Respiratory infections
Community acquired pneumonia: a review of common pathogens

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Respiratory tract anatomy
CAP: general principles

• Pathogenesis
• Clinical presentation
• Diagnostic work up
• Specific organisms:
  – Bacteria (e.g. *S. pneumoniae*)
  – Viral (e.g. Influenza)
  – Fungi (e.g. Histoplasma)
  – Other (e.g. Mycobacterium tuberculosis)

Community acquired pneumonia: CAP

• 5.6 million cases annually = 8-15 per 1000 persons per year
• *Very young* and *very old* usually have highest rates of disease
• Seasonal and geographic variation: WINTER!
• 3 groups for patient management
  – Outpatient, inpatient (non-intensive care unit (ICU), and ICU
• Etiology:
  – *Streptococcus pneumoniae* (#1)
  – “Atypical organisms”
  – Viral (e.g. RSV, influenza, adenovirus)
  – Gram negative
  – Other
Pathogenesis

• Lungs Defenses:
  – Innate (mucociliary escalator/phagocytes and acquired host defenses lungs-antibodies from vaccines)

• Why do you get CAP?
  – Alteration in host defenses, virulent organism or large innoculum

• How do you get CAP?
  – Micro-aspiration, hematogenous, contiguous spread, or macro-aspiration

Predisposing host conditions

• Environmental: smoking, alcoholism (altered conscienciousness), toxic inhalations, travel/geographic

• Altered lung architecture/function: cystic fibrosis, chronic obstructive lung disease (COPD), immotile cilia syndrome, Kartagener's syndrome (ciliary dysfunction, situs inversus, sinusitis, bronchiectasis)

• Altered immune system: chemotherapy, transplant, HIV, malnutrition, uremia, etc
Microbiology of CAP bacteria

- "Typical" organisms
  - S. pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Group A streptococci, Moraxella catarrhalis, anaerobes, and aerobic gram-negative bacteria.

- "Atypical" refers to pneumonia caused by Legionella spp, Mycoplasma pneumoniae, Chlamydophila (formerly Chlamydia) pneumoniae, and C. psittaci

## Microbial causes of CAP in childhood

<table>
<thead>
<tr>
<th>Age</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth to 3 weeks</td>
<td>Group B Streptococcal, Gram negative enteric bacilli, Cytomegalovirus, Listeria monocytogenes, HSV</td>
</tr>
<tr>
<td>3 weeks- 3 months</td>
<td><em>Chlamydia trachomatis</em>, Respiratory syncycial virus (RSV), Parainfluenza virus type 3 (PIV), <em>Streptococcus pneumoniae</em>, <em>Bordetella pertussis</em>, <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>3 months - 5 years</td>
<td>RSV, PIV, influenza, adenovirus, rhinovirus, <em>Streptococcus pneumoniae</em>, <em>Haemophilus influenzae</em>, <em>Mycoplasma pneumoniae</em>, <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>5-15 years</td>
<td><em>Mycoplasma pneumoniae</em>, <em>Chlamydia pneumoniae</em>, <em>Streptococcus pneumoniae</em>, <em>Mycobacterium tuberculosis</em></td>
</tr>
</tbody>
</table>
### Table 6. Most common etiologies of community-acquired pneumonia.

<table>
<thead>
<tr>
<th>Patient type</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td><em>Streptococcus pneumonia</em>, <em>Mycoplasma pneumoniae</em>, <em>Haemophilus influenzae</em>, <em>Chlamydophila pneumoniae</em>, Respiratory viruses&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Inpatient (non-ICU)</td>
<td><em>S. pneumoniae</em>, <em>M. pneumoniae</em>, <em>C. pneumoniae</em>, <em>H. influenzae</em>, <em>Legionella species</em>, Aspiration, Respiratory viruses&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Inpatient (ICU)</td>
<td><em>S. pneumoniae</em>, <em>Staphylococcus aureus</em>, <em>Legionella species</em>, Gram-negative bacilli, <em>H. influenzae</em></td>
</tr>
</tbody>
</table>

<sup>a</sup>Influenza A and B, adenovirus, respiratory syncytial virus, and parainfluenza.

