BACTERIA CAUSING LOWER RESPIRATORY TRACT INFECTIONS

Introduction

I. Age is key determinant for pneumonia
   A. Viruses predominate in childhood pneumonia, bacteria cause secondary infections
   B. Adult pneumonia depends on variety of risk factors

II. Adult pneumonia may be community acquired or hospital acquired
   A. Community risk factors: alcohol abuse, occupational exposure, underlying condition
   B. Risks for nosocomial pneumonia: immunocompromise & mechanical ventilation

III. Geographic variability of primary typical and atypical pneumonias
   A. Primary pneumonia did not involve an initiating infection, typically viral
   B. “Atypical pneumonia” is caused by pathogen other than Streptococcus pneumoniae

Streptococcus pneumoniae [a.k.a. Pneumococcus]

I. Virulence factors relevant to Lower Respiratory Tract Infections
   A. Polysaccharide capsule (84 capsular serotypes)
      1. Composed of complex polysaccharide
      2. Primary virulence factor of S. pneumoniae
      3. Capsule interferes with complement deposition
         a. Prevents C3b complement deposition and engulfment by alveolar macrophages
         b. Phagocyte receptor cannot make contact with C3b due to capsule
      4. Capsule facilitates evasion of lung surfactant
      5. Anti-capsule antibodies confer host immunity to pneumococcus
   B. Pneumolysin
      1. Member of sulfhydryl-activated cytolysins (hemolysins)
         a. Membrane-damaging cytolysin related to Streptolysin O
         b. Cholesterol is the cell membrane receptor
         c. Subunits of pneumolysin oligomerize in cell membrane to form large pore
      2. Pneumolysin acts on many cell types: pulmonary endothelium, PMNs and monocytes
      3. Role in pathogenesis
         a. Facilitates evasion of immune response, clearance from nasopharynx
         b. May permit pneumococci to spread from alveoli to bloodstream⇒ bacteremia
         c. Cell-bound pneumolysin activates complement, contributes to inflammatory response
C. Cell wall teichoic acid and peptidoglycan

1. Contribute to strong inflammatory response
   a. Peptidoglycan fragments & teichoic acid activate alternate complement pathway
   b. Production of IL-1 and TNFα is elicited
2. Response comparable to Gram neg. lipopolysaccharide (LPS)-induced inflammation
3. Inflammatory response elicits fever and lung damage, causes bloody sputum
II. Etiology / Pathogenesis
   A. *S. pneumoniae* is exclusively a human pathogen
      1. Person-person spread by droplet
      2. Up to 30% of adult population as asymptomatic carriers, transient carriage

   B. Pneumococcus is most common cause of acute bacterial pneumonia in any age group
      1. Aspiration of pneumococci from middle respiratory tract
      2. Compromised cough reflex permits pneumococcus into lower respiratory tract
         a. Common causes are stroke, alcoholism, drugs, and anesthesia
         b. Viral infection of middle respiratory tract is also a cause
      3. Alveolar antibodies to capsule usually clear pneumococci from lower respiratory tract

   C. Acute pneumonia caused by *S. pneumoniae*
      1. Infection of lung parenchyma
      2. Cough ⇒ productive sputum that is purulent material from alveoli
      3. Inflammatory response to infection
         a. Complement components increase vascular permeability ⇒ fluid accumulation
         b. Disrupted gas exchange can suffocate patient

   D. Secondary complications: Bacteremia and Acute Purulent Meningitis
      1. Inflammatory response, damage to endothelial cells may cause bacteremia
      2. Bacteremia may lead to meningitis
         a. Pneumococci adhere to vascular endothelium of CNS, cause cell death
         b. Pneumococci breach blood-brain barrier to enter cerebrospinal fluid

III. Clinical identification of organism
   A. Sputum is Gram stained - Important diagnostic tool
      1. Problem is contamination with flora from oropharynx
      2. Sputum contains PMNs and is monomicrobial
      3. Contaminating saliva is polymicrobial and has squamous epithelial cells

   B. *S. pneumoniae* characteristics
      1. Gram positive, lancet-shaped, diplococci stuck together end to end
      2. α-hemolytic: green zone on blood agar
      3. Pneumococcus is not part of Lancefield grouping scheme
C. Biochemical tests
   1. Capsular serotyping
   2. Quellung capsular swelling reaction using anti-capsule antibodies
   3. Optochin (ethylhydrocupreine) or “P disk” susceptibility
   4. Bile solubility to differentiate from viridans streptococci

D. Blood culture for organism
   1. Detects bacteremia and confirms sputum sample
   2. Latex agglutination used to detect circulating pneumococcal antigens

E. Radiology of lung shows bronchopneumonia that can consolidate to lobar pneumonia
**Haemophilus influenzae**

I. Virulence factors relevant to Lower Respiratory Tract Infections
   A. Polysaccharide capsule

   B. Capsule is antiphagocytic and subject to antigenic variation

   C. Capsular serotype b (Hib) most virulent

II. Etiology / Pathogenesis
   A. *H. influenzae* common inhabitant of upper respiratory tract
      1. Typically non-encapsulated, but healthy carriers of encapsulated strains common
      2. Spread is exclusively person-person by droplet

