Respiratory infections
Community acquired pneumonia: a review of common pathogens

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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 (St)
  - “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 inoculum
- How do you get CAP?
  - Micro-aspiration, hematogenous, contiguous spread, or macro-aspiration

Predisposing host conditions
- Environmental: smoking, alcoholism (altered conscientiousness), 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

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)
Microbiology of CAP bacteria

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

• "Atypical" refers to pneumonia caused by Legionella spp, Mycoplasma pneumoniae, Chlamydia pneumoniae, formerly Chlamydia pneumoniae, and C. psittaci.

Microbial causes of CAP in childhood

<table>
<thead>
<tr>
<th>Age</th>
<th>Organisms</th>
</tr>
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<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>Chlamydia trachomatis, Respiratory syncytial virus (RSV), Parainfluenza virus type 3 (PIV), Streptococcus pneumoniae, Bordetella pertussis, Staphylococcus aureus</td>
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<tr>
<td>3 months - 5 years</td>
<td>RSV, PIV, influenza, adenovirus, rhinovirus, Streptococcus pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae, Mycobacterium tuberculosis</td>
</tr>
<tr>
<td>5-15 years</td>
<td>Mycoplasma pneumoniae, Chlamydia pneumoniae, Streptococcus pneumoniae, Mycobacterium tuberculosis</td>
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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
**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 steric acid and N-acetylgalactosamine 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
- Immuno compromised (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 mcg/ml
    - Intermediate MIC 0.1-1 mcg/ml
    - Resistant MIC ≥ 2 mcg/ml
  - Non-meningitis pneumococcal disease:
    - Susceptible — MIC ≤2 mcg/mL
    - Intermediate — MIC >2 mcg/mL
    - Resistant — MIC ≥8 mcg/mL
  - Cephalosporins, vancomycin, macrolides, linezolid
- **Prevention: Vaccines**
  - Conjugated pneumococcal vaccine (Prevnar®)
  - 23 valent pneumococcal vaccine (Pneumovax®)

**Mycoplasma pneumonia**

- **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)**

**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
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)

C. trachomatis xray

Erythema multiforme

Chlamyphila (Chlamydial) pneumonias: 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)

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

Chlamyphila 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. trichomatis pneumonia**

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

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**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 xray variable (lobar, diffuse, bilateral)
- Diagnosis: PCR and serology
- Treatment: macrolide, doxycycline, levofloxacin

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**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

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**Psittacosis**

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**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: 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 (Lgm-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)

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

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  

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  

Pertussis  

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

Binding and uptake by phagocytic cells
Pertussis toxin

- G protein and ADP ribosylation

Toxin production and pathophysiology

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Pertussis toxin ↑ CAMP</td>
<td>↑ secretions (paroxysmal stage)</td>
</tr>
<tr>
<td>Adenylate cyclase and</td>
<td>Inhibit WBC chemotaxis, phagocytosis, and killing</td>
</tr>
<tr>
<td>hemolysin toxin</td>
<td></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>
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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

FIGURE 1: Number of reported pertussis cases, by year — United States, 1922–2008

0 50 100 150 200 250 300
0 50 100 150 200 250 300

Year

Cases (thousands)

Cases (thousands)
"The bad news is, there is no cure for the common cold. The good news is, I think you have pneumonia."