Respiratory Tract Infections Monograph

Dr. Forsythe will be presenting a case-based discussion on Respiratory Tract Infections on November 29, 2018 at 8:30am.

The material presented in the following monograph should be used for students to prepare for the case-based discussion.

Session Objectives
- Summarize the syndromes under the heading “upper respiratory tract infection”, their most common etiologic agents, characteristic clinical presentations
- Define the following pneumonia syndromes and implicated pathogens
  - Community-acquired bacterial pneumonia
  - Community-acquired viral pneumonia
  - Hospital-acquired (nosocomial) pneumonia
  - Aspiration pneumonia
  - Chronic pneumonia
  - Necrotizing pneumonia and lung abscess
  - Pneumonia in the immunocompromised host
- Explain the predisposing factor to the development of pneumonia, characteristic signs and symptoms, and approach to diagnosis
- Outline an empiric plan of antibiotic treatment for community acquired pneumonia in adults. Distinguish antibiotic regimens for outpatient management versus inpatient management and the rationale (ie what micro-organisms are being covered)
- Outline an empiric plan of antibiotic treatment for hospital acquired pneumonia and aspiration pneumonia and the rationale (ie what micro-organisms are being covered)
- Compare and contrast “lobar pneumonia” vs “bronchopneumonia”

During this monograph and the in-class discussion on respiratory tract infections we will be revisiting bacteria covered earlier in the MHD course and antibiotics covered in the Pharmacology and Therapeutic course. Viruses will be noted as etiologic agents of respiratory infections; formal lectures on viruses will be delivered in MHD II.

Upper Respiratory Tract Infections (URIs)
URI’s are the most common infections in the United States, with 75 million physician visits per year.

The syndromes under the designation of URI are
- Rhinitis
- Sinusitis
- Otitis
- Pharyngitis
• Laryngotracheitis
• Epiglottitis
• Bronchitis
There is a seasonal predisposition (fall/winter) to URIs.
The vast majority of these syndrome are **viral and self-limited** and therefore do not require specific antimicrobial treatment.

**Infectious Rhinitis**
“Rhinitis” refers to “a runny nose”; there are multiple potential causes of rhinitis – including infections, allergies, over-use of nasal decongestants, systemic diseases (such as granulomatosis with angitis)
Infectious rhinitis is synonymous with the **“common cold”**.

**Viruses** are the etiologic agents in the vast majority of infectious rhinitis:
Rhinovirus (30%), coronavirus (10%), parainfluenza, influenza, Respiratory Syncytial Virus (RSV), adenovirus

No etiologic agent is identified in >50% of patients with infectious rhinitis simply because
a) the specific cause is not investigated and
b) knowing the specific cause will not change management.

**Acute Sinusitis**
Acute sinusitis refers to an infection in the sinuses themselves. Acute sinusitis is commonly preceded by acute or chronic rhinitis. Impairment of drainage of the sinuses by inflammatory edema of the mucosa is an important contributor to the pathogenesis of acute sinusitis.

The diagnosis for acute infection is a **clinical diagnosis** – patients have congestion, sinus tenderness, fevers, purulent nasal drainage

Obtaining sino-nasal cultures in general is not helpful.

Most (>90%) are viral in etiology; the minority are bacterial are represent bacteria in the oronasal cavity: *S pneumoniae, H. influenzae, Moraxella* and oral anaerobes

**Treatment:** Because the majority of etiologic agents are Viral, for the vast majority of patients, the most appropriate treatment is **NO antibiotics.** However, antibiotics are, unfortunately, still frequently prescribed for patients presenting with acute sinusitis symptoms resulting in inappropriate antibiotic overuse.

If there is strong clinical evidence or suspicion of bacterial sinusitis, antibiotics with spectrum against upper airway bacteria are first line: ampicillin or amoxicillin or trimethoprim-sulfamethoxazole or amoxicillin-clavulanate

**Pharyngitis**
Pharyngitis refers to infection/inflammation of the pharynx.
Patients characteristically present with sore throat and fever.
The etiology is viral in 70% of cases.

“Strep throat” is a pharyngitis caused by group A or B beta hemolytic Streptococcus that presents with high fevers and patchy tonsillar exudates. **Treatment prevents the complications** (rheumatic fever and post strep glomerulonephritis) but does not change the course/duration of the pharyngitis itself.