   B. *H. influenzae* pneumonia
      1. Encapsulated and non-encapsulated (non-typable) strains may cause pneumonia
         a. Encapsulated strains produce disease like pneumococcal pneumonia
         b. Pneumonia due to Hib
            i. Less common than non-encapsulated due to lower colonization rates with Hib
            ii. Increased virulence
            iii. Higher incidence of positive blood cultures compared to non-typable
      2. *H. influenzae* acute epiglottitis and pneumonia peak in 2-5 yr. age group
      3. 2nd most common cause of pneumonia in middle age men (pneumococcus 1st)
      4. Predisposing factors of pneumonia caused by nontypable *H. influenzae*
         a. Chronic bronchitis
         b. Emphysema
         c. Obstructive pulmonary disease

III. Clinical identification of organism
    A. Sample collection
       1. Sputum
       2. Blood cultures
          a. Positive in 10-15% of patients with *Haemophilus* pneumonia
          b. Higher incidence of bacteremia with Hib

    B. Morphology and Cultivation
       1. Small Gram negative, coccobacillary rods
       2. *H. influenzae* require blood products (X & V factors) for growth
Legionella pneumophila

I. Virulence factors relevant to Lower Respiratory Tract Infections
   A. Outer membrane proteins for entry into macrophages
   B. Metalloprotease homologous to Pseudomonas aeruginosa elastase
   C. Defect in organelle trafficking (dot) locus isolated using mutational analyses
      1. Controls phagolysosome fusion in macrophage carrying Legionella
      2. Controls recruitment of ribosomes to lysosome membrane encasing Legionella
   D. Phospholipase C
      1. Damages phospholipid membranes of eucaryotic cells
      2. May permit engulfed bacteria to escape from phagocytic vesicle

II. Etiology / Pathogenesis
   A. Acute pneumonia
      1. History
         a. 1976 Philadelphia outbreak of fatal pneumonia during American Legion Convention
         b. Previous undiscovered due to fastidious growth requirements
      2. Generally low virulence for humans
         a. Serologic studies indicate up to 25,000 exposures/yr.
         b. There is no person-person transmission of L. pneumophila
         c. Most people have antibodies to Legionella antigens due to its ubiquity in nature
      3. Contributing factors to pathogenesis
         a. Nosocomial infections, immunocompromised (e.g. transplant) patients
         b. Smoking, excessive alcohol use, old age
      4. Many Legionella spp. but pneumonia predominantly caused by L. pneumophila
   B. Survival of Legionella in the environment
      1. Legionella is a parasite of fresh water and soil protozoa (Acanthamoeba, Naegleria)
      2. Reservoirs for ameba/bacteria
         a. Cooling towers of air conditioning systems
         b. Plumbing, esp. showerheads and faucet aerators
         c. Hospital respiratory therapy equipment
      3. Organisms are aerosolized through air conditioning ducts or shower heads and inhaled
      4. Routine disinfection of cooling systems is used as prevention
      5. Existence inside ameba provides survival advantage
         a. Legionella spp. more resistant to disinfectants inside ameba
         b. Bacteria may over winter inside the cyst of ameba
         c. Legionella may be capable of living outside ameba in biofilms
C. Two syndromes caused by *L. pneumophila*

1. Legionnaire’s Disease
   a. Severe pneumonia with 2-10 day incubation period
   b. Up to 60% mortality rate, especially among immunocompromised

   a. Nonpneumonic febrile illness with incubation period of 1-2 days, self-limiting
   b. High attack rate following exposure but less common than Legionnaire’s pneumonia
   c. May be immune response to inhalation of dead or low virulence strains of *Legionella*

| CLINICAL MANIFESTATIONS OF LEGIONELLA INFECTIONS |
|----------------|-------------|-------------|-------------|
| Disease        | Pneumonia   | Occurrence  | Frequency   |
| Legionnaire’s disease | Always     | Epidemic, nosocomial & community | Low          | Long (days) |
| Pontiac fever  | Never       | Epidemic, community             | High         | Short (hours) |
| Disseminated infection | Usually    | Isolated cases                   | Rare         | Long (following primary infection) |

D. Pathogenesis of *L. pneumophila*

1. Inhaled organism has tropism for lung alveoli & bronchioles ⇒ microabscesses
2. Surface protein for binding C3 to enhance its own phagocytic uptake
3. Survives as intracellular parasite in monocyte-macrophages
   a. Uptake into alveolar macrophages by “coiling phagocytosis”
   b. Uptake can be devoid of opsonization, by bacteria-induced phagocytosis
4. Transition from extra- to intracellular environment ⇒ 30 new proteins that:
   a. Prevent phagolysosome fusion and acidification of the endocytotic vesicle
   b. Induce accumulation of ribosomes & mitochondria around phagosome
   c. Facilitate scavenging of iron from transferrin
5. Multiplication of *Legionella* is inhibited in activated macrophage
6. Adaptation to survival inside phagocyte probably developed during life in ameba
L. pneumophila Coiling phagocytosis
*L. pneumophila* Multiplication inside phagocyte
III. Clinical identification of organism

A. Classical staining and culture techniques not useful
   1. Stains poorly by Gram stain
      a. Can be visualized with simple stains devoid of decolorization or silver impregnation
      b. Appears as thin, pleomorphic (Gram negative) rod, filamentous forms seen
   2. Growth media
      a. Requires amino acids, L-cysteine, ferric ions
      b. Cultured on buffered medium due to pH restrictions of organism
      c. Growth is slow, 2-5 days
   3. Identification by reference lab, epidemiology by health department using PCR
   4. Most human infections caused by *L. pneumophila*-Philadelphia strain

