Treatment of Hospital-Acquired and Ventilator-Associated Pneumonia

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Disclosures

- No actual or potential conflicts of interest in relation to this presentation
Learning Objectives

**Pharmacists**
1. Define hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)
2. Describe three updates from the 2005 guidelines for treatment of nosocomial pneumonia
3. Select appropriate first-line antimicrobials for empiric treatment of HAP and VAP

**Technicians**
1. Identify symptoms associated with HAP and VAP
2. Define a hospital antibiogram and its role in treatment of HAP and VAP
3. List antimicrobials used in the treatment of HAP and VAP
Terms

- HAP: Hospital-acquired pneumonia
- VAP: Ventilator-associated pneumonia
- CAP: Community-acquired pneumonia
- HCAP: Healthcare-associated pneumonia
- HAI: Hospital-acquired infection
- ICU: Intensive care unit
- IDSA: Infectious Diseases Society of America
- ATS: American Thoracic Society
- MDR: Multi-drug resistant
- BAL: Bronchoalveolar lavage
- PSB: Protected specimen brush
- PCT: Procalcitonin
- sTREM-1: Soluble triggering receptor expressed on myeloid cells
- CRP: C-reactive protein
- CPIS: Clinical pulmonary infection score
- MRSA: Methicillin Resistant S. aureus
- MSSA: Methicillin Susceptible S. aureus
- PK: Pharmacokinetic
- PD: Pharmacodynamic
- ESBL: extended-spectrum beta-lactamase
- GNR: gram negative rod
Background

• Account for 21.8% of HAIs
• VAP
  • 10% of patients who require mechanical ventilation
  • Attributable mortality estimated at 13%
  • Increases mechanical ventilation, hospitalization, cost
• HAP
  • HAP in ICU has similar mortality rate as VAP
  • Complications occur in 50% of patients

Background

- IDSA/ATS Clinical Practice Guidelines
  - 2005: Management of Adults with HAP, VAP, and HCAP
  - 2016: Management of Adults with HAP and VAP
- Where did HCAP go?
  - Patients with “HCAP” NOT high risk for MDR pathogens
  - Patient characteristics are important determinants
  - Coverage for MDR pathogens among community-dwelling patients
    - Validated risk factors for MDR pathogens
    - Spring 2018 CAP Guidelines

ATS/IDSA. Am J Respir Crit Care Med 2005;171:388-416
Definitions

- Pneumonia
  - Presence of new lung infiltrate
  - Clinical evidence the infiltrate is of an infectious origin
    - New onset fever, purulent sputum, leukocytosis, decline in oxygenation
- HAP
  - Not incubating at the time of hospital admission
  - Occurring 48 hours or more after admission
- VAP
  - Occurring >48 hours after endotracheal intubation

Risk Factors for MDR VAP

- Prior intravenous antibiotic use within 90 days
- Septic shock at time of VAP onset
- ARDS preceding VAP
- ≥ 5 days of hospitalization prior to VAP onset
- Acute renal replacement therapy prior to VAP onset
## Risk Factors for MDR Pathogens

<table>
<thead>
<tr>
<th>Risk Factors for MDR HAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prior intravenous antibiotic use within 90 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factors for MRSA HAP/VAP</th>
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<tbody>
<tr>
<td>• Prior intravenous antibiotic use within 90 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Factors for <em>Pseudomonas</em> HAP/VAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prior intravenous antibiotic use within 90 days</td>
</tr>
</tbody>
</table>

Note: structural lung disease (cystic fibrosis and bronchiectasis) also important factor

IDSA/ATS Diagnostic Recommendations
Diagnostic Methods

- Blood Cultures: all patients with suspected HAP/VAP
- Microbiologic Methods
  - VAP
    - Non-invasive sampling with semiquantitative cultures preferred
    - Endotracheal aspiration
    - Invasive quantitative culture cutoffs
      - BAL: $10^4$ CFU/mL
      - PSB: $10^3$ CFU/mL
Diagnostic Methods

• Microbiologic Methods [cont.]
  • HAP
    • Non-invasive sputum sampling preferred over empiric treatment
    • Spontaneous expectoration
    • Sputum induction
    • Nasotracheal suctioning
    • Endotracheal aspiration if requiring mechanical ventilation

Diagnostic Methods

- Biomarkers to diagnose along with clinical criteria
  - PCT – not recommended
  - sTREM-1 – not recommended
  - CRP – not suggested
- Clinical Pulmonary Infection Score (CPIS)
  - Semi-objective scoring tool for VAP (0-12)
  - Not recommended

IDSA/ATS Treatment Recommendations – VAP
VAP – Empiric Treatment

- Antibiograms
  - Local (hospital-specific, unit specific)
  - Population-specific ideal (ie. VAP patients)
  - “Regularly” update and disseminate
- Empiric treatment informed by:
  - Local distribution of pathogens and their susceptibilities