If can be difficult to differentiate between viral and bacterial pharyngitis on the basis of clinical findings alone, therefore a throat culture or rapid diagnostic test should be performed to detect Streptococcal infection.

**Epiglottitis**
Epiglottitis is infection of the epiglottis.

Epiglottitis occurs most often in children 2-7 years of age. Patients with epiglottitis typically present with high fever, sore throat, drooling, sitting upright and signs of systemic toxicity.

Swelling of the epiglottis and surrounding structures can result in **airway compromise and complete airway obstruction** which is a **medical emergency**.

Radiographs of the lateral neck may show an enlarged epiglottis protruding from the anterior wall of the hypopharynx - the so-called “thumb sign”.

Many patients will have positive blood cultures positive for the causative bacteria.

The most common etiologic organisms are Haemophilus influenzae, Group A strep, and *Haemophilus parainfluenzae*.
Fortunately with immunization of infants against *H. Influenzae* B, epiglottitis is being seen less commonly.

Treatment: Emergent evaluation by an otolaryngologist to assess and secure the airway; Antibiotic therapy: amoxicillin-clavulanate or ampicillin-sulbactam or 3rd generation cephalosporin

**Acute bronchitis**
Acute bronchitis refers to infection/inflammation of the large upper airways.
It is common- the 9th most common cause of all outpatient visits; incidence is higher in the fall/winter
The typical presentation is cough for >5 days with purulent sputum production.

Etiologic agents are most commonly **viral**: influenza, parainfluenza, respiratory syncytial virus (RSV) coronavirus, adenovirus, rhinovirus
Bacterial causes include mycoplasma, *Strep pneumoniae, Haemophilus influenzae, Bordetella pertussis*.

A bit more on Bordetella: In children, *Bordetella pertussis* presents as “whooping cough”.
Adults who are infected with *B. pertussis* (because their protection from immunization has waned if not re-immunized) can present with a protracted cough. Treatment is effective only if diagnosed early. Treatment consists of supportive care (rest, drink fluids). Routine antibiotics are not suggested since most cases of acute bronchitis are caused by viruses. Cough syrups and anti-tussives generally do not have much effect. In large trials, mucolytics, which pull fluid into the airways to make the mucus less viscous and easier to cough up, have not been shown to be of much effect either.

**Lower Respiratory Tract Infections**

**Pneumonia** refers to lower airway infection and inflammation.

Pathogens can reach the lungs by one of five routes:
- Direct inhalation; aspiration of upper airway contents; spread along the mucous membrane surface; hematogenous spread; and rarely direct penetration

Epidemiology: There are 5.6 million cases of pneumonia annually and 1.7 million hospital admissions.

Despite the invention of penicillin, the mortality rate of pneumonia has not improved over the years (outpatient mortality 1-5%; inpatient mortality 15-20%). To put mortality into perspective – pneumonia and influenza are the 6th leading causes of death (and the leading causes of death from infection)

Clinical predisposing factors for pneumonia include:
- Old age
- Underlying pulmonary disease
- Smoking (results in injury to mucociliary apparatus resulting in decreased airway clearance)
- Recent viral illness (also results in injury to mucociliary apparatus resulting in decreased airway clearance)
- Diabetes mellitus
- Chronic kidney disease
- Immunodeficiency

The symptoms of pneumonia are **cough, sputum production, shortness of breath and fever**; patients may appear acutely ill/toxic.

Note that elderly patients may not present with this typical constellation of symptoms. They may present with mental status changes or “not acting quite themselves”

There may be signs of consolidation on exam (crackles, rhonchi, increased bronchial breath sounds, vocal fremitus, dullness to percussion over the areas of consolidation), and a leukocytosis.

Diagnostic testing:
- Chest-xray will show a focal infiltrate. If there is an associated pleural effusion, a thoracentesis should be performed to assure the pleural fluid is not infected (empyema)
- The yield of blood and sputum cultures is generally low.
Right upper lobe consolidation with air bronchograms (image source – LUMEN Radiology Vertical Integrated Curriculum)

Pneumonias have been classified as bronchopneumonia and lobar pneumonia (you will still see this in some texts, including Robbins).

*Bronchopneumonia* is patchy, usually involves more than 1 lobe, and represents infection that starts in the bronchioles and spreads to parenchyma.

*Lobar pneumonia* is contiguous, affects all or part of one lobe, and is mostly caused by *Streptococcus pneumoniae*.