B. Microscopic examination of tissue required since Gram stain not useful
   1. Suspected in cases of severe progressive pneumonia with no known etiologic agent
   2. Organism rarely found in sputum
   3. Identification based on antigenic structure and DNA homology tests
      a. Indirect immunofluorescence of serum ⇒ rise in antibody titer to *Legionella* antigens
      b. Difficult to assess due to high exposure rates in population
   4. Lung aspirate, transtracheal aspirate, lung biopsy collected for examination
   5. Direct immunofluorescence positive in 25-50% of cases

*Mycoplasma pneumoniae*

I. Virulence factors relevant to Lower Respiratory Tract Infections

A. Adhesin
   1. Expressed as protrusion from surface of *M. pneumoniae*
   2. Binds sialic acid-containing glycolipids or glycoproteins on bronchial epithelial cells

B. Hydrogen peroxide and superoxide radicals secreted by organism damage tissue

C. Autoantibodies may be generated during infection
   1. Homology exists between host cell and mycoplasma membrane glycolipids
   2. Autoantibodies reactive to lymphocytes, smooth muscle, brain, lung tissue
FIGURE 37-5  Schematic presentation of a *M. pneumoniae* organism attaching to the surface of the ciliary tracheal epithelium, as seen by electron microscopy of a thin section. The clustering of the P1 adhesin on the surface of the attachment organelle at the tip of the mycoplasma is depicted. The $\text{H}_2\text{O}_2$ and $\text{O}_2^-$ excreted by the mycoplasma penetrate into the host cell and cause oxidative damage.
Figure 23.4.

(A) Transmission electron micrograph of *Mycoplasma* (short arrow) attached to cilia (long arrow) of respiratory epithelial cell. (Courtesy of Albert M. Collier, University of North Carolina at Chapel Hill.). (B) Negative staining of intact *Mycoplasma* cell. Note the flask like shape, the truncated tip, the nap (N) on the terminus extending distally to the area marked by the arrowhead.
II. Etiology / Pathogenesis
   A. *M. pneumoniae* is causative agent of acute atypical pneumonia
      1. Accounts for 20% of all cases of pneumonia
      2. 30% of pneumonia in teenagers caused by *M. pneumoniae*
      3. Nonpurulent otitis media can be second site infection
      4. Pneumonia is less severe than other bacterial pneumonias, called “walking pneumonia”
   B. Transmission
      1. Spread by droplet with very low infectious dose (100 organisms)
      2. Long-term shedding of infectious agent
         a. Organisms are shed in respiratory secretions for 2-8 days before onset of symptoms
         b. Shedding can occur for 14 weeks after onset
      3. Transmission is common in closed communities
   C. Pathogenesis
      1. Colonization of bronchial epithelium interferes with ciliary action
      2. Inflammation and exudate primary contributors to pathogenesis
      3. Bronchi initial site; plasma cells and macrophages infiltrate to involve alveoli
      4. Initial antibody response is IgM→IgG; sIgA also important
   D. Sequelae
      1. Immunopathology due to cross-reactive antibodies
      2. Potential complications include hemolytic anemia, aseptic meningitis, pancreatitis

III. Clinical identification of organism
   A. Morphology & Cultivation
      1. Sputum fails to show organisms, organism grows too slow for culture
      2. *Mycoplasma spp.* lack cell wall and have very small genome
      3. Cells are bound by triple membrane containing sterols
      4. Stain poorly, difficult to detect microscopically
      5. Slow growth in enriched liquid or solid media; require cholesterol for growth
   B. Serodiagnosis
      1. Serodiagnosis can be used to detect circulating antigens
      2. Detection of complement-fixing antibody
         a. Antibody to *M. pneumoniae* antigens is diagnostic
         b. Disease has long incubation period⇒ patient presents with high titers
   C. DNA hybridization and PCR also being developed for detection
**Chlamydia pneumonia**

I. Virulence factors relevant to Lower Respiratory Tract Infections

A. Elementary body (EB)
   1. Infectious stage carries adhesin for receptor binding
   2. Attaches to and induces endocytosis into columnar epithelial cells

B. Reticulate body (RB)
   1. EB becomes RB that replicates ⇒ ~1000/cell
   2. RB is metabolically active and uses host ATP-generating potential
   3. RB reorganizes ⇒ infectious EB that are released from cell

![Figure 29–1. Reproduction cycle of *Chlamydia*.](image-url)
II. Etiology / Pathogenesis

A. Pharyngitis, Bronchitis, Atypical Pneumonia
   1. Acute atypical (a.k.a. walking) pneumonia in school children and young adults
   2. 10% of pneumonia & 5% of bronchitis in young adults caused by *C. pneumoniae*
   3. Clinical picture resembles *Mycoplasma pneumoniae* infection

B. Humans are only host & ~50% of adults are seropositive, but reinfection is common

<table>
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<tr>
<th>CHARACTERISTICS OF CHLAMYDIA</th>
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<tr>
<td><strong>Species</strong></td>
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<tr>
<td><em>pneumoniae</em></td>
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<tr>
<td><em>trachomatis</em></td>
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<tr>
<td><em>psittaci</em></td>
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III. Clinical identification of organism

A. Morphology & Growth characteristics
   1. Gram negative outer membrane but no cell wall
   2. Cocccobacillary morphology

B. Detection techniques
   1. Direct immunofluorescent staining of outer membrane proteins
   2. DNA or RNA detected using probes and PCR
   3. *C. pneumoniae* does *not* form glycogen-containing inclusion bodies like *C. trachomatis*

