in children under 5 years of age, the primary focus of tuberculosis enlarges, erodes bronchi and may spread throughout the lung or disseminate to other organs (e.g. kidneys, adrenals. spleen and liver).

Secondary (cavitary) tuberculous occurs when organisms proliferate in a previously infected person. The organisms may be newly acquired bacilli or may be dormant ones in a patient "newly predisposed" to reemergence of the infection by immunosuppressive therapy, AIDS, old age, cancer, etc. In lung reinfection, bacilli proliferate, incite an inflammatory response that leads to local consolidation with subsequent ***necrosis, cavity formation, and granulomatous response***. Secondary effects include localized pulmonary scarring and calcification, spread to other areas, pleural fibrosis and adhesions, rupture of a caseous lesion with spilling of bacilli into the pleural cavity, erosion into a bronchus with seeding of bacilli along the airway, and "miliary" spread throughout the lymphatics and bloodstream.

2. A variety of ***fungi***, causing the diseases of ***histoplasmosis, coccidioidomycosis, blastomycosis, sporotrichosis and paracoccidioidomycosis***, can also produce chronic granulomas in the lung with extensive caseation and necrosis. Along with tuberculosis, they may progress from a primary infection to a dormant one in normal hosts or to a progressive primary infection or secondary infection in malnourished or immunodeficient patients.

D. Lung abscesses

Case History: The two-year old son of a diplomat stationed in an central African country developed severe pulmonary symptoms(cough, dyspnea and cyanosis), but, because of the unavailability of medical facilitates, went untreated for 10 days. When finally seen in a hospital, chest x-rays revealed consolidation of the both lower lobes. After aggressive treatment with antibiotics over a period of two months, the consolidation cleared somewhat to reveal multiple cysts (with air/fluid levels) of both lower lobes.

1. ***Staphylococcus aureus*** pulmonary infection may present as a purulent bronchopneumonia, a hemorrhagic bronchopneumonia, a lobar pneumonia or a pneumonia secondary to septicemia. S. Aureus, however along with ***Klebsiella pneumoniae***, ***Proteus mirabilis***, and some anaerobic bacteria, among others, may cause local destruction of acini resulting in the formation of abscesses, which when healed may appear as "pneumatoceles", i.e. air-filled sacs.

2. Fungi, such, as ***Candida albicans***, may also produce abscesses (see below).

E. Pneumonia in immunosuppressed or neutropenic patients

Case History: A 27 year-old chronic drug user had been HIV positive for 3 years. He presents with chronic dry cough and mild dyspnea. Chest x-ray reveals bilateral interstitial and alveolar infiltrates, most prominently seen in the hilar regions and lower lung fields.

1. ***Pneumocystis carinii pneumonia*** is the most prevalent infection seen in AIDS

patients, but was first described in malnourished infants nearly 50 years ago. It is also seen with some frequency in immunosuppressed patients undergoing chemotherapy for malignant disease or following organ transplantation. P. carinii is an organism of uncertain classification whose life cycle resembles a protozoa, but whose genetic analysis is more like a fungus. Virtually all humans are exposed to pneumocystis during the first years of life, but in the vast majority the infections remains latent. Patients whose disease "reactivates", present with fever, dry cough and dyspnea and typically demonstrate radiographically, peripheral and basilar infiltrates.

Grossly, the lungs are expanded and on cut section exude a thick, bubbly fluid. Microscopically, alveoli are filled with a foamy, pink-staining material containing characteristic ***crescent or cup-shaped cysts*** that are readily demonstrated by silver stains. Alveolar walls are infiltrated by lymphocytes and a few plasma cells and histiocytes. Less frequently, the foamy exudate is absent, epithelial granulomas with P. carinii cysts are present, and the alveolar septum is fibrotic as well as infiltrated by lymphocytes.

In AIDS patients, P. carinii may produce *cystic-cavitary lesions* which can rupture producing a *pneumothorax*. P. carinii may also spread to extrapulmonary sites, most frequently lymph nodes, liver, spleen and bone marrow.

2. ***Mycobacterium avium-intracellulare*** (MAI) is another AIDS related organism, seen in as many as 5% of AIDS patients. The organism enters the body through the lungs and GI tract, but may also be sexually transmitted in AIDS patients. The infection is disseminated to lymph nodes, spleen, liver, GI tract and bone marrow in over 50% of cases and occurs in the lung in only about 15%. The lesions present as small granulomas with *histiocytes filled with organisms*. MAI is frequently seen in association with other infectious agents whose pathologic changes may partially mask the organism.

3. ***Candida albicans***, a normal inhabitant of the oral cavity, gastrointestinal tract and vagina in many individuals, is the most frequent disease-causing fungus of the lung and many other systems (e.g. producing vaginitis in women, diaper rash in infants). In immunocompromised patients, widespread mucocutaneous (*thrush*) involvement may occur which can spread systemically with the development of abscesses in many organs (kidney, heart, brain, eye, liver and lung). The lung lesions may manifest as irregular or "cannonball" abscesses of varying sizes.