While these distinctions between bronchopneumonia and lobar pneumonia might make sense pathologically, clinically there is much overlap, and so the move have been made to categorize pneumonias as pneumonia syndromes.

Pneumonia is classically classified into 7 syndromes which will be discussed:
- Community-acquired bacterial pneumonia
- Community-acquired viral pneumonia
- Hospital-acquired (nosocomial) pneumonia
- Aspiration pneumonia
- Chronic pneumonia
- Necrotizing pneumonia and lung abscess
- Pneumonia in the immunocompromised host

Ultimately, what is most important for patient care is knowing which microbial agents are most likely to be the etiologic agents for a given pneumonia syndrome because this will determine the most appropriate empiric antimicrobial treatment. If a specific etiologic agent is determined, treatment can be further tailored.
**Pneumonia Syndromes:**

*Community acquired pneumonia* refers to lung infection in individuals who develop infection from the normal environment (in contrast to those who acquire infection in the hospital or healthcare environment). Community acquired pneumonia is further classified into bacterial and viral etiologies. In previous versions of Robbins it was classified as typical and atypical, but this terminology is being used less and less often.

Community acquired bacterial pneumonia is classically of acute onset with cough, sputum, fever, shaking chills. X-ray findings include focal infiltrates. Sputum gram stains have many polymorphonuclear cells (PMNs) and bacteria.

The bacteria that are the most common etiologic agents of community acquired pneumonia: *Strep pneumoniae*, *H. influenza*, *Moraxella catarrhalis*, and *Staphylococcus aureus*.

Other organisms identified include: *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophilia*. These agents previously were referred to as "atypical" pneumonia or "walking pneumonia". As compared to the first group of bacterial agents, these may present with subacute symptoms, a longer prodrome of milder symptoms and a bronchopneumonia pattern.

Additional comments on Legionella:
Legionella (also known as Legionnaire’s disease and Pontiac Fever). In general patients present headache, myalgias (there may be a longer prodrome) high fever, cough and sputum production.
Remember from your earlier lectures on Legionella – the organisms flourish in artificial aquatic environments. Transmission of the bacteria is NOT person to person but via exposure to inhalation of a contaminated water source.
Outbreaks can and have occurred. Patients who present with pneumonia after a cruise or hotel stay – consider Legionella!
Legionella can progress to multiorgan system failure
Legionella is NOT cultured from blood or sputum. The bacteria is diagnosed via urinary legionella antigen.

For patients with pneumonia - No organism is found in 30-50% of patients.

Additional comments on *Streptococcus pneumoniae* – it is the number 1 cause of typical community acquired bacterial pneumonia (and a frequent topic for exam questions). Patients present with fever, shaking chills (it may be a single chill), RUSTY COLORED SPUTUM, shortness of breath and pleuritic chest pain. Remember *S. pneumoniae* appear as lancet shaped diplococci on gram stain.

Empiric therapy is selected based on the most common etiologic agents:
Outpatient therapy:
**Macrolides or doxycycline**
If co-morbid illness or recent antibiotic therapy - **respiratory fluoroquinolone**
Inpatient therapy:
If patients are sick enough to be in the hospital or ICU - **macrolide + beta lactam**.

**Duration of therapy is at least 5 days, longer if the patient is sick**

There are multiple ways to predict mortality for community acquired pneumonia patients, but the most commonly used is a score called CURB-65. One point is assigned for each of the following criteria:

- **C**- confusion
- **U**- uremia (BUN > 19 mg/dl)
- **R**- RR > 30
- **B**- blood pressure, SBP<90, DBP<60
- 65- age >65

Scores of 0-1 are low risk (30 day mortality <3%) and can probably be treated as an outpatient. A score of 2 is moderate risk (6.8% 30 day mortality) and should be considered for inpatient therapy. Scores of 3-5 are considered high risk (15-30% 30 day mortality) and should be treated inpatient.

**Community acquired viral pneumonia**

Viral pneumonias are generally seasonal and can be difficult to differentiate from bacterial pneumonias. In addition, a viral pneumonia can develop into a secondary bacterial pneumonia. Influenza, RSV, adenovirus, parainfluenza are the most common viral causes of pneumonia. Although specific viruses can be identified via PCR of respiratory secretions, only influenza has specific therapy.