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<th>SEROLOGIC DIAGNOSIS OF “ATYPICAL” PNEUMONIA</th>
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<tr>
<td><strong>Pathogen</strong></td>
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<tr>
<td><em>Mycoplasma pneumoniae</em></td>
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<tr>
<td><em>Legionella pneumophila</em></td>
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<tr>
<td><em>Chlamydia pneumoniae</em></td>
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<tr>
<td><em>Coxiella burnetii</em></td>
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**Staphylococcus aureus**

I. Etiology / Pathogenesis  
   A. Acute pneumonia  
      1. Secondary to some other insult to lung such as influenza  
      2. Pathology similar to other bacterial pneumonias  

   B. Empyema  
      1. Purulent infection of pleural space  
      2. *S. aureus* gains access by contiguous spread from infected lung  

   C. Lung abscess  
      1. Complication of acute or chronic pneumonia  
      2. May be caused by aspiration of oral or gastric contents  

I. Clinical identification of organism  
   A. Samples include sputum, lung abscess aspirate, blood culture for disseminated infection  
      1. Gram positive cocci in clusters  
      2. Catalase & Coagulase test positive  

   B. Antibiotic susceptibility assays necessary  

   C. Lung abscess is diagnosed radiologically
Mycobacterium tuberculosis

I. Virulence factors relevant to Lower Respiratory Tract Infections

A. Mycolic acid (a.k.a. cord factor) in cell wall
   1. Consists of long-chain (> 60 C) fatty acid
   2. Provides resistance to drying and most disinfectants
   3. Promotes hypersensitivity granuloma
   4. Promotes inflammatory response (TNFα), damage to lung tissue

B. Lipoarabinomannan
   1. Cell wall glycolipid
   2. Suppresses T cell proliferation, prevents macrophage activation

C. Sulfolipids (polyanionic lipids), inhibit macrophage phagosome-lysosome fusion

D. Catalase that degrades hydrogen peroxide

E. Ammonia production, prevents acidification in phagolysosome

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Figure 26-2  Schematic drawing of the cell wall of M. tuberculosis.
II. Etiology / Pathogenesis

A. Pathogenic *Mycobacteria spp.*
   1. *M. tuberculosis* is primary cause of TB
   2. *M. bovis* (infected milk) rarely causes TB, eradicated through pasteurization
   3. *M. africanum* is *M. tuberculosis* variant causing TB in Africa
   4. *M. avium* complex
      a. *M. avium* and *M. intracellulare* are opportunistic pathogens
      b. Cause disseminated infections in AIDS patients
   5. *M. leprae* causes leprosy (Hansen’s disease)
      a. Degenerative disease of skin and nerves
      b. Rare in the US

B. Epidemiology
   1. Annual infection rates worldwide
      a. 100 million infected
      b. 10 million contract disease
      c. Estimated mortality of 3 million people
      d. One infectious individual may spread to 20 contacts in underdeveloped country
   2. US infection rates
      a. Approximately 20,000 cases in the US with ~1,000 deaths
      b. Incidence among AIDS patients and immigrants is significant
      c. Outbreaks in closed communities (crowded nursing home, shelters, prisons)
   3. Chopin, Thoreau, Gibran, Vivien Leigh died of TB (a.k.a. consumption)
### PATHOGENIC MYCOBACTERIA

<table>
<thead>
<tr>
<th>species</th>
<th>clinical disease</th>
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<tbody>
<tr>
<td><strong>slow growers</strong></td>
<td></td>
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<tr>
<td><em>M. tuberculosis</em></td>
<td>tuberculosis</td>
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<tr>
<td><em>M. bovis</em></td>
<td>bovine tuberculosis</td>
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<tr>
<td><em>M. leprae</em></td>
<td>leprosy</td>
</tr>
<tr>
<td><em>M. avium</em></td>
<td><strong>disseminated infection in AIDS patients</strong></td>
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<tr>
<td><em>M. intracellulare</em></td>
<td></td>
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<tr>
<td><em>M. kansasii</em></td>
<td>lung infections</td>
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<tr>
<td><em>M. marinum</em></td>
<td>skin infections and deeper infections (e.g., arthritis, osteomyelitis) associated with aquatic activity</td>
</tr>
<tr>
<td><em>M. scrofulaceum</em></td>
<td>cervical adenitis in children</td>
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<tr>
<td><em>M. simiae</em></td>
<td>lung, bone and kidney infections</td>
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<tr>
<td><em>M. szulgai</em></td>
<td>lung, skin and bone infections</td>
</tr>
<tr>
<td><em>M. ulcerans</em></td>
<td>skin infections</td>
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<tr>
<td><em>M. xenopi</em></td>
<td>lung infections</td>
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<tr>
<td><em>M. paratuberculosis</em></td>
<td>? association with Crohn's disease</td>
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<tr>
<td><strong>rapid growers</strong></td>
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<tr>
<td><em>M. fortuitum</em></td>
<td>opportunist infections with introduction of organisms into deep subcutaneous tissues; usually associated with trauma or invasive procedures.</td>
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<tr>
<td><em>M. chelonae</em></td>
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*slow growers require >7 days for visible growth from a dilute inoculum; rapid growers require <7 days for visible growth from a dilute inoculum*

**M. avium** complex; recent studies show that the two species are distinct. Of the *M. avium* complex, serotypes 1–6 and 8–11 are assigned to *M. avium*, serotypes 7, 12–17, 19, 20 and 25 assigned to *M. intracellulare*