VAP – Empiric Treatment

• Empiric regimens should cover:
  • *Staphylococcus aureus*  • Other gram-negative bacilli
  • *Pseudomonas aeruginosa*

<table>
<thead>
<tr>
<th>Organism</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>20-30%</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>10-20%</td>
</tr>
<tr>
<td>Enteric Gram Negative Bacilli</td>
<td>20-40%</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>5-10%</td>
</tr>
</tbody>
</table>

VAP – Empiric Treatment

• *Staphylococcus aureus* coverage
  • MRSA if one of the following:
    o IV antibiotics in last 90 days (risk factor for MRSA VAP)
    o Risk factor for MDR VAP
    o Local MRSA prevalence >10-20%
    o Local MRSA prevalence unknown
  • MSSA coverage if none present

VAP – Empiric Treatment

• *Pseudomonas aeruginosa*/gram-negative coverage

• 2 agents if one of the following:
  o Risk factor for MDR VAP
  o Local gram-negative resistance >10% for single agent used
  o Local gram-negative resistance unknown
  o Structural lung disease (cystic fibrosis, bronchiectasis)

• 1 agent if none present

### Empiric Treatment Regimens for VAP

<table>
<thead>
<tr>
<th>MRSA Agents</th>
<th>AP Beta Lactams</th>
<th>AP Non-Beta Lactams</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycopeptide</td>
<td><strong>Antipseudomonal</strong> Penicillins</td>
<td>Fluoroquinolones Ciprofloxacin</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Piperacillin-tazobactam</td>
<td>Levofloxacin</td>
</tr>
<tr>
<td><strong>Oxazolidinones</strong></td>
<td><strong>Cephalosporins</strong> Cefepime Ceftazidime</td>
<td>Aminoglycosides Amikacin Gentamicin Tobramycin</td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Carbenapenems</strong> Imipenem Meropenem</td>
<td>Polymyxins (not preferred) preferred Colistin Polymyxin B</td>
</tr>
<tr>
<td></td>
<td><strong>Monobactams</strong> Aztreonam</td>
<td></td>
</tr>
</tbody>
</table>
VAP – Empiric Treatment

• No MRSA empiric coverage indicated
  • Include antipseudomonal with MSSA activity
    o Piperacillin-tazobactam, Cefepime, Levofloxacin, Imipenem, Meropenem
• Avoid aminoglycosides if possible
• Avoid colistin if possible
HAP – Empiric Treatment

- Antibiograms
  - Local (hospital-specific, unit specific)
  - Population-specific ideal (ie. HAP patients)
  - “Regularly” update and disseminate
- Empiric treatment informed by:
  - Local distribution of pathogens and their susceptibilities
HAP – Empiric Treatment

- Empiric regimens should cover:
  - *Staphylococcus aureus*
  - *Pseudomonas aeruginosa*
  - Other gram-negative bacilli

<table>
<thead>
<tr>
<th>Organisms Associated with VAP</th>
<th>Prevalence</th>
</tr>
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<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>16%</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>13%</td>
</tr>
<tr>
<td>Enteric Gram Negative Bacilli</td>
<td>19%</td>
</tr>
<tr>
<td>Acinetobacter baumannii</td>
<td>6%</td>
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HAP – Empiric Treatment

- *Staphylococcus aureus* coverage
  - MRSA if one of the following:
    - IV antibiotics in last 90 days (risk factor for MRSA HAP)
    - Local MRSA prevalence >20%
    - Local MRSA prevalence unknown
    - High risk of mortality
      - Ventilatory support due to HAP or septic shock
  - MSSA coverage if none present

HAP – Empiric Treatment

• *Pseudomonas aeruginosa*/gram-negative coverage

• 2 agents if one of the following:
  o Risk factor for MDR HAP (IV antibiotics within 90 days)
  o High risk of mortality
    ▪ Ventilatory support due to HAP or septic shock
  o Structural lung disease (cystic fibrosis, bronchiectasis)
  o Numerous and predominant gram-negative bacilli on gram stain

• 1 agent if none present

# Empiric Treatment Regimens for HAP

<table>
<thead>
<tr>
<th>Not high risk for mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>No MRSA risk factors</td>
</tr>
<tr>
<td>One of the following:</td>
</tr>
<tr>
<td>• Piperacillin-tazobactam</td>
</tr>
<tr>
<td>• Cefepime</td>
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<td>• Levofloxacin</td>
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<tr>
<td>• Imipenem</td>
</tr>
<tr>
<td>• Meropenem</td>
</tr>
<tr>
<td>• Aztreonam</td>
</tr>
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<table>
<thead>
<tr>
<th>High risk of mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV antibiotics within 90 days</td>
</tr>
<tr>
<td>Two of the following:</td>
</tr>
<tr>
<td>• Piperacillin-tazobactam</td>
</tr>
<tr>
<td>• Cefepime</td>
</tr>
<tr>
<td>• Ceftazidime</td>
</tr>
<tr>
<td>• Imipenem</td>
</tr>
<tr>
<td>• Meropenem</td>
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<td>• Aztreonam</td>
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<th>Plus one of the following:</th>
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<td>• Vancomycin</td>
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HAP – Empiric Treatment

