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)

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
- 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
      - Pao2/Fio2 < 250
    - Multilobar infiltrates
    - Confusion
    - Uremia
    - Neutropenia
    - Thrombocytopenia
    - Hypothermia

Pneumonia Diagnosis

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

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 sp
  - K. pneumoniae (ESBL positive)
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


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

Nosocomial Pneumonias

Early-onset pneumonia
- S. pneumoniae (~10%)
- H. influenzae (~50%)
- M. catarrhalis
- C. pneumoniae
- L. pneumophila
- Mycoplasma (~20%) (~10%)
- Viruses
- Fungi
- Less Common pathogens
- N. meningitidis
- S. pyogenes
- M. tuberculosis
- Chlamydia psittaci
- Coxiella burnetii
- B. anthracis
- Y. pestis
- F. tularensis


Late-onset pneumonia
- Aerobic gram-negative bacilli
- Pseudomonas
- Enterobacter
- Acinetobacter
- Klebsiella
- Staphylococcus aureus (~30%; may be present in mixed infections)
- Legionella (5% - 10%)
- Influenza A and B (~1%)
- Respiratory syncytial virus (~1%)
- Aspergillus (~1%)
- Pneumocystis carinii (~1%)
- Multiresistant bacteria
- Group 4 (n=84)
  - MV ≥ 7
  - ABT = yes
- Group 3 (n=17)
  - MV ≥ 7
  - ABT = no
- Group 2 (n=12)
  - MV < 7
  - ABT = yes
- Group 1 (n=22)
  - MV < 7
  - ABT = no

Organisms
- Multiresistant bacteria
- P. aeruginosa
- A. baumannii
- S. maltophilia
- Other bacteria

Other bacteria

Organisms
- Group 2 (n=5)
- Group 3 (n=5)

Other bacteria

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

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
  - ≥10^4 CFU/mL BAL
  - ≥10^3 CFU/mL PSB

Clinical management
- Clinical criteria
- Nonquantitative evaluation of nonbronchoscopic isolates


Effect of Mechanical Ventilation and Prior Antibiotic Use on Development of Multiresistant Pathogens

413 patients with suspected VAP
32% enrolled surgical patients

Invasive management
- BAL or bronchoscopic protected specimen brush (PSB)
- Quantitative sputum cultures
  - ≥10^4 CFU/mL BAL
  - ≥10^3 CFU/mL PSB

Clinical management
- Clinical criteria
- Nonquantitative evaluation of nonbronchoscopic isolates

Diagnosis of Suspected VAP

Intention-to-Treat Analysis

<table>
<thead>
<tr>
<th>End Point</th>
<th>Invasive (n=204)</th>
<th>Clinical (n=209)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 14 days, n (%)</td>
<td>33 (16.2)</td>
<td>54 (26.8)</td>
<td>0.022</td>
</tr>
<tr>
<td>Mortality at 28 days, n (%)</td>
<td>63 (30.9)</td>
<td>81 (38.6)</td>
<td>0.099</td>
</tr>
<tr>
<td>Antibiotic-free days at 14 days</td>
<td>5.6 ± 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>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative culture</td>
<td>55.9%</td>
<td>14.4%</td>
<td></td>
</tr>
<tr>
<td>Monomicrobial pneumonia</td>
<td>31.9%</td>
<td>40.2%</td>
<td></td>
</tr>
<tr>
<td>Polymicrobial pneumonia</td>
<td>12.3%</td>
<td>45.5%</td>
<td></td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>22.3%</td>
<td>18.3%</td>
<td></td>
</tr>
<tr>
<td>S. aureus</td>
<td>16.5%</td>
<td>12.8%</td>
<td></td>
</tr>
<tr>
<td>H. influenzae</td>
<td>7.4%</td>
<td>3.8%</td>
<td></td>
</tr>
<tr>
<td>A. baumannii</td>
<td>5.0%</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>Enterobacter spp.</td>
<td>3.3%</td>
<td>3.8%</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>TRUST 7 2003</th>
<th>TRUST 8 2004</th>
<th>TRUST 9 2005</th>
<th>TRUST 10 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>17.3%</td>
<td>18.6%</td>
<td>15.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>27.5%</td>
<td>25.0%</td>
<td>28.8%</td>
<td>31.9%</td>
</tr>
<tr>
<td>Trimeth/Sulfa</td>
<td>23.9%</td>
<td>21.2%</td>
<td>20.3%</td>
<td>21.5%</td>
</tr>
<tr>
<td>Ceftriaxone*</td>
<td>1.5%</td>
<td>1.4%</td>
<td>0.7%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.9%</td>
<td>1.1%</td>
<td>0.8%</td>
<td>0.6%</td>
</tr>
<tr>
<td>No. of institutions</td>
<td>227</td>
<td>220</td>
<td>184</td>
<td>157</td>
</tr>
<tr>
<td>No. of isolates</td>
<td>4452</td>
<td>4309</td>
<td>4958</td>
<td>3932</td>
</tr>
</tbody>
</table>

* Penicillin R = MIC > 2 µg/ml; NCCLS – central lab, Focus Technologies

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
- Joint IDSA/ATS HAP/ VAP / HCAP Guidelines 2005
2007 ATS/IDSA CAP Guidelines
Mandell, LA et al CID 44(suppl 2) 2007

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

Inpatient Non-ICU
• Respiratory fluoroquinolone
  - Macrolide (or Doxycycline) & beta-lactam
    – Cefotaxime, Ceftriaxone, Ampicillin, or Ertapenem

Inpatient ICU
• Azithromycin or respiratory fluoroquinolone plus beta-lactam
  – Cefotaxime, Ceftriaxone, or Ampicillin/Sulbactam

2007 ATS/IDSA CAP Guidelines
Mandell, LA et al CID 44(suppl 2) 2007

Community Acquired MRSA (CA-MRSA)
• Common following a viral infection
• CA-MRSA prolific toxin producer
• Treatment (No preference)
  – 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
  – Note: Daptomycin binds to lung surfactant & cannot be used for pneumonia

CAP Prevention
Mandell, LA et al CID 44(suppl 2) 2007
MMWR December 15, 2006 Vol 55

• Persons > 50yrs, healthcare workers, risk patients should receive annual influenza vaccination
• Persons > 65 yrs or at risk should receive pneumococcal vaccine

• CDC recommends Td 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

• Document
  - 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

750-mg, Short-Course Levofloxacin for CAP: Clinical Success by PSI Class

Dunbar et al Clin Infect Dis. 2003;37:752-760
**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**

<table>
<thead>
<tr>
<th>Aminoglycoside or Ciprofloxacin</th>
<th>Antipseudomonal Agent</th>
<th>Glycopeptide or Linezolid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

• Initial empiric therapy for HAP, VAP, & HCAP in patients with late onset or risk for MDR
  - Ceftriaxone (1-2Gm Q8-12H) or Ceftazidime (2Gm Q8H)
  - Imipenem (500mg Q8H) or Meropenem (1Gm Q8H)
  - Piperacillin/Tazobactam (4.5Gm Q8H)
  
  One of the above plus
  - Gentamicin or Tobramycin 7 mg/Kg/Day
  - Amikacin 20 mg/Kg/Day
  - Levofloxacin 750 mg QD or Ciprofloxacin 400 mg Q8H
  
  One of the above plus
  - Vancomycin 15 mg/Kg Q12H or Linezolid 600 mg Q12H
  - Daptomycin binds to lung surfactant & should not be used

**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></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)**

---

**Hoffman G, Niederman MS. Chest. 2002;122:2183-2196.**
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

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