Diagnosis and stratification of patients at risk for MDR in Hospital-acquired Pneumonia

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Epidemiology of Nosocomial Pneumonia in US

- Second commonest hospital-acquired infection (15%)
- Approximately 300,000 cases annually
- 5–10 cases per 1,000 admissions
- Up to 20 times more in ventilated pts
- Mortality
  - Crude mortality as high as 70%
  - Attributable mortality 33% to 50%
  - Increased in older and critically ill pts

# Epidemiology, Etiology and Diagnosis of HAP and VAP in Asian Countries

<table>
<thead>
<tr>
<th></th>
<th>6 to 21 per 1000 hospital admissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAP in ICU</td>
<td>9% to 23% of ICU Admissions</td>
</tr>
<tr>
<td>VAP</td>
<td>3.5 to 46 per 1000 ventilator-days</td>
</tr>
<tr>
<td>HAP &amp; VAP mortality</td>
<td>25% to 58% of total HAP (and VAP) cases</td>
</tr>
</tbody>
</table>

Healthcare-associated pneumonia is a relatively new clinical entity that includes a spectrum of adult pts who have a close association with acute-care hospitals or reside in chronic-care settings that increase their risk for pneumonia caused by MDR pathogens.

- **CAP** = community-acquired pneumonia
- **HCAP** = healthcare-associated pneumonia
- **HAP** = hospital-acquired pneumonia
- **VAP** = ventilator-associated pneumonia

Getting Therapy Right First Time

There is now significant evidence that adequate antibiotic therapy will save more lives than virtually all other ICU therapy.

Resistance Makes Choosing Appropriate Empiric Therapy Difficult

- Methicillin/S. aureus: 57.1%
- Imipenem/P. aeruginosa: 22.3%
- Quinolone/P. aeruginosa: 32.8%
- 3rd Ceph/K. pneumoniae: 14%
- 3rd Ceph/P. aeruginosa: 30.2%
- 3rd Ceph/Enterobacter spp: 32.2%

% Resistance Jan-Dec 2002

Case study-Post-Op Pneumonia (POP)

- 57 yr old woman
- Sudden GI bleeding and emergency surgery
- Febrile (T 38.9) the second day, cough sputum, infiltrate on X-ray-POP
- ABG: PaO₂ = 56 mmHg on air
- Carbapenem + anti-MRSA + antifungal
- Pneumonia getting better in 4 days
  - what to do next?
  - Shall we continue on this regimen?
Start from ABC to go further

- Considerations in adequate empiric antibiotic therapy - the very basics

- Diagnosis and stratification of patients at risk for MDR in HAP
For Any Infectious Disease
Considerations in Adequate Antibiotic therapy

- **Which antibiotic?**
  - possible pathogens on site of infection
  - antibiotics requirements
    - coverage
    - resistance pattern
    - tissue penetration
    - safety/cost

- Optimizing PK/PD

- Physiology and pathophysiology
  - advanced age/children/pregnant women/breast feeding
  - renal/heptic dysfunction/combined dysfunction

- Other considerations
  - cidal or static/mono or combination/IV or Oral/duration

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cover probable bugs including resistant ones

not an excuse for cover everything by using wide spectrum abx including combination therapy FREELY

how to diagnose patients at risk for resistant bugs infection?
Risk factors for MDR bugs - general rules

- Aged above 65 years
- Residence in a long-term care facility
- Severe underlying disease (Chronic liver, lung, or vascular disease Neutropenia)
- Previous/multiple hospitalization/increased LOS/Stay in an ICU
- Prior or prolonged exposure to antibiotics
- Presence of invasive indwelling device
- Neonate
- Presence and size of a wound
- Dialysis
- Exposure to colonized or infected patient

MRSA colonization or infection

*Infect Control Hosp Epidemiol 2000;21:718-23*
## Risk factors for infection with ESBL producers (MDR) outside hospital

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_x$ 3 gen ceph</td>
<td>15.8</td>
</tr>
<tr>
<td>$R_x$ 2 gen ceph</td>
<td>10.1</td>
</tr>
<tr>
<td>Hospital in last 3 months</td>
<td>8.95</td>
</tr>
<tr>
<td>$R_x$ quinolone</td>
<td>4.1</td>
</tr>
<tr>
<td>$R_x$ penicillins</td>
<td>4.0</td>
</tr>
<tr>
<td>Antibiotic $R_x$ in last 3 months</td>
<td>3.23</td>
</tr>
<tr>
<td>Age &gt;60 years</td>
<td>2.65</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.57</td>
</tr>
</tbody>
</table>