• No MRSA empiric coverage indicated
  • Include antipseudomonal with MSSA activity
    o Piperacillin-tazobactam, Cefepime, Levofloxacin, Imipenem, Meropenem
• Avoid aminoglycoside monotherapy
• Avoid colistin if possible
IDSA/ATS Additional Recommendations – HAP/VAP
PK/PD Dosing

- Utilize PK/PD data for antibiotic dosing
- Examples
  - Antibiotic blood concentrations: Vancomycin
  - Extended and continuous infusions: β-Lactams
    - Penicillins, cephalosporins, carbapenems
  - Weight-based dosing: Aminoglycosides
- Reduced mortality, ICU length of stay
- Improved clinical cure rate

Inhaled Antibiotics

- Both inhaled and systemic antibiotics
  - VAP due to gram negative bacilli
    - Susceptible ONLY to aminoglycosides/polymyxins
    - Not responding to IV antibiotics alone
  - Tobramycin, gentamicin, and colistin
  - Improves clinical cure rate
  - No effect on mortality, adverse drug reactions

# HAP/VAP – Directed Treatment

<table>
<thead>
<tr>
<th>Proven Organism</th>
<th>Agent(s) of Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA</td>
<td>Oxacillin, Nafcillin, Cefazolin</td>
</tr>
<tr>
<td>MRSA</td>
<td>Vancomycin, Linezolid</td>
</tr>
<tr>
<td><em>Pseudomonas</em> <em>spp.</em></td>
<td>Based on susceptibilities*, avoid aminoglycosides</td>
</tr>
<tr>
<td>ESBL-producing GNR</td>
<td>Based on susceptibilities (Carbapenems?)</td>
</tr>
<tr>
<td><em>Acinetobacter</em> <em>spp.</em></td>
<td>Carbapenems, Ampicillin/Sulbactam, (Colistin IV/INH)</td>
</tr>
<tr>
<td>Carbapenem-resistance</td>
<td>Polymyxins IV + Colistin INH</td>
</tr>
</tbody>
</table>

*Consider 2 agents if in septic shock or high risk of death (>25%)

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HAP/VAP – Length of Therapy

- 7-day course recommended for all patients
  - **Reduced:**
    - Antibiotic exposure
  - **No difference:**
    - Mortality
    - Recurrent pneumonia
    - Treatment failure
    - VAP due to MDR pathogens
    - Length of stay
    - Mechanical ventilation

HAP/VAP – Final Recommendations

- De-escalate when susceptibilities known
- Discontinuation of antibiotics along with clinical criteria
  - PCT: suggested
    - If used, baseline PCT then daily
  - CPIS: not suggested

Summary
Pneumonia ≥ 48 hours after:

Hospitalization (HAP)
- Any of the following?
  - IV antibiotics in last 90 days
  - Ventilator support
  - Septic shock

Are S. aureus isolates:
- >10-20% MRSA? (VAP)
- >20% MRSA? (HAP)
- Unknown? (HAP/VAP)

Treatment:
- MRSA coverage plus
- 2 anti-pseudomonal agents
- Different classes

Intubation (VAP)
- Any of the following?
  - IV antibiotics in last 90 days
  - Septic shock
  - ARDS preceding VAP
  - ≥ 5 days hospitalization
  - Acute RRT prior to VAP

Treatment:
- MRSA coverage plus
- Anti-pseudomonal agent(s)

Any of the following?
- Structural lung disease
- >10% pseudomonal resistance to monotherapy (VAP)
- Local susceptibilities unknown (VAP)
- Numerous/predominant GN bacilli on gram stain (HAP)

Treatment:
- 1 anti-pseudomonal agent
- MSSA activity (if no MRSA)

Treatment:
- 2 anti-pseudomonal agents
- 1 with MSSA activity (if no MRSA)
- Different classes

Step 1: Risk/Severity
Step 2: GP Risk
Step 3: GN Risk
Takeaway Points

• Removal of the term “HCAP”
• Removal of the term “early-onset” and “late-onset”
• Development of hospital/unit-specific antibiograms
  • Minimize unnecessary dual gram-negative coverage
  • Minimize unnecessary MRSA coverage
• Risk factor assessment – see treatment algorithm
• PK/PD dosing preferred
• Directed therapy preferred
• Short-course (7 days) preferred over longer course
Assessment Question #1

Hospital acquired pneumonia (HAP) is defined as a pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after hospital admission.