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*Fig. 17.20 Many species of mycobacteria are associated with occasional disease, but the major pathogens of the genus are *M. tuberculosis*, *M. bovis* and *M. leprae.*
C. Types of tuberculosis

1. Primary infection
   a. Inapparent in 95% of cases
   b. Localized lung lesion, delayed type hypersensitivity (DTH) reaction
   c. Gohn (primary) complex: lung granuloma + enlarged lymph nodes

2. Progressive primary tuberculosis
   a. Occurs in 5% of cases when primary infection does not resolve
   b. Disseminated infection, bloodborne or miliary TB (from millet seed)

3. Disseminated tuberculosis
   a. Dissemination through lymph or erosion of necrotic tubercle in lung
   b. Infection of liver, spleen, kidney, bone, meninges possible

4. Reactivation tuberculosis
   a. Low percentage of cases
   b. Incidence increases with age, alcoholism, diabetes, decreased immune function
   c. Reactivation risk increases 300-fold with acquisition of HIV
   d. Common site is apex of lung with highest oxygen tension

<table>
<thead>
<tr>
<th>STAGES OF PRIMARY TB</th>
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<tbody>
<tr>
<td>Stage</td>
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<table>
<thead>
<tr>
<th>DIFFERENCES BETWEEN PRIMARY &amp; POST-PRIMARY TB</th>
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<tbody>
<tr>
<td>Characteristics</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Local lesion</td>
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<tr>
<td>Lymphatic involvement</td>
</tr>
<tr>
<td>Cavity formation</td>
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<tr>
<td>Tuberculin reactivity</td>
</tr>
<tr>
<td>Infectivity (pulmonary)</td>
</tr>
<tr>
<td>Site</td>
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<tr>
<td>Local spread</td>
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</table>
D. Tuberculin skin test
1. Purified protein derivative (PPD)
   a. Autolyzed bacteria containing protein & lipid, polysaccharide, nucleic acid
   b. Injected under skin, reaction read in 48-72 hr.
2. DTH reaction to PPD
   a. Local induration and erythema is a positive reaction
   b. Positive tuberculin reaction seen 6 weeks after primary infection
3. Significance of positive DTH reaction to tuberculin
   a. Coincides with tubercle (hypersensitivity granuloma) formation
   b. Indicates exposure but not necessarily active disease
      i) Only ~5% of skin test positive cases progress to active disease
      ii) Reaction indicates exposure to *M. tuberculosis* or cross-reactive species
4. Significance of negative DTH reaction
   a. No exposure to organisms
   b. Individual may be in the prehypersensitivity stage (up to 6 weeks post-exposure)
   c. Loss of sensitivity due to disappearance of antigen from primary complex
   d. Anergy due to immunocompromise (poor prognostic indicator)
E. Pathogenesis of *M. tuberculosis*
1. Transmitted via aerosol, obligate aerobe ⇒ primary focus is lung
2. Engulfed by alveolar macrophages and carried to lymph nodes
3. Resists innate defenses (PMNs, inactivated macrophages, lysozyme)
4. Humoral response (IgM) weak, no effective complement-mediated killing
5. CMI response to infection
   a. Helper and cytotoxic T cells activate alveolar macrophages to ingest organism
   b. Activated macrophages can prevent replication of *M. tuberculosis*
   c. Inadequate response ⇒ organism can replicate in macrophage phagosome
   d. Slow replication rate contributes to pathogenesis
   e. Cytokine response to organism causes systemic TB symptoms (weight loss, fever)
6. Containment of pathogen in tubercle = microscopic granuloma
   a. Composition: multinucleated giant cells, activated macrophages, lymphocytes
   b. Granulomas can become necrotic and caseous (cheesy)
   c. Fibroblasts and collagen accumulate at lesion
   d. Tissue destruction causes chronic productive cough, blood-stained sputum
7. Potential fates of tubercle
   a. Become fibrotic or calcified with dead bacteria - will show up on chest X-ray
   c. Tubercle bacilli may remain dormant for years ⇒ source for reactivation
   d. Necrotic tubercle may erode into blood vessel ⇒ disseminated (miliary) TB
8. DTH reaction confers long-lived memory, protection from re-infection
   a. Loss of prior DTH = bad prognostic indicator ⇒ rapidly progressing disease
   b. DTH is basis of tuberculin skin test
Figure 26-1 Steps in the pathogenesis of TB.
III. Clinical identification of organism
A. Specimen collected: sputum, sometimes biopsy; blood with miliary TB
B. Staining of sputum important - provides diagnosis before bacteria will grow
   1. *Mycobacteria* considered Gram (+) but Gram stain poorly due to cell wall lipid
   2. Acid-fast bacillus (AFB) stain (e.g., Ziehl-Neelsen)
      a. Fuchsin (red) stain dissolved in phenol and heated to penetrate cell wall lipid
      b. Decolorize with acidified alcohol and counterstain with methylene blue
      c. *Mycobacteria* are acid-fast, other bacteria decolorize (except *Nocardia*)
   3. Chemotherapy is monitored by periodic examination for AFB counts
C. Cultivation of *M. tuberculosis*
   1. Sputum must be decontaminated (4% NaOH) to inhibit fast growing bacteria
   2. Very slow growth: 24 hr. doubling time (*E. coli* doubles in 20 min.)
      a. Appearance of visible colonies can take up to 2 weeks on solid media
      b. Solid media contains compounds to inhibit growth of contaminants
         i) Lowenstein-Jensen (LJ) agar most common
         ii) Middlebrook agar
D. Rapid identification procedures
   1. Growth in $^{14}$C-palmitic acid, catabolized into $^{14}$CO$_2$ that is measured
   2. rRNA and DNA probes
   3. PCR to detect insertion sequence common to *M. tuberculosis* strains
E. Drug susceptibility tests are done in reference labs (e.g., Michigan DPH)