### Table 8. Epidemiologic conditions and/or risk factors related to specific pathogens in community-acquired pneumonia.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Commonly encountered pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism</td>
<td><em>Streptococcus pneumonia</em>, oral anaerobes, <em>Klebsiella pneumoniae</em>, <em>Acinetobacter species</em>, <em>Mycobacterium tuberculosis</em></td>
</tr>
<tr>
<td>COPD and/or smoking</td>
<td><em>Haemophilus influenzae</em>, <em>Pseudomonas aeruginosa</em>, <em>Legionella species</em>, <em>S. pneumoniae</em>, <em>Moraxella catarrhalis</em>, <em>Chlamydophila pneumoniae</em></td>
</tr>
<tr>
<td>Aspiration</td>
<td>Gram-negative anaerobic pathogens, oral anaerobes</td>
</tr>
<tr>
<td>Lung abscess</td>
<td><em>CA-MRSA</em>, oral anaerobes, endemic fungal pneumonia, <em>M. tuberculosis</em>, atypical mycobacteria</td>
</tr>
<tr>
<td>Exposure to dust or bird droppings</td>
<td><em>Histoplasma capsulatum</em></td>
</tr>
<tr>
<td>Exposure to birds</td>
<td><em>Chlamydophila psittaci</em>, poultry, avian influenza</td>
</tr>
<tr>
<td>Exposure to rabbits</td>
<td><em>Francisella tularensis</em></td>
</tr>
<tr>
<td>Exposure to farm animals or parturient cats</td>
<td><em>Clostridium perfringens</em> (Q fever)</td>
</tr>
<tr>
<td>HIV infection (early)</td>
<td><em>S. pneumoniae</em>, <em>H. influenzae</em>, <em>M. tuberculosis</em></td>
</tr>
<tr>
<td>HIV infection (late)</td>
<td>The pathogenic listed for early infection plus <em>Pneumocystis jiroveci</em>, <em>Cryptococcus</em>, <em>Histoplasma</em>, <em>Aspergillus</em>, atypical mycobacteria (especially <em>Mycobacterium kansasi</em>, <em>P. aeruginosa</em>, <em>H. influenzae</em>)</td>
</tr>
<tr>
<td>Host or cruise ship stay in previous 2 weeks</td>
<td><em>Legionella species</em></td>
</tr>
<tr>
<td>Travel to or residence in southwestern United States</td>
<td><em>Coccidioides species</em>, <em>Klebsiella</em></td>
</tr>
<tr>
<td>Travel to or residence in Southeast and East Asia</td>
<td><em>Burkholderia pseudomallei</em>, avian influenza, SARS</td>
</tr>
<tr>
<td>Influenza active in community</td>
<td><em>Influenza</em>, <em>S. pneumoniae</em>, <em>Staphylococcus aureus</em>, <em>H. influenzae</em></td>
</tr>
<tr>
<td>Cough&gt;2 weeks with whoop or posttussive vomiting</td>
<td><em>Bordetella pertussis</em></td>
</tr>
<tr>
<td>Structural lung disease (e.g., bronchiectasis)</td>
<td><em>Pseudomonas aeruginosa</em>, <em>Burkholderia cepacia</em>, <em>S. aureus</em></td>
</tr>
<tr>
<td>Injection drug use</td>
<td><em>S. aureus</em>, <em>anaerobes</em>, <em>M. tuberculosis</em>, <em>S. pneumoniae</em></td>
</tr>
<tr>
<td>Endobronchial obstruction</td>
<td><em>Anaerobes</em>, <em>S. pneumoniae</em>, <em>H. influenzae</em>, <em>S. aureus</em></td>
</tr>
<tr>
<td>In context of bioterroism</td>
<td><em>Bacillus anthracis</em> (anthrax), <em>Yersinia pestis</em> (plague), <em>Francisella tularensis</em> (tularemia)</td>
</tr>
</tbody>
</table>

<sup>Note</sup>: CA-MRSA, community-acquired methicillin-resistant *Staphylococcus aureus*; COPD, chronic obstructive pulmonary disease; SARS, severe acute respiratory syndrome.
Pneumonia: presentation and working up the etiology