True or False.
Assessment Question #1

Hospital acquired pneumonia (HAP) is defined as a pneumonia not incubating at the time of hospital admission and occurring 48 hours or more after hospital admission.

True or False.
Assessment Question #2

Which of the following durations is appropriate for most patients treated for HAP or VAP?

a. 3 days
b. 7 days
c. 10 days
d. 14 days
Assessment Question #2

Which of the following durations is appropriate for most patients treated for HAP or VAP?

a. 3 days
b. 7 days
c. 10 days
d. 14 days
Assessment Question #3

Which of the following combinations represents the most appropriate empiric treatment regimen for hospital-acquired pneumonia (HAP) where the prevalence of MRSA is >20% and the patient has not had IV antibiotics in the last 90 days and is not at high risk of mortality?

a. Daptomycin + piperacillin-tazobactam
b. Linezolid + tobramycin
c. Vancomycin + cefepime
d. Vancomycin + cefepime + levofloxacin
Assessment Question #3

Which of the following combinations represents the most appropriate empiric treatment regimen for hospital-acquired pneumonia (HAP) where the prevalence of MRSA is >20% and the patient has not had IV antibiotics in the last 90 days and is not at high risk of mortality?

a. Daptomycin + piperacillin-tazobactam
b. Linezolid + tobramycin

**c. Vancomycin + cefepime**

d. Vancomycin + cefepime + levofloxacin
References

Questions?
**Table 1. Clinical Pulmonary Infection Score Calculation**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature, °C</td>
<td></td>
</tr>
<tr>
<td>36.5–38.4</td>
<td>0</td>
</tr>
<tr>
<td>38.5–39.4</td>
<td>1</td>
</tr>
<tr>
<td>≥39.0 and ≤30.0</td>
<td>2</td>
</tr>
<tr>
<td>Blood leukocyte level, leukocytes/mm³</td>
<td></td>
</tr>
<tr>
<td>4000–11,000</td>
<td>0</td>
</tr>
<tr>
<td>≤4000 or &gt;11,000</td>
<td>1</td>
</tr>
<tr>
<td>Plus band forms &gt;500</td>
<td>2</td>
</tr>
<tr>
<td>Tracheal secretions</td>
<td></td>
</tr>
<tr>
<td>&lt;1+</td>
<td>0</td>
</tr>
<tr>
<td>&gt;1+</td>
<td>1</td>
</tr>
<tr>
<td>Plus purulence</td>
<td>2</td>
</tr>
<tr>
<td>Oxygenation, PaO₂/FiO₂ mm Hg</td>
<td></td>
</tr>
<tr>
<td>&gt;240 or ARDS</td>
<td>0</td>
</tr>
<tr>
<td>≤240 and no ARDS</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary radiograph finding</td>
<td></td>
</tr>
<tr>
<td>No infiltrate</td>
<td>0</td>
</tr>
<tr>
<td>Diffuse or patchy infiltrate</td>
<td>1</td>
</tr>
<tr>
<td>Localized infiltrate</td>
<td>2</td>
</tr>
<tr>
<td>Culture of tracheal aspirate specimen (semiquantitative: 0–1, −2, or 3+)</td>
<td></td>
</tr>
<tr>
<td>Pathogenic bacteria cultured ≤1 or no growth</td>
<td>0</td>
</tr>
<tr>
<td>Pathogenic bacteria cultured &gt;1+</td>
<td>1</td>
</tr>
<tr>
<td>Plus some pathogenic bacteria on Gram stain &gt;1+</td>
<td>2</td>
</tr>
</tbody>
</table>

*N.B.*: ARDS, acute respiratory distress syndrome; PaO₂/FiO₂, ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen.
Figure 1: Guidelines for starting, continuing, or stopping of antibiotics according to procalcitonin concentrations

*Excludes situations requiring immediate antibiotic treatment (eg, septic shock, purulent meningitis.

Supplemental Slides

- Piperacillin-tazobactam (PT) vs. cefepime (C) with concomitant vancomycin (V)
  - AKI in VPT vs. VC (retrospective, matched cohort); Navalkele et al. 2017
    - VPT 81/279 [29%] vs. VC 31/279 [11%] (HR 4.27, 95% CI 2.73-6.68)
    - VPT faster onset than VC (3 vs 5 days; p<0.0001)
  - AKI in V with PT vs. V without PT (meta-analysis); Hammond et al. 2017
    - VPT associated with AKI (OR 3.12, 95% CI 2.04-4.78)
  - AKI in VPT SI vs. VPT EI (retrospective, matched cohort); Mousavi et al. 2017
    - VPT SI 24/140 [17.1%] vs VPT EI 25/140 [17.9%] (p>0.99)
    - Median time to onset 4 (IQR 3-6) days, no difference