Lower Respiratory Tract Infections

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Infection Types

- Pneumonia
  - community-acquired
  - aspiration
  - atypical
  - hospital-acquired

- AECB, ABECB
Community Acquired Pneumonia
Epidemiology

- Most common cause of infection-related mortality and morbidity (13.7% at 30 days)
- 4 million CAP cases per year
- 1 million hospitalizations per year
- 6th most common cause of death in U.S.
Routes of Infection

- Aspiration
- Inhalation
- Hematogenous spread
Microbiology: Outpatients

- *Streptococcus pneumoniae*
- *Mycoplasma pneumoniae*
- *Haemophilus influenzae*
- *Chlamydia (Chlamydophila) pneumoniae*
- Influenza
Microbiology: Inpatients

- *Streptococcus pneumoniae*
- *Mycoplasma pneumoniae*
- *Chlamydia (Chlamydophila) pneumoniae*
- *Haemophilus influenzae*
- *Legionella spp.*
- *Staphylococcus aureus* (ICU)
- Gram - bacilli (ICU)
- Influenza
Demographic Concerns

- Age
- Comorbidities
- Social history
  - travel
  - tobacco/alcohol use
- Pathogen exposure
Clinical Presentation: Symptoms

- Cough (> 90%)
- Dyspnea (66%)
- Sputum production (66%)
- Pleuritic chest pain (50%)
- Fever, chills, etc.
Physical Findings

- Tachypnea
- Tachycardia
- Inspiratory crackles
- ↓ breath sounds
- ↑ WBC, possible left shift
Diagnosis: Chest X-Ray

- Essential for accurate diagnosis
  - R/O other causes of respiratory failure
  - typical presentation: dense lobar or segmental infiltrates
  - rarely negative in presence of pneumonia
- Can sometimes help to identify organism
- Useful in determining prognosis, need for hospitalization
CXR Results
Diagnosis: Sputum Evaluation

- Adequate collection and handling is essential
- Gram stain
  - helps to rule out less common organisms
  - validation of subsequent culture results
- Culture
  - definitive diagnosis of pathogen
  - absence of *Staphylococcus aureus* or Gram - bacilli excludes these organisms
Sputum Characteristics for Diagnosis

- Mucopurulent
- Scant/watery
- "Rusty"
- Dark red, mucoid
- Foul-smelling

bacterial
atypical
pneumococcal
staphylococcal
*K. pneumoniae*
anaerobic
Gram Stain
Other Diagnostic Tests

- Blood cultures
  - relatively low sensitivity
  - major indications: severe CAP, immunocompromisation
- Urinary antigen tests:
  - *Streptococcus pneumoniae*
  - *Legionella pneumophila*
  - influenza
Atypical Pneumonia

- Usual signs/symptoms not always present
- Older patients, comorbidities, travel history
  - age > 60
- Pathogens:
  - *Mycoplasma pneumoniae*
  - *Chlamydia (Chlamydophila) pneumoniae*
  - *Legionella pneumophila* (less common)
Aspiration Pneumonia

- 5-10% nosocomial pneumonia
- Also occurs in outpatients, but rarely
- Risk factors
  - altered consciousness due to alcohol or drug overdose or seizures
  - gingival disease
- Organisms: oral flora, GI flora, anaerobes
Treatment: CAP
Risk Stratification

- Age: > 60-65 years is common target value
- Comorbidities
  - severity determinants: neoplasm, hepatic disease, CHF, CVD, renal disease
  - pathogen determinants: alcoholism, smoking/COPD, poor dentition
Who Should be Hospitalized?

Base decision on:

- Risk of death and complications
- Presence of metastatic disease
- Presence of comorbidities
- Infection by high-risk pathogen (e.g., \textit{S. aureus})
- Compliance
- Pneumonia Severity Index (PSI) score
Goals of Therapy

- Microbiologic eradication
- Minimize future resistance development
- Minimize adverse effects
- Optimize compliance
- Cost-effectiveness
Treatment Principles

• Determine severity of infection
  – outpatient management vs hospitalization
• Disease stratification
  – age, comorbidities
• Determine likely pathogen(s)
  – typical vs atypical
  – DRSP, Gram -
• Begin empiric therapy
<table>
<thead>
<tr>
<th>Organism</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRSP</td>
<td>age &gt; 65 years</td>
</tr>
<tr>
<td></td>
<td>β-lactam therapy within 3 months</td>
</tr>
<tr>
<td></td>
<td>alcoholism</td>
</tr>
<tr>
<td></td>
<td>immunosuppression</td>
</tr>
<tr>
<td></td>
<td>multiple medical comorbidities</td>
</tr>
<tr>
<td></td>
<td>exposure to child in daycare</td>
</tr>
<tr>
<td>Enteric Gram -</td>
<td>nursing home residence</td>
</tr>
<tr>
<td></td>
<td>underlying cardiopulmonary disease</td>
</tr>
<tr>
<td></td>
<td>multiple medical comorbidities</td>
</tr>
<tr>
<td></td>
<td>recent ABX therapy</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>structural lung disease (e.g., CF)</td>
</tr>
<tr>
<td></td>
<td>corticosteroid therapy</td>
</tr>
<tr>
<td></td>
<td>broad-spectrum ABX for &gt; 7 days</td>
</tr>
<tr>
<td></td>
<td>malnutrition</td>
</tr>
</tbody>
</table>