- **Common complaints**
  - Dyspnea, fever, cough (productive or not), chills, chest pain, myalgia, headache
- **History**
  - Age, co-morbidities, sick contacts, unusual exposures, social situation/support
- **Physical exam findings**
  - Oxygen saturation
  - Rales, tactile fremitus, decreased breath sounds, rhonchi
- **Radiology**
  - Confirming the diagnosis; may or may not help narrow the diagnosis e.g. *S. pneumoniae*: lobar; *S. aureus*: multilobar/abscess; Mycoplasma- diffuse interstitial

Clinical scenario 1

- Francisco is a 2 year old, previously well
- Presented with URI symptoms and fever to PMD in July
- Respiratory symptoms worsened, cxr revealed right sided pneumonia, WBC 24K with 80% PMN and 3% bands
- Initially treated with IV therapy without resolution in 4 days
- CT scan showed large right sided effusion
Complicated pneumonia with empyema
**Streptococcus pneumoniae**

- Gram-positive; oval or lancet-shaped, occur in pairs or short chains (diplococci)
- Capsular polysaccharide is most important virulence factor; approximately 90 capsular types
  - Most common serotypes are 6, 14, 18, 19, and 23
- Organism causes pneumonia, meningitis, otitis media, sinusitis, bacteremia, pericarditis, arthritis
From colonization to disease

- **Adherence** - cell wall proteins (phosphorylcholine) allow for adherence to receptor for platelet activating factor. Other binding sites include sialic acid and N-acetylglactosamine b1-4 galactose
  - Facilitated by viral infections
- **Secretory IgA protease** - inhibits function of secretory IgA which normally binds bacteria to mucin to facilitate clearance from the respiratory tract
- **Capsule** - antiphagocytic
- **Invasion** - cell wall, adhesins, and the cytotoxin pneumolysin promotes intra-alveolar replication, penetration of pneumococci from the alveoli into the interstitium, and dissemination of the organisms into the bloodstream and cell death
- **Host inflammatory response** - cell wall (lipoteichoic acid) initiates alternative complement pathway, induce production of cytokines, nitric oxide (tissue damage), and PAF and initiate influx of neutrophils

Risk factors for pneumococcal pneumonia

- Alcohol, smoking, and asthma
- Hyposplenism or splenectomy
- Immunocompromised (HIV, chemotherapy, etc)
- Others

Risk factors resistance to β-lactam antibiotics

- Age >65
- Recently taking antibiotics within 3 months
- Alcoholism
- Immune suppression
- Multiple medical co-morbidities
- Exposure to child in daycare
**S. pneumoniae**

- **Diagnosis**
  - Blood culture
    - (6-10% CAPs are bacteremia and 60% of these are *S. pneumoniae*)
  - Urine antigen test
  - Sputum culture
- **Antimicrobial susceptibility testing is key especially**
  - Penicillin: 60% susceptible, 20% intermediate, 20% resistant

**S. Pneumoniae**

**treatment and prevention**

- **Treatment: Beta-lactam antibiotics**
  - PCN Resistance classified by breakpoints
    - Meningitis (only a fraction of plasma concentration gets in to CSF):
      - Sensitive MIC ≤ 0.6
      - Intermediate MIC 0.1–1 mcg/ml
      - Resistant MIC ≥ 2 mcg/ml
    - Non-meningitis pneumococcal disease
      - Susceptible — MIC ≤2 mcg/mL
      - Intermediate — MIC =4 mcg/mL
      - Resistant — MIC ≥8 mcg/mL
  - Cephalosporins, vancomycin, macrolides, linezolid
- **Prevention: Vaccines**
  - Conjugated pneumococcal vaccine (Prevnar®)
  - 23 valent pneumococcal vaccine (Pneumovax®)
Clinical scenario 2

- Myra is a 21 year old medical student living in the dorm room studying for exams
- She goes to student health complaining of low grade fever, headache, non-productive cough, sore throat and general malaise
- Her exam reveals mild fine inspiratory rales-nothing impressive
- The Dr sends her for an xray that reveals bilateral infiltrates

Mycoplasma pneumonia
Mycoplasma

- Does not have a cell wall
- Cell membrane contains sterols not present in other bacteria
- Special enriched media needed for growth
- Laboratory cultures rarely done- diagnosis usually by serology (IgG)
- PCR testing not routinely available
- Bedside test- cold agglutinins