*Pseudomonas aeruginosa*

I. Virulence factors relevant to Lower Respiratory Tract Infections
A. Adhesins
   1. Protein pilus adhesin for binding asialoGM1
   2. Non-pilus adhesin for binding to mucus
B. Alginate
   1. Polysaccharide capsule for biofilm formation
   2. Permits colonization of lung and evasion of host immune response
   3. Regulated in response to environmental signals
C. Elastase degrades lung elastin
D. Multiple resistance to antimicrobials and disinfectants
   1. Mutation leading to loss of porin and decreased entry of antimicrobials
   2. Alteration of LPS to form that does not bind antibiotics
II. Etiology / Pathogenesis
A. Acute pneumonia, empyema (pleural cavity), abscess

B. Infections in cystic fibrosis (CF) patients
   1. CF lung
      a. Increased mucus secretion
      b. Defect in cystic fibrosis transmembrane conductance regulator (CFTR)
      c. CFTR defect causes decreased sialylation of surface glycolipids
   2. CF lung more susceptible to colonization by *P. aeruginosa*
      a. *P. aeruginosa* is ubiquitous in the environment
      b. Adhesin binds to asilaoglycolipid on CF respiratory epithelium
   3. Resistance to phagocytosis
      a. *P. aeruginosa* infecting CF lung express phenotypic switch to mucoid form
      b. Alginate gel and excess mucus in CF lung provides physical barrier to phagocytosis
      c. Anti-pseudomonas antibodies in CF patients may be defective
   4. Resistance to antimicrobials
      a. Alginate gel and excess mucus in CF lung provides physical barrier to and drugs
      b. *P. aeruginosa* infection common in 15-20 year old age group
         i) Primary infection in younger age group caused by *S. aureus*
         ii) Colonizing *P. aeruginosa* strains develop resistance to anti-staphylococcal drugs
   5. Lung tissue damage
      a. Persistent colonization and protease (elastase) release by pathogen
      b. Recruited neutrophils release powerful protease that contributes to tissue damage
   6. Infection rarely extends beyond lungs in CF patients

III. Clinical Identification
A. Gram negative rods in sputum sample

   B. Aerobic, oxidase positive

   C. OF Dextrose tubes to demonstrate aerobic growth
Pathogenesis of *P. aeruginosa* in CF lung. Alginate and excess mucus protect bacteria from opsonization and antibiotics. Bacterial and phagocyte proteases contribute to lung damage.

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Classification</th>
<th>Syndrome</th>
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</thead>
<tbody>
<tr>
<td><em>Nocardia spp.</em></td>
<td>Gram positive rod</td>
<td>Chronic pneumonia &amp; Abscess</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>Gram negative rods</td>
<td>• Acute pneumonia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Empyema, Abscess</td>
</tr>
</tbody>
</table>

* These bacteria are opportunistic pathogens of the lower respiratory tract.
FUNGI CAUSING LOWER RESPIRATORY TRACT INFECTIONS

Aspergillus spp.

I. Virulence factors relevant to Lower Respiratory Tract Infections
   A. Infectious conidia that germinate to mold form
   B. Hyphae bind fibrinogen and complement components
   C. Aflatoxin produced by A. flavus growing on peanuts is potent carcinogen

II. Etiology / Pathogenesis
   A. Aspergillus spp. considered emerging etiologic agent of nosocomial pneumonia
      1. Opportunistic pathogen
      2. Predisposing factors to acute pneumonia:
         a. Asthma, chronic bronchitis, tuberculosis
         b. Immunosuppression is major contributing factor to opportunistic infection
   B. Aspergillus may cause acute pneumonia and lung abscess
      1. Common environmental mold
      2. Infection requires frequent inhalation of infectious conidia
      3. Allergic aspergillosis from inhalation of fungal elements or colonization
         a. Inhalation of large numbers of spores
         b. Referred to as Farmer’s lung
   C. Aspergillus may colonize the respiratory tract
      1. Colonization may lead to tissue invasion by hyphae
      2. Principal host defense is pulmonary neutrophil killing of invasive hyphae

III. Clinical identification of organism
   A. Lung aspiration, bronchial lavage, or biopsy required
      1. Mold form grows rapidly and is easily identified
      2. Aspergillus spp. has typical septate hyphae with conidia (spore)
   B. Radiologically visible fungus ball may form in pulmonary cavity

Fig. 17.25 Aspergillus fumigatus. (a) Lactophenol cotton blue stained preparation showing the characteristic conidiophores. (b) Aspergiloma. Tomogram showing fungus ball contained within the lung cavity, outlined by air space. (Courtesy of JA Innes.) (c) Invasive aspergillosis. Histologic section showing fungal hyphae invading the lung parenchyma and blood vessels. (Grocott stain) (Courtesy of C Kibbler.)
**Histoplasma capsulatum**

I. **Virulence factors relevant to Lower Respiratory Tract Infections**
   A. Dimorphic growth phases
      1. Mold in environment (22 °C) produces infectious conidia
      2. Conversion to pathogenic yeast form in tissue at 37 °C
   B. Capacity to grow in macrophages, survive oxidative burst

