Objectives

Following the presentation, the participant will be able to:

1. Identify typical, atypical, & hospital respiratory pathogens.
2. Identify diagnostic criteria used to establish a diagnosis of pneumonia.
3. Identify differences in pathogens causing HAP vs CAP and the required differences in antibiotic coverage.
4. Identify underlying mechanisms of antibiotic resistance for typical bacterial pathogens.
5. Using IDSA/ATS guidelines for CAP & HAP/VAP/HCAP identify appropriate initial antibiotic therapy.

Pneumonia

- Community acquired pneumonia (CAP)
- Aspiration pneumonia
- Hospital
  - Hospital acquired pneumonia (HAP)
  - Ventilator associated pneumonia (VAP)
  - Healthcare associated pneumonia (HCAP)

Diagnosis

- Fever, cough, SOB & pleuritic chest pain
- Chest x-ray infiltrate
- HAP, VAP, & HCAP
  - Sputum culture should be obtained prior to antibiotics
  - Quantitative or semiquantitative culture required
- Sputum gram stain & culture
  - <10 epithelial cells & > 25 PMN’s per field
  - Appropriate cultures of blood and CSF

2007 ATS/IDSA CAP Guidelines

Mandell, LA et al CID 44(suppl 2) 2007

Patient screening

- Determine whether to treat as outpatient or in-patient (ICU vs Ward)
- Objective scoring systems
  - Pneumonia Severity Index
    - CURB-65
      - Confusion
      - Urea > 7 mmol/L
      - Respiratory Rate ≥ 30 / min
      - Blood pressure < 90 mm Hg & diastolic ≤ 60 mm Hg
      - Age ≥ 65 years
      - ICU Admit (3 minor criteria present)
    - Respiratory rate ≥ 30 / min
    - P<0.85 < 250
    - Multilobar infiltrates
    - Confusion
    - Uremia
    - Neutropenia
    - Thrombocytopenia
    - Hypothermia

Bacterial Resistance in Pneumonia

- Penicillin Resistant S. pneumoniae
- Macrolide Resistant S. pneumoniae
- Ampicillin Resistant H. influenzae
- Beta-lactamase producing M. catarrhalis
- MRSA & CA-MRSA
- Multiple Drug Resistant Gram Negative Pathogens
  - P. aeruginosa
  - S. maltophilia
  - Acinetobacter spp
  - K. pneumoniae or E. coli (ESBL positive)
  - KPC (+) Klebsiella spp
Potential CAP Pathogens

**Typical**
- S. pneumoniae
- H. influenzae
- M. catarrhalis

**Atypical**
- C. pneumoniae
- L. pneumophila
- Mycoplasma

**Viruses**
- Fungi
- Less Common pathogens
  - N. meningitidis
  - S. pyogenes
  - M. tuberculosis
  - Chlamydia psittaci
  - Coxiella burnetii
  - B. anthracis
  - Y. pestis
  - F. tularensis
  - CA-MRSA

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**ATS Pathogen Risk Factors for Penicillin NS/R S. pneumoniae**

> 65 years
- Multiple co-morbidities
- Alcoholism
- Exposure to children in day care
- Immunosuppressed
- Smoking
- Use of beta-lactam within last 90 days

_Am J Respir Crit Care Med_ 163:1730-1754, 2001

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**Nosocomial Pneumonias**

- Aerobic gram-negative bacilli (~80%)
- Pseudomonas
- Enterobacter
- Acinetobacter
- Klebsiella
- Staphylococcus aureus (~20%)
- P. aeruginosa (~58.6%)
- A. baumannii (~21.7%)
- S. maltophilia (~13.2%)
- M. tuberculosis (~2.6%)
- Other organisms (~12.5%)

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**ATS Guidelines for HAP, VAP, & HCAP**