Influenza: typical symptoms are fever, cough, headache, sore throat- patients feel MISERABLE. Influenza infection can progress to pneumonia, respiratory failure, and death. During influenza season, it is best practice to test patients suspected to have influenza and isolate them from other patients early to prevent spread of the infection. There are effective antiviral therapies for influenza (oseltamivir or zanamivir) which should be started within 48 hours of clinical symptoms. It is best to prevent influenza with annual immunization.

**Community Pneumonia in the pediatric population**

Children may not present with the typical symptoms of pneumonia. They may have tachypnea, fever, mild cough, dyspnea

Etiologic agents to consider:

- Under 2 years of age – Viral (RSV, rhinovirus)
- 5-10 years old - Mycoplasma
- 10-16 years old – S. pneumoniae, Chlamydia

**Hospital acquired (nosocomial) pneumonia**

Hospital acquired pneumonias are defined as pulmonary infections acquired in the course of a hospital stay.

1% of all hospitalized patients with develop pneumonia (more in the ICU).

Hospital acquired pneumonia increases the length of time patients need to stay in the
hospital by 7-9 days, increases costs and markedly increases mortality.

Pathogenesis- Hospitalized patients will become colonized with gram negative rods that can be aspirated. The patient’s host defenses are lowered by the co-existent illness (especially underlying lung disease, heart disease, or kidney disease requiring dialysis). Anything that bypasses the natural defenses (endotracheal intubation, decreased mental status) will increase the risk of developing pneumonia.

**Key Organisms** to be considered as etiologic agents of hospital acquired pneumonia: Klebsiella pneumoniae, E coli, Enterobacter, Proteus, Serratia, Pseudomonas, Acinetobacter

Therapy: Early initiation of empiric antibiotic treatment is important. Broad empiric therapy typically consists of

**Anti-pseudomonal cephalosporin, or**

**Antipseudomonal Carbapenem, or**

**Beta lactam + beta lactamase**

IF there is a clinical concern for MRSA and the etiologic agent, Vancomycin should be included

Treatment is subsequently narrowed based on culture results

**Aspiration pneumonia**

Aspiration of gastric contents into the lung typically occurs in:
- Markedly debilitated patients
- Patients with loss of gag reflex or swallowing reflexes
- Patients with repeated emesis.

The right lung is most often involved due to anatomy (right main bronchus follows a more straight path down), particularly the lower segments of the right upper lobe and the upper segments of the right lower lobe.

The resulting pneumonia is in part a chemical reaction from the irritating effects of the gastric acid (chemical pneumonitis) followed by bacterial infection.

Aspiration pneumonia can become necrotic and progress to abscess development

Etiologic Organisms: aspiration pneumonia is usually polymicrobial - a mix of gram negative aerobes and anaerobes

Therapy consists of broad spectrum antibiotics, covering gram negatives and anaerobes

- **beta lactam + beta lactamase or**
- **3rd generation cephalosporin + metronidazole for the anaerobes**

**Chronic pneumonia**

Chronic pneumonia is characterized by the subacute onset of symptoms, typically >6 weeks

It is caused by:
- Slow growing organisms (Mycobacterium, Nocardia, Actinomyces)
-Endemic fungi (Histoplasmosis, Blastomycosis, Coccidiomycosis)
-Coxiella
-Tularemia
-an anatomic problem (obstructed airway)

Treatment is challenging because of the wide array of potential etiologies. Attempts at culture and pathologic diagnosis are important in order to prescribe appropriate therapy and duration.

Lung abscess/empyema
Abscess refers to a parenchymal infection that leads to tissue destruction, necrosis, suppuration and cavitation.

Abscesses can result from:
- any necrotizing pneumonia (Staphylococcus aureus, Streptococcus pneumoniae, Klebsiella, Pseudomonas)
- Aspiration
- Tooth abscess
- Septic emboli

Commonly isolated organisms include anaerobic mouth organisms (bacteroides, fusobacterium, peptostreptococcus), aerobic and anaerobic streptococcus and gram negative rods.
Abscesses are often polymicrobial

Therapy: piperacillin-tazobactam or clindamycin (recall clindamycin covers anaerobes above the diaphragm)
**Duration of therapy is prolonged (up to 4-6 weeks)**

Empyema refers to infection that has spread into the pleural space. Most will not be cured with antibiotics alone and will need to be drained. Failure to drain the lung will result in organization of the empyema and fibrosis within the pleural space.