II. **Etiology / Pathogenesis**
   A. Environmental growth
      1. Grows in soil, esp. with abundance of bird and bat droppings
      2. Predominately found in Ohio and Mississippi River Valleys
   B. Pulmonary infection by inhalation of conidia
      1. Not transmitted person to person
      2. Primary infection site is pulmonary
      3. Inhaled conidia convert to pathogenic yeast form in host
   C. *H. capsulatum* causes a chronic pneumonia
      1. Grows inside macrophages
      2. Primary lesion resembles pulmonary tuberculosis
      3. Granulomatous inflammation and necrosis in pulmonary site
      4. May disseminate to infect organs of reticuloendothelial system
   D. Immune response
      1. T-cell activation of macrophages provides inhibition of intracellular growth
      2. Long-lasting immunity to reinfection

III. **Clinical identification of organism**
   A. Clinical samples
      1. Chest radiograph shows granulomas resembling TB
      2. Sputum sample not useful, blood or biopsy required
      3. Disseminated infection: biopsy of liver, spleen, and lymph nodes
      4. Bone marrow is good site for isolation of yeast cells
   B. Cultural isolation or histologic demonstration of infection required for firm diagnosis
      1. *H. capsulatum* grows slowly (weeks) on blood and Sabouraud agar
      2. Fungus appears dimorphic, yeast and mold forms
      3. Mold produces tuberculate macroconidia = finger-like projections carrying spores
   C. Serologic tests
      1. Widespread exposure and cross-reactivity with other pathogens
      2. DTH skin reaction to mycelial antigen used for epidemiologic analyses
      3. Complement fixing antibody test for yeast & mycelial antigens predicts prognosis
   D. Immunodiffusion test to detect mycelial antigen & DNA probe commercially available
Blastomyces dermatitidis

I. Virulence factors relevant to Lower Respiratory Tract Infections
   A. Similar to *Histoplasma capsulatum*:
      1. Dimorphic growth phases
      2. Mold at 22 °C and pathogenic yeast form in tissue at 37 °C
   B. Contrast to *H. capsulatum*: *B. dermatitidis* yeast cells extracellular, not in macrophages

II. Etiology / Pathogenesis
   A. Geographic distribution similar to histoplasmosis
      1. Middle and Southeastern US
      2. Occurs 10X more in males than in females - perhaps due to occupational exposure
   B. Pathogenesis
      1. Conidia inhaled from soil⇒ pulmonary infection with yeast cells
      2. Neutrophil infiltration and granuloma formation⇒ chronic pneumonia
      3. Chronic pneumonia may mimic pulmonary tumor or tuberculosis

Histologic section of the lung showing yeast forms of *Histoplasma capsulatum*. 
4. Dissemination to secondary sites possible
   a. Chronic infection of skin & bone most common
      i. Number of subclinical pulmonary cases disseminating to skin indeterminable
      ii. Necrosis and fibrosis at infected area ⇒ disfigurement
   b. Dissemination to urogenital tract also occurs
C. Immune response
   1. T cell-mediated response and cytokine-activated macrophages
   2. Large yeast cells resist oxidative and nonoxidative killing mechanisms

III. Clinical identification of organism
   A. Biopsy samples ⇒ large yeast cells with broad buds
   B. Growth on mycological media is very slow (4 wk.)
   C. Antigenic cross-reactivity with other fungi hampers serodiagnosis
      1. Immunodiffusion and complement fixation tests lack sensitivity
      2. There is no skin test

Tissue form of *Blastomyces dermatitidis*. Large, thick-walled yeast cells with broad buds.
**Coccidioides immitis**

I. Virulence factors relevant to Lower Respiratory Tract Infections
   A. Dimorphic growth phases
   B. Mold produces infectious arthroconidia
   C. Spherule is the invasive tissue form, produces reproductive endospores

II. Etiology / Pathogenesis
   A. Coccidiomycosis usually mild disease limited to Southwestern US
      1. “Valley fever” is acute pulmonary infection with cough, chest pain, myalgia
      2. Pulmonary form may become chronic pneumonia
         a. Chronic cases occur with decreased T-cell response (AIDS, chemotherapy)
         b. *C. immitis* may become disseminated (<1% of cases) to skin, bone, joints, meninges
   B. Pathogenesis
      1. Arthroconidia inhaled and convert to spherule
      2. Neutrophils and macrophages response
         a. Spherule grows too large for phagocytosis
         b. *C. immitis* can prevent phagolysosome fusion and survive phagocytosis
      3. Release of endospores from spherule induces strong inflammatory response
      4. Inflammatory response accompanied by granuloma formation, 15% of cases cavitate
   C. Immune response to *C. immitis* infection
      1. Cell mediated (PMN, T-cell) immunity to arthroconidia or endospores
      2. Chronic or progressive infection
         a. Accompanied by T cell anergy
         b. Increased B cell response ⇒ poor prognosis
         c. Strong T cell response accompanied by little antibody ⇒ good prognosis

