CAP, HAP, VAP, & HCAP

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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

Pneumonia
• Community acquired pneumonia (CAP)
• Aspiration pneumonia
• Hospital
  – Hospital acquired pneumonia (HAP)
  – Ventilator associated pneumonia (VAP)
  – Healthcare associated pneumonia (HCAP)

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

Potential CAP Pathogens
• 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
- Immunocompromised
- 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**

- **Early-onset pneumonia**
  - Streptococcus pneumoniae (~10%)
  - Neisseria meningitidis (~5%)

- **Late-onset pneumonia**
  - Anaerobes (50% may be present in mixed infections)
  - Legionella (0% - 10%)
  - Influenza A and B (<1%)
  - Respiratory syncytial virus (~1%)
  - Aspergillus (<1%)
  - Pneumocystis carinii (<1%) (Multiresistant bacteria)


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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
  - ≥10⁵ CFU/mL BAL
  - ≥10⁴ CFU/mL PSB

**Clinical management**

- Clinical criteria
- Nonquantitative evaluation of nonbronchoscopic isolates


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

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Group 1 (MV ≥ 7 ABT = yes)</th>
<th>Group 2 (MV &lt; 7 ABT = yes)</th>
<th>Group 3 (MV ≥ 7 ABT = no)</th>
<th>Group 4 (MV &lt; 7 ABT = no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiresistant</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P. aeruginosa</td>
<td>12 (5.2)</td>
<td>4 (9.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>6</td>
<td>1 (2.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>S. maltophilia</td>
<td>0</td>
<td>8</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>MRSA</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other bacteria</td>
<td>47 (19.6)</td>
<td>14 (17.1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*p < 0.05 versus Group 1, 2, or 4
†p < 0.0001 versus Group 4

*Adapted from Trouillet JL, et al. Am J Respir Crit Care Med. 1998;157:531-539*

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**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</td>
<td>33 (16.2)</td>
<td>54 (25.8)</td>
<td>0.022</td>
</tr>
<tr>
<td>Mortality at 28 days</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 ± 9.1</td>
<td>2.2 ± 3.0</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><em>P. aeruginosa</em></td>
<td>22.3%</td>
<td>18.3%</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>16.5%</td>
<td>12.8%</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>7.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td><em>A. baumannii</em></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>


**Antimicrobial Resistance Trend: S. pneumoniae – USA - 2003-2006**

<table>
<thead>
<tr>
<th>Antimicrobial</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/Slufla</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>Levofoxacin</td>
<td>0.9%</td>
<td>1.1%</td>
<td>0.8%</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

No. of Institutions: 227, 220, 184, 157
No. of isolates: 4452, 4309, 4958, 3932

* Penicillin R = MIC > 2 µg/ml; NCCLS broth microdilution

**S. pneumoniae Penicillin Resistance**

- Influx-Block Porin Channel
- Efflux Pump (mefA)
- Enzyme Inactivation
- Metabolic Block & Bypass

**S. pneumoniae Macrolide Resistance**

- Influx-Block Porin Channel
- Efflux Pump (mefA)
- Enzyme Inactivation
- Metabolic Block & Bypass

**Pneumonia Treatment Guidelines**

**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 2006

**2003 IDSA CAP Guidelines**

Healthy & no previous antibiotic therapy (3 months)
- Macrolide or Doxycycline

Healthy but has had previous antibiotic therapy
- Respiratory fluoroquinolone
- Advanced macrolide plus high dose amoxicillin
- Advanced macrolide plus high dose amoxicillin/clavulanate

**Comorbidities present (COPD, CHF, diabetes...)**
- No previous antibiotics
- Advanced macrolide or Respiratory fluoroquinolone
- Previous antibiotics within past 3 months
  - Respiratory fluoroquinolone or Advanced macrolide and beta-lactam