Pneumonia in the immunocompromised
Pneumonia is a serious complication in patients with suppressed immune defenses. A wide variety of infectious agents, some which do not cause infection in normal hosts, can be etiologic agents and are called “opportunistic infections”.

Neutrophil dysfunction
Causes: chemotherapy, leukemia, Chronic Granulomatous Disease (CGD)
Organisms: gram negative rods, Staph, Aspergillus, Candida

T cell dysfunction
Causes: AIDS, T cell lymphoma, solid organ transplant, DiGeorge Syndrome
Organisms: Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Pneumocystis, Listeria, Candida, Aspergillus, Cryptococcus,
Mycobacteria

B cell dysfunction
- Causes: splenectomy, lymphoma, myeloma, gamma globulin deficiency
- Organisms: S pneumoniae, H flu, Neisseria, Klebsiella, E coli, Giardia

Additional Pearls:
Some conditions or risk factors related to specific etiologic agents of pneumonia:

<table>
<thead>
<tr>
<th>Exposure to bat or bird droppings</th>
<th>Histoplasma capsulatum</th>
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<tr>
<td>Exposure to birds</td>
<td>Chlamyphila psittaci</td>
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<tr>
<td>Exposure to rabbits</td>
<td>Francisella tularensis (tularemia)</td>
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<tr>
<td>Exposure to farm animals</td>
<td>Coxiella burnetti</td>
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<tr>
<td>Hotel or cruise ships</td>
<td>Legionella</td>
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<tr>
<td>Travel to SW USA</td>
<td>Coccidiosis</td>
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<tr>
<td>Structural lung disease (bronchiectasis)</td>
<td>Pseudomonas</td>
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<tr>
<td>Alcoholism</td>
<td>anaerobes, Klebsiella</td>
</tr>
</tbody>
</table>

Things to think about if no response to empiric therapy:
- Inadequate dosing of antibiotic
- Wrong antibiotic (resistant pathogen)
- Wrong diagnosis (maybe it is not pneumonia, but pulmonary embolism, ARDS, pulmonary edema or hemorrhage)
- Complication (empyema, abscess, drug fever, another infection).
- Host factors (older patients respond slower)

Summary Table: If bacteria are being considered as etiologic agents of respiratory tract infection

<table>
<thead>
<tr>
<th>Condition</th>
<th>Potential Etiologic Bacteria</th>
<th>Empiric Antibiotic options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Sinusitis</td>
<td>S pneumoniae, H. influenzae Moraxella Oral Anaerobes</td>
<td>-Ampicillin or -Amoxicillin or -Trimethoprim-Sulfamethoxazole or -Amoxicillin-clavulanate</td>
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<td>Epiglottitis</td>
<td>Haemophilus influenzae, Group A strep,</td>
<td>-Amoxicillin-clavulanate or</td>
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<td>Category</td>
<td>Pathogens</td>
<td>Treatment</td>
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<tr>
<td><strong>Community Acquired Bacterial Pneumonia</strong></td>
<td>Haemophilus parainfluenza, Strep pneumoniae, H. influenzae, Moraxella catarrhalis, Staphylococcus aureus, Mycoplasma pneumoniae, Chlamydia pneumoniae, Legionella</td>
<td>Ampicillin-sulbactam or 3rd generation cephalosporin</td>
</tr>
<tr>
<td><strong>Community Acquired Viral Pneumonia</strong></td>
<td>Influenza, RSV, Adenovirus, parainfluenza</td>
<td>oseltamivir or zanamivir for influenza</td>
</tr>
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<td><strong>Hospital Acquired Pneumonia</strong></td>
<td>Klebsiella pneumoniae, E. coli, Enterobacter, Proteus, Serratia, Pseudomonas, Acinetobacter, MRSA</td>
<td>Antipseudomonal cephalosporin or Antipseudomonal carbapenem or Beta lactam-beta lactamase If MRSA suspected Vancomycin to be added</td>
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<td><strong>Aspiration pneumonia</strong></td>
<td>Mix of gram negative aerobes and anaerobes</td>
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<td><strong>Abscess</strong></td>
<td>Polymicrobial: anaerobic mouth organisms (bacteroides, fusobacterium, peptostreptococcus), aerobic and anaerobic streptococcus, gram negative rods</td>
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