III. Clinical identification of organism
   A. Detection of characteristic spherules in histologic sections is best diagnostic tool
   B. Organism may be cultured to observe mold form - but highly infectious
   C. Detection of complement-fixing antibodies indicates progression of disease
      1. Low titers ⇒ primary pulmonary disease with good cell mediated immune response
      2. High titers ⇒ disseminated disease and anergy
   D. Skin test detects DTH reaction to *C. immitis* antigens, but of limited value
      1. Coccidioidin skin test
         a. Positive 1-4 wk after onset
         b. Skin test is positive for life indicating immunity to reinfection
      2. Negative skin test may be due to:
         a. Performing test too soon after exposure
         b. Disease has progressed to anergy
   E. Immunodiffusion to detect mycelial antigen & DNA probe also available
**Coccidioides immitis spherule.** Spherule form may be detected in sputum or tissue sample. Note that this spherule has just burst releasing endospores.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen</th>
<th>Dimorphism</th>
<th>Distribution</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coccidiomycosis (Valley fever)</td>
<td><em>Coccidioides immitis</em></td>
<td>Hyphae (20°C) → Spherule (37°C)</td>
<td>Southwestern US, Mexico</td>
<td>Pulmonary, meningeal, osteomyelitis</td>
</tr>
<tr>
<td>Histoplasmosis</td>
<td><em>Histoplasma capsulatum</em></td>
<td>Hyphae (20°C) → Yeast (37°C)</td>
<td>Ohio &amp; Miss. River Valleys</td>
<td>Pulmonary, RE system</td>
</tr>
<tr>
<td>Blastomycosis</td>
<td><em>Blastomyces dermatitidis</em></td>
<td>Hyphae (20°C) → Yeast (37°C)</td>
<td>Middle &amp; Southeast US</td>
<td>Pulmonary, skin</td>
</tr>
</tbody>
</table>
**Pneumocystis carinii**

I. Etiology / Pathogenesis

A. *P. carinii* infection is very common
   1. *P. carinii* generally of low virulence
   2. Latent infections demonstrated by indirect immunofluorescence and lung biopsy
      - a. Serologic studies show that 75% of children have antibodies to *P. carinii* by age 4
      - b. Pneumocystosis in immunocompromised patients
          i. Disease may result from activation of latent infection
          ii. Patient to patient spread observed in cancer wards
          iii. Nursery epidemics amongst premature infants ⇒ aerosol transmission

B. *P. carinii* causes pneumonia in immunocompromised hosts:
   1. Premature infants
   2. Patients undergoing chemotherapy for cancer
   3. Organ transplant patients on suppressive therapy
   4. AIDS is primary predisposing factor for pneumocystosis in the US

C. Pneumocystosis is a presenting manifestation of AIDS
   1. >60% of AIDS patients develop pneumocystis pneumonia, 30-50% mortality rate
   2. Disease occurs due to loss of adequate T cell function
   3. Risk of pneumocystosis increases when CD4\(^+\) T cell count falls below 200 cells/mm\(^3\)

D. *P. carinii* can cause acute pneumonia, lethal pneumonitis
   1. Progressive, diffuse pneumonia following:
      - a. Corticosteroid use and leukemia
      - b. AIDS onset
          i. Onset in AIDS patients and the newborn is insidious
          ii. Lesions outside the lung may be seen with AIDS patients
   2. Concurrent infections with bacterial, fungal, parasitic or viral agents common
   3. Alveoli become filled with desquamated cells, organisms, monocytes, and fluid
      - a. Alveoli have characteristic “foamy appearance” with pneumocystis pneumonia
      - b. X-ray shows diffuse alveolar infiltrates

II. Clinical identification of organism

A. *P. carinii* is of uncertain classification: Fungus or Protozoan?
   1. Classified as protozoan based on morphology & drug susceptibility
      - a. Forms cysts that rupture to release sporozoites that mature to trophozoites
      - b. *P. carinii* is susceptible to antiprotozoal but not antifungal agents
   2. Classified as fungus based on rRNA sequence homology with other fungi
B. Sample collection

1. Sputum induced with hypertonic saline positive only in 50% of AIDS patients
   a. AIDS patients have insidious onset pneumocystosis & larger numbers of organisms
   b. Sputum sample not useful with other patients

2. Bronchoalveolar lavage and transbronchial biopsies are more helpful
   a. Positive in 90% of infected AIDS patients
   b. Positive in 50% of those with other predisposing conditions

C. Diagnosis by histology is definitive

1. Extracellular cysts & trophs seen in tissue by phase contrast or fluorescence microscopy
   a. Variety of stains (e.g. Giemsa, Wright, Gram) used for cysts
   b. Immunofluorescence using monoclonal antibody to P. carinii available

2. Latent infections characterized by scattered cysts in contact with alveolar cells

3. Only rodent strains of P. carinii have been cultivated

4. PCR for detection of P. carinii

Stages in the life cycle of Pneumocystis carinii
Lung biopsy containing *Pneumocystis carinii* cysts

D. Diagnosis of Pneumocystosis by symptoms

1. Fever is mild or low grade
2. Typical signs of pneumonia are absent - cough is nonproductive
3. Progressive dyspnea (shortness of breath) and tachypnea (rapid breathing rate)
4. Cyanosis (blue skin) and hypoxia (decrease oxygen to tissues)
5. Death is by asphyxiation
CASE STUDY FOR
LOWER RESPIRATORY TRACT INFECTIONS

An outbreak of severe pneumonia with several fatalities among the residents of a nursing home was traced to contaminated respiratory therapy equipment. Specimens were collected from the equipment and grown using special culture media. The causative agent was eventually isolated from the cytoplasm of fresh water protozoa living on the respiratory equipment.

Questions:
1. What is the most likely etiologic agent causing this outbreak?
2. How does this pathogen survive inside macrophages?
3. What age group is most susceptible to pneumonia caused by this pathogen?
4. What is the incubation period for symptoms to appear?