Microbiology-Determined Treatment

- *S. pneumoniae*
  - rapid emergence of resistance in last decade
- *H. influenzae, M. catarrhalis*
  - more likely to spontaneously resolve
- Atypical
  - generally only empirically treated in U.S.
- Anaerobes
  - usually no need to include anaerobic coverage
Resistance: *S. pneumoniae*

- **Penicillins**
  - PRSP (DRSP) in the Northwest: ~ 12%
  - uncertain impact on outcomes
- **Macrolides**
  - overall *in vitro* resistance in U.S. is 25-35%
  - 2/3 of this resistance is *mef* rather than *erm*
  - overall ~ 6-12% all *S. pneumoniae* resistant
- **Fluoroquinolones**
  - FQ-resistant *S. pneumoniae*: < 1%
Effect of PRSP

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Penicillin Susceptibility</th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>94 (78)</td>
<td>49 (77)</td>
<td>46 (82)</td>
<td>189 (79)</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>26 (22)</td>
<td>15 (23)</td>
<td>10 (18)</td>
<td>51 (21)</td>
<td></td>
</tr>
</tbody>
</table>

# (%) of patients

## Disease-Specific Breakpoints

### Interpretive Standards for *Streptococcus pneumoniae*

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>MIC (mg/L)</th>
<th>Interpretive Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td><strong>Meningitis:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime or Ceftriaxone</td>
<td>≤ 0.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nonmeningitis:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime or Ceftriaxone</td>
<td>≤ 1</td>
<td>2</td>
</tr>
</tbody>
</table>
Resistance: CA-MRSA

- Currently rare (~2% of all CA-MRSA infections)
- More often associated with influenza infection
- Easily ruled out by sputum Gram stain
Antibiotic Characteristics
Doxycycline

- Active against 90-95% *S. pneumoniae*, *H. influenzae*, atypicals
  - moderate activity against DRSP
- Inexpensive
- Possibly underused?
  - limited efficacy data
Macrolides

- Erythromycin
  - less active against *H. influenzae*
  - use is limited due to activity, ADR, dosing frequency
- Clarithromycin (Biaxin®)
  - QD dosing, but relatively long course
- Azithromycin (Zithromax®, Zmax®)
  - poor results in terms of microbiologic eradication
  - high # MD visits, samples, etc.
Ketolides

• Telithromycin (Ketek\textsuperscript{R}) approved in 2004
• Main advantage in comparison to macrolides is activity against macrolide-resistant organisms
• Fairly high rate of GI adverse effects
  – diarrhea 10-12%
  – nausea 5-8%
• Fatal hepatic ADR first reported in 2006
Fluoroquinolones

• Differentiate based on activity vs *S. pneumoniae*
• “Respiratory” fluoroquinolones:
  – gatifloxacin (Tequin<sup>R</sup>)
  – levofloxacin (Levaquin<sup>R</sup>)
  – moxifloxacin (Avelox<sup>R</sup>)
  – gemifloxacin (Factive<sup>R</sup>)
• Resistance not currently a major concern
Treatment of Specific Organisms
Streptococcus pneumoniae

- Amoxicillin adequate if PSSP
- Cephalosporins (IV)
  - ceftriaxone
- Macrolides
  - erythromycin, clarithromycin, azithromycin
- Doxycycline
- Fluoroquinolone
  - gatifloxacin, moxifloxacin > levofloxacin
DRSP

- Penicillin resistance: 25-35%
- Resistance to macrolides, fluoroquinolones rising
- Options:
  - ceftriaxone
  - macrolide (erythromycin may be suboptimal)
  - fluoroquinolone
  - linezolid
  - telithromycin
**Haemophilus influenzae**

- β-lactam/β-lactamase inhibitor
- Cephalosporins
- Macrolides *(not* erythromycin)*
- Doxycycline
- Fluoroquinolones
Atypicals

• Pathogens:
  – *M. pneumoniae, C. pneumoniae*
  – *Legionella* species (treat for 10-21 days)

• Treatment:
  – macrolides (± rifampin for *Legionella*)
  – doxycycline
  – fluoroquinolones

• No penicillins or cephalosporins
Legionella pneumophila

- Present in water, soil
- Risks: middle aged or older, comorbidities, immunocompromised, outbreaks
- Symptoms: high fever, malaise, myalgia, nonproductive cough, abdominal pain, diarrhea, MS changes
- Diagnosis: culture (3-7 days), urinary Ag
- Treatment: macrolide, fluoroquinolone
Aspiration Pneumonia

- **Pathogens:**
  - peptostreptococcus
  - *S. pneumoniae*
  - enteric Gram -

- **Treatment:**
  - clindamycin
  - β-lactam/β-lactamase inhibitor
  - fluoroquinolones
  - carbapenems
IDSA/ATS Guidelines

Initial Empiric Therapy
CAP Diagnosis - OUTPATIENT

Comorbidities Present?
Use of Antibiotics in Previous 3 Months?