Beta-lactam/Macrolide Combination Therapy

- IDSA/ATS recommendations CAP antibiotic therapy are primarily based on retrospective data
- Macrolide component may have immunomodulating properties and/or adds coverage for atypical pathogens
- Fluoroquinolone monotherapy performs comparably to beta-lactam/macrolide combination therapy
- Logistical issues
  - More complicated regimen for patient & healthcare system
  - Often cannot duplicate IV to PO antibiotics
  - Increases cost of therapy
  - Increases risk of adverse drug reactions

**2003 IDSA CAP Guidelines**

- Suspected aspiration
  - Clindamycin or Amoxicillin/clavulanate
- Inpatient – no recent antibiotics (3 months)
  - Respiratory fluoroquinolone
  - Advanced macrolide plus beta-lactam
  - Advanced macrolide plus high dose amoxicillin/clavulanate
- Inpatient – recent antibiotic therapy (3 months)
  - Respiratory fluoroquinolone
  - Advanced macrolide and beta-lactam

**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

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

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>H. influenzae or MSSA</td>
<td>Levofoxacin, Moxifloxacin, or Ciprofloxacin or Ampicillin/subactam or Ertapenem</td>
</tr>
<tr>
<td>Antibiotic Sens</td>
<td></td>
</tr>
<tr>
<td>E. coli</td>
<td></td>
</tr>
<tr>
<td>Enterobacter sp</td>
<td></td>
</tr>
<tr>
<td>Proteus sp</td>
<td></td>
</tr>
<tr>
<td>S. marcescens</td>
<td></td>
</tr>
</tbody>
</table>

**Antibiotic Treatment**

Presence of MDR bacteria?

- Initial empiric therapy for HAP, VAP, & HCAP in patients with late onset or risk for MDR
  - Cefepime (1-2Gm Q8-12H) or Ceftazidime (2Gm Q8H)
  - Imipenem (500mg Q6H) or Meropenem (1Gm Q8H)
  - Piperacillin/Tazobactam (4.5Gm Q6H)
  - Gentamicin or Tobramycin 7 mg/Kg/Day
  - Amikacin 20 mg/Kg/Day
  - Levofoxacin 750 mg QD or Ciprofloxain 400 mg Q8H
  - Vancomycin 15 mg/Kg Q12H or Linezolid 600 mg Q12H
  - Daptomycin binds to lung surfactant & should not be used

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
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 & more effective
- Would FDA allow a change in the vancomycin product insert?

Predictors of Mortality for MRSA HCAP: Specific Evaluation of Vancomycin PK Indices

Retrospective study N= 102 over 6.5 years
- BAL confirmed MRSA HCAP
- Extrapolated \( C_{\text{min}} \) & estimated AUC
- No MIC done (S, I, R)

Survivors NonSurvivors

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>( C_{\text{min}} ) mg/L</th>
<th>AUC</th>
<th>( \text{CrCl} ) mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survivors</td>
<td>70</td>
<td>13.6</td>
<td>13.9 mg/L</td>
<td>351+143</td>
</tr>
<tr>
<td>NonSurvivors</td>
<td>32</td>
<td>13.9</td>
<td>13.9 mg/L</td>
<td>354+109</td>
</tr>
</tbody>
</table>

* No evidence that greater vancomycin \( C_{\text{min}} \) or AUC values correlated with hospital outcome
* Aggressive dosing strategies for vancomycin may not offer any advantage over traditional dose targets.

Increased Incidence of Nephrotoxicity with Higher Vancomycin Serum Trough Concentrations.

M. N. JEFFRES KT89 (ICAAC 2006)

- 94 patients (N=43 < 15 mg/L, N=51 \( \geq \) 15 mg/L)
- Nephrotoxicity was defined as a 25% decrease in estimated CrCl
- Trough concentrations \( \geq 15 \) mg/L & length of therapy are associated with increased risk of renal toxicity
- Nephrotoxicity occurred in 13 patients (30.2%) with troughs < 15 mg/L and 30 patients (58.8%) with troughs \( \geq 15 \) mg/L (p=0.006)

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

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 \textit{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