Mycoplasma- pathogenesis and immunity

- Toll-like receptor 2 important for binding to respiratory epithelium
- P1- protein attachment factor- facilitates attachment to sialic acid receptors of respiratory epithelium and RBC surface
- Remains extracellular
- Causes local destruction of cilia, interferes with normal airway clearance which leads to mechanical irritation and persistent cough
- Acts as a super antigen stimulating PMS’s and macrophages to release cytokines (TNFα, IL1, and IL 6)
A common atypical pneumonia
“Walking pneumonia”

- Lacks seasonal pattern, spread by droplet secretions
- Common in children and young adults
  - 7-20% of CAP especially for non-hospitalized cases
- Mild respiratory symptoms
- Complications: otitis media, erythema multiforme, hemolytic anemia, myocarditis, pericarditis, neurologic abnormalities
- Treatment: macrolides (erythromycin, azithromycin, clarithromycin) or fluoroquinolones (levofloxacin)

Erythema multiforme
Clinical scenario 3

- JM 10 week old infant born to a 16 year old mom
- Pregnancy history limited due to lack of prenatal care but baby born full term, no complications, left hospital 2 days
- Seen by pediatrician at 2 weeks old with eye discharge was given eye drops
- Returned to ER: RR 60, cough but no fever
- Xray done and bloods drawn

\[ C. \textit{trachomatis} \text{ xray} \]
Chlamydophila (Chlamydia) pneumonias: \textit{trachomatis, pneumoniae, psittaci}

- Intracellular parasites - use host high energy phosphate compounds
- Trilaminar outer membrane which contains LPS
- Two phase life cycle - Elementary body (infectious) and reticulate body (divides by binary fission in the host)

Chlamydia pneumonias

- Infect non-ciliated columnar cells
- Multiply in alveolar macrophages
- Perivascular and peribronchiolar infiltrates
- Clinical symptoms due to host immune response
- Immunity not long-lasting
- Diagnosis by serology - four fold rise in titer
**C. trachomatis pneumonia**

- Neonatal infection presents at 1-3 months of age
- Staccato-like cough, rapid respiratory rate
- NO FEVER
- Evaluation: minimal chest findings, x-ray hyperinflation and diffuse infiltrates, peripheral eosinophilia
- Treatment: erythromycin
- Prevention: maternal screening

**C. pneumoniae**

- Single strain- TWAR
- Prolong incubation period
- Common in school age children and elderly (over 65)
- Indolent course-sore throat, chronic cough, no fever
- Chest x-ray variable (lobar, diffuse, bilateral)
- Diagnosis: PCR and serology
- Treatment: macrolide, doxycycline, levofloxacin
C. psittaci

- History: Parrot exposure
- Mild clinical respiratory symptoms, fever, rash
- Concomitant symptoms: CNS- headache, confusion, cranial nerve palsy, seizures; hepatitis; pericarditis
- Xray-consolidation, reticular nodular pattern, adenopathy
- Titers: > 1:64 diagnostic
- Treatment: doxy, tetracycline, erythromycin

Psittacosis
Clinical scenario 4

- Charlie is a 68 year old retired plumber who recently underwent a renal transplantation
- Felt great and was tinkering around his house updating his bathroom fixtures
- Came for follow up visit complaining of high fever, cough, chills and his wife said that he was acting confused at times
- Laboratory studies reveal WBC 35,000 with left shift, LDH >1000
- Chest xray reveals multilobar process
Legionella species

The 1976 Legionnaire’s Convention, Philadelphia, PA

- 29/180 patients died due to pneumonia
- Identification of a gram negative bacilli
- Epidemiologic link to being in the lobby of Hotel A; historical link to 1966 outbreak in a psychiatric hospital
- National panic- worries about biologic and chemical warfare- media frenzy
- 6 months to identify the organism
**Legionella pneumophila and micdadei**

- 2-6% community acquired pneumonias
- Risk: immunocompromised, hospitalized, and outbreak situations
- Gram negative bacilli- don’t stain with common reagents
- 50 species and 70 serogroups- most common *L. pneumophila* and most common serogroups 1, 4, 6
- Fastidious and grow on supplemented media
- Organisms contaminate water sources: air conditioning systems and water tanks