Colodner et al EJC MID 2004 23, 163.
Demographic and Clinical Characteristics of Patients with or without Isolates of MDR Gram-Negative Bacilli Recovered at Hospital Admission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Case patients (n = 55)</th>
<th>Control patients (n = 55)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 years</td>
<td>35 (64)</td>
<td>24 (44)</td>
<td>2.3 (0.98–5.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Male sex</td>
<td>20 (36)</td>
<td>26 (47)</td>
<td>0.6 (0.3–1.5)</td>
<td>.3</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>43 (78)</td>
<td>32 (58)</td>
<td>2.6 (1.04–6.5)</td>
<td>.02</td>
</tr>
<tr>
<td>Other</td>
<td>12 (22)</td>
<td>23 (42)</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>Resident of a long-term care facility</td>
<td>24 (43)</td>
<td>6 (11)</td>
<td>5.2 (1.7–17.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Transferred hospitals</td>
<td>6 (11)</td>
<td>5 (9)</td>
<td>0.8 (0.2–3.5)</td>
<td>.8</td>
</tr>
<tr>
<td>Reason for hospital admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>24 (44)</td>
<td>22 (40)</td>
<td>1.2 (0.5–2.7)</td>
<td>.7</td>
</tr>
<tr>
<td>Medical</td>
<td>31 (56)</td>
<td>33 (60)</td>
<td>Reference group</td>
<td></td>
</tr>
<tr>
<td>Charlson score of ≥3</td>
<td>39 (71)</td>
<td>19 (35)</td>
<td>4.6 (1.9–11.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥2 Hospitalizations during the prior year</td>
<td>30 (55)</td>
<td>12 (22)</td>
<td>4.3 (1.7–10.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous ICU stay</td>
<td>21 (38)</td>
<td>5 (9)</td>
<td>3.1 (1.1–10.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Received a solid-organ transplant &lt;sup&gt;a&lt;/sup&gt;</td>
<td>9 (16)</td>
<td>0 (0)</td>
<td>...</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Received long-term hemodialysis</td>
<td>3 (5)</td>
<td>3 (5)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Previous surgery &lt;sup&gt;b&lt;/sup&gt;</td>
<td>19 (35)</td>
<td>5 (9)</td>
<td>5.3 (1.7–19.5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Prior exposure to antibiotics for ≥14 days &lt;sup&gt;b&lt;/sup&gt;</td>
<td>31 (56)</td>
<td>4 (7)</td>
<td>16.5 (4.9–69.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Data are no. (%) of patients, unless indicated otherwise. ICU, intensive care unit.  
<sup>a</sup> There were no bone marrow transplant recipients in the study.  
<sup>b</sup> Within 90 days before admission.

Pop-Vicas AE et al. CID 2005
### Stratification for Risk for MDR Gram-Negative Pathogens

<table>
<thead>
<tr>
<th>No Risk Factors for MDR Pathogens</th>
<th>Risk Factors for MDR Enterobacteriaceae&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Risk Factors for MDR Pseudomonas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health care contact</td>
<td>Yes! (eg, recent hospital admission, nursing home, dialysis) without invasive procedure</td>
<td>Yes, Long hospitalization and/or infection following invasive procedures (&gt;5 days)</td>
</tr>
<tr>
<td>Recent Abx</td>
<td>Yes! (≥14 days in past 90 days)</td>
<td>Yes ! (≥14 days in past 90 days)</td>
</tr>
<tr>
<td>Patient characteristics</td>
<td>≥65 yrs</td>
<td>co-morbidities such as CF, structural lung disease, advanced AIDS, neutropenia, or other severe immunodeficiency</td>
</tr>
<tr>
<td>Young few comorbidities</td>
<td>≥65 yrs</td>
<td>co-morbidities such as TPN or renal insufficiency</td>
</tr>
</tbody>
</table>

<sup>a</sup>Except nonfermenters/non-Pseudomonas species.

Start from ABC to go further

- Considerations in adequate empiric antibiotic therapy - the very basics
- Diagnosis and stratification of patients at risk for MDR in HAP
The Microbiology of HAP-ATS/IDSA

- **Gram-negative = 48%**
  - *Pseudomonas* spp.
  - *Acinetobacter* spp.
  - *Klebsiella* spp.
  - *E.coli*