- Risk for MDR Pathogens
  - Antibiotic therapy in previous 90 days
  - Current hospitalization of > 5 days
  - High frequency of antibiotic resistance
- Risk factors for HCAP
  - Hospitalization for > 2 days in previous 90 days
  - Residence in nursing home or ECF
  - Home infusion therapy
  - Chronic dialysis within 30 days
  - Home wound care
  - Family member with MDR pathogen
- Immunosuppressive disease

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**Diagnosis of Suspected VAP**

- 413 patients with suspected VAP
- 32% enrolled surgical patients

**Invasive management**
- BAL or bronchoscopic protected specimen brush (PSB)
- Quantitative sputum cultures
  - ≥10^5 CFU/mL BAL
  - ≥10^4 CFU/mL PSB

**Clinical management**
- Clinical criteria
- Nonquantitative evaluation of nonbronchoscopic isolates

Diagnosis of Suspected VAP

<table>
<thead>
<tr>
<th>End Point</th>
<th>Invasive (n=206)</th>
<th>Clinical (n=210)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 14 days, n (%)</td>
<td>33 (16.2)</td>
<td>54 (25.8)</td>
<td>0.022</td>
</tr>
<tr>
<td>Mortality at 28 days, n (%)</td>
<td>63 (30.9)</td>
<td>81 (38.8)</td>
<td>0.099</td>
</tr>
<tr>
<td>Antibiotic-free days at 14 days</td>
<td>5.0 ± 5.1</td>
<td>2.2 ± 3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antibiotic-free days at 28 days</td>
<td>11.5 ± 9.0</td>
<td>7.5 ± 7.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emergence of Candida spp., n (%)</td>
<td>23 (11.3)</td>
<td>47 (22.5)</td>
<td>0.0025</td>
</tr>
</tbody>
</table>


Bacteriology

<table>
<thead>
<tr>
<th>Feature or Organism</th>
<th>Invasive (n=204)</th>
<th>Clinical (n=209)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative culture</td>
<td>55.9%</td>
<td>14.4%</td>
</tr>
<tr>
<td>Monomicrobial pneumonia</td>
<td>31.9%</td>
<td>40.2%</td>
</tr>
<tr>
<td>Polymicrobial pneumonia</td>
<td>12.3%</td>
<td>45.5%</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>22.3%</td>
<td>18.3%</td>
</tr>
<tr>
<td>S. aureus</td>
<td>16.5%</td>
<td>12.8%</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>7.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td>A. baumannii</td>
<td>5.0%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>3.3%</td>
<td>3.8%</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>% S</th>
<th>% I</th>
<th>% R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>99.4</td>
<td>0.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Meropenem</td>
<td>99.4</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Ceftiraxone (nomeningitis)</td>
<td>94.0</td>
<td>4.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Amox-clav (nomeningitis)</td>
<td>86.7</td>
<td>3.1</td>
<td>10.2</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>79.8</td>
<td>0.3</td>
<td>19.9</td>
</tr>
<tr>
<td>Ceftazolin (oral)</td>
<td>77.4</td>
<td>3.4</td>
<td>19.2</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>77.0</td>
<td>2.8</td>
<td>20.2</td>
</tr>
<tr>
<td>Trimethoprim-sulfa</td>
<td>73.7</td>
<td>7.9</td>
<td>18.4</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>66.5</td>
<td>0.1</td>
<td>33.4</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>66.7</td>
<td>0.4</td>
<td>32.9</td>
</tr>
<tr>
<td>Penicillin (oral)</td>
<td>62.7</td>
<td>21.6</td>
<td>15.7</td>
</tr>
</tbody>
</table>

In vitro activity does not necessarily correlate with clinical results. All isolates were vancomycin susceptible. Breakpoints (S/I/R) for other antimicrobials are CLSI.