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**Legionella: pathogenesis and immunity**

- Aspiration or inhalation of organism
- Flagellae and pili allow attachment to respiratory epithelium and macrophages
- Trafficking within cell due to dot (defective organelle trafficking) and icm (intracellular multiplication) genes which allow the organism to evade phagosome-lysosome fusion
- Intracellular replication facilitated by intracellular multiplication locus (Lgn-1) and by Mip
- Virulence factors: exotoxins, including a hemolysin, cytotoxin, deoxyribonuclease, ribonuclease, and various proteases cause destruction by killing the infected respiratory cells leading to formation of microabscesses
- Immunity primarily cell mediated immunity (T cells) (inhibited by glucocorticoids and immune suppressive agents e.g. transplant medications)
Legionnaires disease

- Incubation period up to 10 days
- Clinical- influenza like illness or severe manifestation= pneumonia
- Fever (105), rigors, cough, headache
- Multilobular infiltrates and microabscesses
- Extrapulmonary manifestations: CNS, diarrhea, abdominal pain, nausea
- High white counts, abnormal liver, renal panel
- High mortality-15-20% depending on host

Legionella: Diagnosis, prevention and treatment

- Urine antigen detection assays- EIA for L. pneumophila only
- Serology >1:128 positive however late development of antibodies
- Culture on special media
- Treatment: macrolide or levofloxacin
- Prevention: hyperchlorination, super heating, continuous copper-silver ionization
Clinical scenario 5
(Loyola Univ Medical Center)

- Jerry, a 7 month old child, comes to clinic with a running nose, sneezing and slightly irritable
- Diagnosed with URI
- Returns 2 weeks later because he is turning blue with coughing spells. Spells are worse at night, seems to have spasms and then he “whoops” for air.
- Examination reveals mildly dehydrated, not distressed, clear lung exam
- WBC reveals leucocytosis with lymphocytosis

Bordetella pertussis
Pertussis

- Affects children under 1 and adults with waning immunity
- Three stages of disease:
  - Catarrhal
  - Paroxysmal
  - Convalescent

Pertussis clinical symptoms
Bordetella pertussis  
“Whooping cough” 
- Fastidious, gram negative coccobacilli 
- *Pertussis, parapertussis, and bronchiseptica* 
- Spread by respiratory droplets 
- Rapid multiplication in mucus membrane 
- No bacteremia 
- Toxins cause local tissue damage 

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Binding and uptake by phagocytic cells
Pertussis toxin

G protein and ADP ribosylation
Toxin production and pathophysiology

<table>
<thead>
<tr>
<th>Pertussis toxin- ↑ CAMP</th>
<th>↑ secretions (paroxysmal stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenylate cyclase and hemolysin toxin</td>
<td>Inhibit WBC chemotaxis, phagocytosis, and killing</td>
</tr>
<tr>
<td>Heat-labile toxin</td>
<td>Local tissue destruction</td>
</tr>
<tr>
<td>Tracheal cytotoxin</td>
<td>Destroys ciliated cells, IL-1 (fever), NO (kills epithelial cells)</td>
</tr>
<tr>
<td>Lipid A and Lipid X</td>
<td>Activate alternative complement, cytokine release</td>
</tr>
</tbody>
</table>

Pertussis: diagnosis, Rx and prevention

- **Diagnosis:**
  - Special media- Bordet-Gengou- blood, charcoal, and starch.
  - Nasopharyngeal culture
  - Serologic testing: acute and convalescent titers
  - PCR testing
- **Treatment- decrease symptoms and transmission- best if early in disease**
  - Erythromycin or Macrolide (better tolerated, shorter course)
  - Alternative for some: trimethoprim-sulfamethoxazole
- **Prevention**
  - Antimicrobial prophylaxis- close contacts and high risk individuals
  - Vaccination- during childhood and booster vaccine for those over 18 (Tdap)
Summary: Community acquired pneumonia CAP

- Understand historical elements, physical examination finding and exposures relative for CAP
- Inpatient or outpatient management
  - Perform diagnostic tests
- Empirical antimicrobial therapy
- Prevention: smoking cessation, vaccination, etc
"The bad news is, there is no cure for the common cold. The good news is, I think you have pneumonia."