No
macrolide (any)
doxycycline

Yes
respiratory fluoroquinolone
(LEV dose must be 750 mg)
macrolide + β-lactam:
high-dose amoxicillin
high-dose amoxicillin/clavulanate
ceftriaxone/cefpodoxime/cefuroxime

CAP Diagnosis - **INPATIENT**

Patient Admitted to the ICU?

No

- respiratory fluoroquinolone
  - (LEV dose must be 750 mg)
  - macrolide + β-lactam:
    - high-dose amoxicillin
    - high-dose amoxicillin/clavulanate
    - ceftriaxone/cefpodoxime/cefuroxime

Yes

- β-lactam:
  - cefotaxime/ceftriaxone
  - ampicillin-sulbactam
  - PLUS
  - azithromycin
  - OR
  - respiratory fluoroquinolone

<table>
<thead>
<tr>
<th>Organism</th>
<th>Preferred Antibiotic(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSSP</td>
<td>penicillin G, amoxicillin</td>
</tr>
<tr>
<td>DRSP</td>
<td>cefotaxime or ceftriaxone, respiratory fluoroquinolone</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>2nd or 3rd generation cephalosporin, amoxicillin/clavulanate</td>
</tr>
<tr>
<td>Atypicals (not <em>Legionella</em> spp.)</td>
<td>macrolide, doxycycline, respiratory fluoroquinolone</td>
</tr>
<tr>
<td><em>Legionella</em> spp.</td>
<td>respiratory fluoroquinolone, azithromycin</td>
</tr>
</tbody>
</table>
Prevention

- **Influenza vaccine**
  - all > 50 y.o.
  - at risk of influenza complications
  - household contacts of high-risk persons
  - healthcare workers

- **Pneumococcal vaccine**
  - all > 65 y.o.
  - selected high-risk concurrent diseases
Nosocomial Pneumonia
(Hospital Acquired Pneumonia)
Epidemiology

- 3rd most common hospital infection
- Primarily occurs in critically ill
- Risk factors:
  - prior antibiotic use
  - intubation (> 72h)
  - advanced age
  - comorbidities
  - $\text{H}_2$ antagonist use?
  - sedation
Microbiology

- SPACE organisms
  - MDR strains of *Pseudomonas aeruginosa*, etc.
- Gram - enterics:
  - *Klebsiella pneumoniae*
  - *Escherichia coli*
- *Staphylococcus aureus*
Clinical Presentation: Symptoms

- Worsening respiratory status
- New infiltrate appears on CXR
- Fever, leukocytosis, etc.
- Increased secretion production
Diagnosis

- Same as for CAP, but diagnosis may be more difficult due to confounding illnesses and comorbidities
- Culture of infecting organism probably more important
Treatment
Treatment Principles

• Broad-spectrum activity until pathogen cultured
  – consider risk for MDR organisms
  – cover \textit{P. aeruginosa}? \\
• Be aware of institutional resistance \\
• Caution if prior antibiotic treatment 
  – major resistance risk 
  – use agents not already received by patient
Risk Factors for MDR Pathogens

- ABX in preceding 90 days
- Hospitalization for ≥ 5 days
- High frequency of resistance in community
- Risk factors for HCAP:
  - residency in a nursing home or prior hospitalization
  - home infusion therapy or wound care
  - chronic dialysis
- Immunosuppressive disease/therapy
ATS / IDSA Guidelines
HAP Suspected

Obtain lower respiratory tract sample for culture

Begin empiric antimicrobial therapy

Day 2 and 3: check cultures and assess clinical response (temp, WBC, CXR, sputum, hemodynamics, organ function)

Clinical improvement at 48-72 hours?

No

Search for other diagnoses or adjust antibiotics

Yes

Stop or de-escalate antibiotics
HAP Diagnosis

Late Onset or Risk for MDR Pathogens?