New FDA Pneumonia Breakpoints for S. pneumoniae (2008)

- **Sensitive**
  - PCN MIC ≤ 2 (Previously 0.06 mg/L)
- **Non-susceptible**
  - PCN MIC = 4 (Previously 0.12 to 1.0 mg/L)
- **Resistant**
  - PCN MIC ≥ 8 mg/L (Previously ≥ 2 mg/L)
- Meningitis breakpoint for penicillin sensitive remains at ≤ 0.06 mg/L
- Mechanism of resistance is alteration of penicillin binding proteins not beta-lactamase production

S. pneumoniae Penicillin Resistance

- Influx-Block Porin Channel
- Efflux- Pump (mefA)
- Enzyme Inactivation
- Target Alteration(PBP)
- Environment Factors
- Metabolic Bypass

S. pneumoniae Macrolide Resistance

- Influx-Block Porin Channel
- Efflux- Pump (mefA)
- Enzyme Inactivation
- Target Alteration(ermB)
- Environment Factors
- Metabolic Bypass
Pneumonia Treatment Guidelines 1993-Present

- American Thoracic Society (ATS)
  - First published 1993
  - Revision – Am J Respir Crit Care Med 163:1730-1754, 2001
- Infectious Diseases Society of America (IDSA)
  - First published April 1998
- New Joint IDSA/ATS CAP Guidelines 2007
  - Mandell, LA et al Clin Infect Dis 44(suppl 2) 2007
- Joint IDSA/ATS HAP/ VAP / HCAP Guidelines 2005

2007 ATS/IDSA CAP Guidelines

- Healthy & no risk factors for DRSP
  - Macrolide or Doxycycline
- Comorbidities present – Antibiotic Use in last 90 days, heart, lung, or renal disease, diabetes, DRSP risk factors...
  - Respiratory fluoroquinolone
    - Moxifloxacin, Levofloxacin, or Gemifloxacin
  - Macrolide (or doxycycline) & beta-lactam
    - Ampicillin & Clavulanate, Ceftriaxone, Cefpodoxime, or Cefuroxime
- Note: gatifloxacin has been removed from guidelines & no recommendation is offered for telithromycin

2007 ATS/IDSA CAP Guidelines

Inpatient Non-ICU

- Respiratory fluoroquinolone
- Macrolide (or Doxycycline) plus beta-lactam
  - Cefotaxime, Ceftriaxone, Ampicillin, or Ertapenem

Inpatient ICU

- Azithromycin or respiratory fluoroquinolone plus beta-lactam
  - Cefotaxime, Ceftriaxone, or Ampicillin/Sulbactam

Community Acquired MRSA (CA-MRSA)

- Common following a viral infection
  - Check Gram stain & Check X-ray for cavitary infiltrates
- CA-MRSA prolific toxin producer
- Treatment (No preference given)
  - Vancomycin
    - Possible issues with lung penetration, slow kill rate, failure to shut down toxin production, & cell lysis upon death
  - Linezolid
  - Antibiotic recommendations for pneumonia different than S/STI recommendations
    - Daptomycin binds to surfactant & can’t be used for pneumonia

Possible Tip Offs for Patients with CA-MRSA Pneumonia

Patients tend to be younger
Contact with CA-MRSA carrier or infection
Previous or concomitant influenza
Not current on influenza vaccination
Gram positive cocci on Gram stain
Multi-lobar involvement
Cavitary pneumonia
Evidence of airway hemorrhage

CAP Prevention

Persons > 50yrs, healthcare workers, risk patients should receive annual influenza vaccination
Persons > 65 yrs or at risk should receive pneumococcal vaccine
CDC recommends $T_{dep}$ for adults 19-64 years
Vaccination status should be evaluated at time of admission
Patients should be offered influenza vaccination at discharge or outpatient treatment in the fall and winter
Smoking cessation should be offered to patients who smoke
  - Smokers should be vaccinated against pneumococci & influenza
Suggest appropriate respiratory hygiene & IC practices to patients with a cough
**CAP Hospital Quality Standards**
- Influenza vaccination
- Pneumococcal vaccination
- Offer of smoking cessation therapy (if patient a smoker)
- Appropriate diagnostics & monitoring used
- Initial antibiotics consistent with CAP guidelines
- Antibiotics started at site of CAP diagnosis (ED) for hospitalized patients (Old standard 4 hours)
- May initially need broad spectrum coverage
- May be able to de-escalate after pathogen known
- Duration
- Prophylaxis for thromboembolic disease