- **Gram-positive = 43%**
  - *S. aureus*
  - *S. pneumoniae*

- **Others = 9% (viruses 1%)**

#### Epidemiology, Etiology and Diagnosis of HAP and VAP in Asian Countries

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>India*</th>
<th>Pakistan*</th>
<th>China</th>
<th>Korea</th>
<th>Malaysia*</th>
<th>Taiwan*</th>
<th>Thailand*</th>
<th>Philippines</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pseudomonas</em> spp</td>
<td>20%</td>
<td>15-18%</td>
<td>18%</td>
<td>23%</td>
<td>17.6%</td>
<td>21%</td>
<td>17.8%</td>
<td>42.1%†</td>
</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>38%</td>
<td>58.5%</td>
<td>16%</td>
<td>9%</td>
<td>23%</td>
<td>20%</td>
<td>28.2%</td>
<td>13.1%†</td>
</tr>
<tr>
<td>MRSA</td>
<td>5%</td>
<td>18%</td>
<td>16%</td>
<td>23%</td>
<td>11.6%</td>
<td>18%</td>
<td>7.6%</td>
<td></td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>23%</td>
<td>No data</td>
<td>14%</td>
<td>11%</td>
<td>5.8%</td>
<td>9%</td>
<td>7.7%</td>
<td>26.3%†</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>6.1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.6%</td>
<td>2.8%</td>
<td></td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
<td>8.2%</td>
<td>8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>S. maltophilia</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.8%</td>
<td></td>
<td>3.4%</td>
<td></td>
</tr>
</tbody>
</table>

*Local data.
†VAP.


Causative Agents

- **Enteric G(-) bacilli**
  - Most frequent, particularly in patients with late-onset disease and in patients with serious underlying disease often already on broad-spectrum antibiotics.
  - Prior use of broad-spectrum abx and an immunocompromised state make resistant gram-negative organisms more likely.

- **P. aeruginosa and Acinetobacter**
  - Common in late-onset HAP, particularly in late-onset VAP
Causative Agents

- **S. aureus**
  - in about 20~40% of cases and is particularly common in
    - ventilated pts after head trauma, neurosurgery, and wound infection
    - in pts who had received prior antibiotics or prolonged care in ICU

- **Anaerobes**
  - common in pts predisposed to aspiration
  - more often with oropharyngeal intubation than nasopharyngeal intubation.
Legionella pneumophilia

- Occurs sporadically
- But be endemic in hospitals with contaminated water systems.
- Incidence is underestimated because test to identify Legionella not performed routinely.
- Patients who are immunocompromised, critically ill, or on steroids are at highest risk for infection.
Question 1.

what do you think is more important in choosing an appropriate empiric antibiotic therapy for HAP

1. risk factors for MDROs
2. disease severity
Keypad Question

Which is more important in Initial Empiric Antibiotic Therapy for HAP?

1. Risk factors for MDR
2. Duration of HAP/VAP
3. Disease severity?
Initial Empiric Antibiotic Therapy for HAP

Which is more important?

- Risk factors for MDR-the most important
  - previous antibiotic exposure
- Time of onset of HAP/VAP-the second most important
  - core pathogens, probably resistance pattern
- Disease severity? –my personal perspective
  - hint for some specific pathogens (L pneumophila)
  - not predictive for resistance
Microbiology of HAP

- Generally concerned about
  - EGNB
  - S. aureus
  - Polymicrobial in 50% patients on MV

- **How to diagnose Risk factors for MDROs in HAP/VAP**
  - Risk factors for MDR organisms in general
    - Previous antibiotic exposure
  - Spontaneous breathing vs ventilated patient
  - Time of onset (early-onset vs late-onset)

Stratification of Patients at Risk for MDR Organisms

-Risk Factors for MDR Pathogens

- Antimicrobial therapy in preceding 90 days
- Current hospitalization of ≥5 days
- High frequency of community or hospital-unit antibiotic resistance
- Presence of risk factors for HCAP
  - Hospitalization for ≥2 days in preceding 90 days
  - Residence in a nursing home or LTC facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 days
  - Home wound care
  - Family member with MDR pathogen
- Immunosuppressive disease and/or therapy

Stratification of Patients at Risk for MDR Organisms

- spontaneously breathing vs ventilated

- The differences not firmly settled
- Available data indicate in spontaneously breathing pts
  - potentially drug resistant microorganisms may play a minor role
  - GNEB (abx susceptible), S aureus (MSSA) and S pneumoniae as leading pathogens

Stratification of Patients at Risk for MDR Organisms

- early onset vs late-onset

**Time from Hospitalization (days)**

0 1 2 3 4 5 6 7

**Early-onset HAP**

**Late-onset HAP**

**Time from Intubation (days)**

0 1 2 3 4 5 6 7

**Early-onset VAP**

**Late-onset VAP**

<table>
<thead>
<tr>
<th></th>
<th>Early HAP/VAP</th>
<th>Late HAP/VAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>Within five days of admission or mechanical ventilation</td>
<td>Five days or more after admission or mechanical ventilation</td>
</tr>
<tr>
<td><strong>Bacteriology</strong></td>
<td><em>S. pneumoniae</em>&lt;br&gt;<em>H. influenzae</em>&lt;br&gt;Methicillin-sensitive <em>S. aureus</em>&lt;br&gt;Susceptible gram-negative bacteria</td>
<td><em>P. aeruginosa</em>&lt;br&gt;<em>Acinetobacter</em>&lt;br&gt;Methicillin-resistant <em>S. aureus</em>&lt;br&gt;Other multi-resistant organisms</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Less severe, little impact on outcome&lt;br&gt;Mortality minimal</td>
<td>Higher attributable mortality and morbidity</td>
</tr>
</tbody>
</table>