No

Limited Spectrum Therapy

Yes

Broad Spectrum Therapy for MDR Pathogens

## Narrow Spectrum Therapy

<table>
<thead>
<tr>
<th>Organism</th>
<th>Recommended Antibiotic(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
<td>ceftriaxone</td>
</tr>
<tr>
<td>MSSA</td>
<td>or</td>
</tr>
<tr>
<td>Gram - bacilli:</td>
<td>levofloxacin, moxifloxacin, ciprofloxacin</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>or</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>ampicillin/sulbactam</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp.</td>
<td>or</td>
</tr>
<tr>
<td><em>Proteus</em> spp.</td>
<td>ertapenem</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td></td>
</tr>
</tbody>
</table>
# Broad Spectrum Therapy

<table>
<thead>
<tr>
<th>Organism</th>
<th>Recommended Antibiotic(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All previous, plus: Pseudomonas aeruginosa</td>
<td>cefepime, ceftazidime&lt;br&gt; or&lt;br&gt; imipenem, meropenem&lt;br&gt; or&lt;br&gt; piperacillin, piperacillin/tazobactam</td>
</tr>
<tr>
<td>Klebsiella pneumoniae (ESBL)</td>
<td>PLUS&lt;br&gt; ciprofloxacin, levofloxacin&lt;br&gt; or&lt;br&gt; amikacin, gentamicin, tobramycin</td>
</tr>
<tr>
<td>Acinetobacter spp.</td>
<td></td>
</tr>
</tbody>
</table>
AECB, ABECB
(Exacerbations of Bronchitis)
Definitions

- Bronchitis: inflammation of bronchi (large airways in tracheobronchial tree)
  - acute: occurs in all age groups
  - chronic: primarily in adults
Definitions

• **AECB**: acute exacerbation of chronic bronchitis
  – viral etiology in most cases

• **ABECB**: acute bacterial exacerbation of chronic bronchitis
  – implies AECB in which bacterial etiology has been confirmed
Acute Bronchitis

- Higher incidence in winter months
- Irritants: cold/damp climates, cigarette smoke, air pollution
- Pathogens:
  - viruses: common cold, rhinovirus, coronavirus, influenza, adenovirus, RSV
  - bacteria (rare): *M. pneumoniae*, *C. pneumoniae*, *B. pertussis*
Acute Bronchitis: Clinical Presentation

- Begins as upper respiratory infection
- Nonspecific symptoms
  - malaise, headache, sore throat
  - cough: progresses from nonproductive to productive; may persist after other symptoms resolved
- Physical exam: coarse, bilateral rhonchi
- CXR: usually appears normal
Acute Bronchitis: Treatment

- Self-limiting in absence of infection
- Goals:
  - palliative care
  - treatment of associated complications (dehydration, respiratory compromise)
Chronic Bronchitis

- Occurs primarily in adults
  - 10-25% of adults > 40 y.o.
  - 5% of total population

- Contributing factors:
  - cigarette smoke
  - dusts, fumes (air pollution)
  - infection
Chronic Bronchitis

• Pathogenesis
  – secretory, mucociliary functions disturbed
  – thickened bronchial walls
  – proliferation of mucus-secreting cells
  – impaired lung defenses 2° mucus
  – bronchial scarring
  – weakening of bronchial walls
  – airway obstruction
Chronic Bronchitis: Clinical Presentation

- Cough
  - mild to severe, easily stimulated
- Sputum production
  - greatest in AM; tenacious, white to yellow/green
- Inspiratory/expiratory rales, rhonchi
- Diagnosis:
  - productive cough most days $\geq 3$ months/year for $\geq 2$ years
Chronic Bronchitis: Treatment

• Goals:
  – reduce symptom severity
  – treat acute bacterial exacerbations

• Nonpharmacologic
  – minimize irritant exposure
  – moist air

• Pharmacologic
  – bronchodilators
  – antibiotics – limit use
Differentiating AECB, ABECB

- Symptoms:
  - subjective increase in dyspnea, increased sputum volume, or increased sputum purulence
- Must reliably diagnose episodes with a bacterial etiology
  - bacteria isolated in 60% of cases
Anthonisen Severity Scale

- Type 1 (severe): all 3 clinical findings of dyspnea, increased sputum volume, increased purulence
- Type 2 (moderate): any 2 of these clinical findings
- Type 3 (mild): 1 of these clinical findings plus 1 of:
  - URTI in the previous 5 days
  - fever with no other apparent cause
  - increased cough or wheezing
  - 20% increase in respiratory rate or heart rate
## ABECB: Microbiology

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Incidence (%)</th>
</tr>
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<tbody>
<tr>
<td>Haemophilus influenzae</td>
<td></td>
</tr>
<tr>
<td>Haemophilus parainfluenzae</td>
<td></td>
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<tr>
<td>Streptococcus pneumoniae</td>
<td></td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>30% - 50%</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td></td>
</tr>
<tr>
<td>Other Gram - bacilli</td>
<td>10% - 15%</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>&lt; 5% - 20%</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td></td>
</tr>
</tbody>
</table>