**CAP Antibiotic Overview**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>BL</th>
<th>MAC</th>
<th>FQ</th>
<th>DOX</th>
<th>Ket</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PCN-R</td>
<td>±</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Macro-R</td>
<td>±</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Atypicals</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Antibiotic choice highly dependent on specific agent selected
For S. pneumoniae with PCN MIC > 2 mg/L, vancomycin, FQ, or ketolide probably best choice depending on circumstances
BL-beta-lactam, MAC-macrolide, FQ-fluoroquinolone, DOX-doxycycline, Ket-ketolide

**Antibiotic Treatment**

- Presence of MDR bacteria?
- Combination Therapy
  - Aminoglycoside or Ciprofloxacin
  - Antipseudomonal Beta-lactam
  - Glycopeptide or Linezolid

**Vancomycin Treatment Guidelines**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Organ</th>
<th>Dose</th>
<th>Trough (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAP/VAP</td>
<td>ATS</td>
<td>15 mg/KgQ12H</td>
<td>15-20</td>
</tr>
<tr>
<td>Meningitis</td>
<td>IDSA</td>
<td>15-20*</td>
<td>15-20</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>BSAC</td>
<td>1GmQ12H</td>
<td>10-15</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>AHA</td>
<td>15 mg/KgQ12H</td>
<td>10-15*</td>
</tr>
</tbody>
</table>

* Graded Recommendation
Vancomycin Trough Recommendations from Treatment Guidelines

- Guidelines recommending vancomycin trough concentration of 10-20 mg/L based on expert opinion not clinical trial data
- No data that empiric doses will produce desired vancomycin trough concentrations
- No data that higher vancomycin trough concentrations are safe &/or more effective
- Would FDA allow a change in the vancomycin product insert?

Superior results for linezolid vs vancomycin in ventilator-associated pneumonia (VAP)

<table>
<thead>
<tr>
<th></th>
<th>Linezolid/aztreonam</th>
<th>Vancomycin/aztreonam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-treat VAP</td>
<td>45.4</td>
<td>36.7</td>
</tr>
<tr>
<td>S. aureus VAP</td>
<td>48.9</td>
<td>35.2</td>
</tr>
<tr>
<td>MRSA VAP</td>
<td>62.2</td>
<td>21.2</td>
</tr>
</tbody>
</table>

ATS Guidelines for HAP, VAP, & HCAP

- Combination vs Monotherapy
  - Synergy only documented in-vitro, in patients with neutropenia, or bacteremic patients
  - Clinical relevance is unclear
  - Preventing the emergence of resistance during therapy not well documented
- Meta-analysis of >1200/7586 patients with HAP/VAP beta-lactam monotherapy vs combination beta-lactam plus aminoglycoside, clinical failure more common with combination therapy
  - No advantage for P. aeruginosa
  - Combination therapy did not prevent emergence of resistance
  - More nephrotoxicity with combination

Summary

- LRTI/URTI's remain a serious and expensive problem
- Level of antibiotic resistance among common respiratory pathogens is concerning & could grow
- Need better diagnostic methods
- Antibiotics often over utilized in URTI & LRTI
  - Need to be more responsible with antibiotic resources
  - Increase the rate of vaccination for S. pneumoniae
  - Use oral therapy whenever possible
  - Use antibiotics for as short a time as possible
  - Remain watchful for antibiotic resistance & ADR’s

Summary

Optimizing Therapy:

- Get in quick with appropriate empiric antibiotics
- Hit hard with definitive therapy once pathogen is identified and dose appropriately
- Get out ASAP limiting collateral damage
  - 5 days of therapy for CAP
  - 7 days of therapy for HAP, VAP, & HCAP for non- MDR pathogens
- Streamline therapy per culture results