Bugs of Hosp-acquired pneumonia

Early
- Strep
- H flu

Middle
- Staph aureus
- MRSA
- Enterobacter
- Klebsiella, E coli
- Pseudomonas aeruginosa
- Acinetobacter sp

Late
- Stenotrophomonas

1  3  5  10  15  20

Antibiotic pressure
135 episodes of VAP

<table>
<thead>
<tr>
<th>variables</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV &gt;7 days</td>
<td>6.0</td>
<td>.009</td>
</tr>
<tr>
<td>Previous ABs</td>
<td>13.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Wide-spectrum ABs</td>
<td>4.1</td>
<td>.025</td>
</tr>
</tbody>
</table>

Recent Antibiotic Therapy and Pseudomonal Resistance

- *P. aeruginosa* VAP: 34 isolates piperacillin and multi-drug resistant; 101 sensitive
- Use of antibiotics (*imipenem, third generation cephalosporin and quinolone*) within 15 days of VAP increased PA resistance to the same agent-patient-specific abx rotation

### Resistance of *P aeruginosa* Strains To Imipenem, Ceftazidime, or Ciprofloxacin, According to Previous Therapy With Imipenem, a 3rd-generation Cephalosporin, or a Fluoroquinolone

<table>
<thead>
<tr>
<th>Strain resistance</th>
<th>No. (%) of patients, by previous drug therapy received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Imipenem</td>
</tr>
<tr>
<td>To imipenem</td>
<td>Imipenem</td>
</tr>
<tr>
<td></td>
<td>No (n=114)</td>
</tr>
<tr>
<td></td>
<td>Yes (n=21)</td>
</tr>
<tr>
<td>To ceftazidime</td>
<td>Imipenem</td>
</tr>
<tr>
<td></td>
<td>Third-generation cephalosporin</td>
</tr>
<tr>
<td></td>
<td>No (n=100)</td>
</tr>
<tr>
<td></td>
<td>Yes (n=35)</td>
</tr>
</tbody>
</table>

\[\text{a} P = .0009 \quad \text{b} P = .003 \quad \text{c} P = .001 \quad \text{d} P = .05\]
**FQ resistance in S. pneumoniae is also a concern**

Previous exposure to FQ lead to marked higher resistance to levo and gati, not moxi.
Microbiology of HAP

- Generally concerned about
  - EGNB
  - S. aureus
  - Polymicrobial in 50% patients on MV

- **How to diagnose** Risk factors for MDROs in HAP/VAP
  - Risk factors for MDR organisms in general
    - Previous antibiotic exposure
  - Spontaneous breathing vs ventilated patient
  - Time of onset (early-onset vs late-onset)

Consensus in managing HAP

HAP, VAP, or HCAP Suspected

Obtain Lower Respiratory Tract (LRT) Sample for Culture (Quantitative or Semi-quantitative) and Microscopy

Unless There Is Both a Low Clinical Suspicion for Pneumonia and Negative Microscopy of LRT Sample,

**Begin Empiric Antimicrobial Therapy**

Patient-specific Assessment

for Risk Factors for MDR Bugs
Keypad Question: Which of these statements about empiric therapy in HAP is correct?

1. Monotherapy with selected agents can be used for pts without resistant pathogens.
2. Combination therapy is a common practice in suspected and proven MDR gram negative HAP/VAP.
3. Use an agent from a different antibiotic class since recent abx increases probability of inappropriate therapy and predispose to resistance to that same class of antibiotics.
4. All of the above
Summary

- **Nosocomial pneumonia**
  - Leading causes of death due to infection/Increase morbidity, mortality, and cost

- **Most frequent infecting pathogens**
  - Gram-negative: *P. aeruginosa*, *K. pneumoniae*, *E. cloacae*, Gram-positive organisms-particularly *S. aureus*

- **Initiate antimicrobial therapy immediately**

- **Stratify pts on risk for MDROs to decide abx therapy**
  - Risk factors for MDR organisms in general
    - Previous antibiotic exposure
  - Spontaneous breathing vs ventilated patient
  - Time of onset (early-onset vs late-onset)