Appropriate antimicrobial therapy in HAP: What does this mean?

Jaehee Lee, M.D.
Kyungpook National University Hospital, Korea
Empiric antimicrobial choice: right spectrum, right time, right dose

Combination vs monotherapy

Duration

When to de-escalate
Clinical outcome in HAP; dependent on an interplay of several factors

- Host
- Pathogen
- Antimicrobial property

Factors:
- Immune state
- Comorbidity
- Inoculum
- Virulence factor
- Severity of clinical presentation
- Concentration
- Intrinsic activity
Appropriate vs adequate

Appropriate

Susceptible antibiotics

Adequate

Susceptible antibiotics
Optimal dose
Correct route
Combination if necessary
Effect of initial antibiotic therapy on 21 day mortality

Mortality (%)

Inadequate initial therapy
\[ n = 89 \]
59.5%

Adequate initial therapy
\[ n = 97 \]
18.5%

\[ P < 0.001 \]
Effect of switching initial antimicrobial therapy on 21 day mortality

Predictors of Mortality in Patients with Bloodstream Infections Caused by Extended-Spectrum-β-Lactamase-Producing Enterobacteriaceae: Importance of Inadequate Initial Antimicrobial Treatment

Mario Tumbarello, Maurizio Sanguinetti, Eva Montuori, Enrico M. Trecarichi, Brunella Posteraro, Barbara Fiori, Rita Citton, Tiziana D'Inzeo, Giovanni Fadda, Roberto Cauda, and Teresa Spanu

Mortality (%)

<table>
<thead>
<tr>
<th>Mortality (%)</th>
<th>Switching after susceptibility results (n=75)</th>
<th>Adequate treatment within a few hours (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>52 %</td>
<td>18 %</td>
</tr>
</tbody>
</table>

P<0.001
Failure to provide adequate antimicrobial therapy within the first 72h of infection was an independent predictor of mortality.

Getting the antibiotic treatment right the first time is an important aspect of care for hospitalized patients with serious infections.
Appropriate antimicrobial therapy - 2

Predictors of 30-Day Mortality and Hospital Costs in Patients With Ventilator-Associated Pneumonia Attributed to Potentially Antibiotic-Resistant Gram-Negative Bacteria

Katherine E. Kollef, Garrett E. Schramm, Angela R. Wills, Richard M. Reichley, Scott T. Mioek and Marin H. Kollef

K-M plot showing proportion of patients alive over time according to whether or not appropriate initial antibiotic was administered

P < 0.001
### Risk Factors for Death Due to Nosocomial Infection in Intensive Care Unit Patients: Findings From the Krankenhaus Infektions Surveillance System

P. Gastmeier, MD; D. Sohr, PhD; C. Geffers, MD; M. Behnke; H. Rüden, MD

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio for mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-resistant <em>S. aureus</em></td>
<td>2.39 (1.81-3.12)</td>
</tr>
<tr>
<td>Multidrug-resistant <em>P. aeruginosa</em></td>
<td>3.00 (1.90-4.63)</td>
</tr>
</tbody>
</table>

The type of pathogen, MDR pathogen is a strong predictor of the outcome of ICU patients
Inadequate Antimicrobial Treatment: An Important Determinant of Outcome for Hospitalized Patients

Marin H. Kollef

Department of Internal Medicine, Pulmonary and Critical Care Division, Washington University School of Medicine, and Medical Critical Care and Respiratory Care Services, Barnes-Jewish Hospital, St. Louis, Missouri

Ranking of bacterial pathogen associated with inadequate antimicrobial treatment of VAP

- **P. aeruginosa**: 35%
- **S. aureus**: 20%
- **Acinetobacter species**: 15%
- **Klebsiella pneumoniae**: 10%
- **Enterobacter species**: 5%
- **Streptococcus pneumoniae**: 0%

Appropriate antimicrobial therapy - 4
Clinicians must be aware of the prevailing pathogens that account for nosocomial infections in their hospital.

Antibiograms should be updated on a regular basis to report and detect changes in their antimicrobial resistance patterns of these pathogens.
**Appropriate antimicrobial therapy - 5**

Initial empiric therapy for early onset HAP without risk factors for MDR pathogen

<table>
<thead>
<tr>
<th>Potential pathogen</th>
<th>Recommended antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumonia</em></td>
<td>Ceftriaxone</td>
</tr>
<tr>
<td><em>Hemophilus influenza</em></td>
<td>or</td>
</tr>
<tr>
<td>Methicillin-sensitive <em>Staphylococcus aureus</em></td>
<td>Levofloxacin, moxifloxacin, ciprofloxacin</td>
</tr>
<tr>
<td>Antibiotic sensitive gram-negative bacilli</td>
<td>or</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>Ampicillin/sulbactam</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>or</td>
</tr>
<tr>
<td><em>Enterobacter species</em></td>
<td>Ertapenem</td>
</tr>
<tr>
<td><em>Proteus species</em></td>
<td></td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td></td>
</tr>
</tbody>
</table>
### Initial empiric therapy for HAP with late onset or risk factors for MDR pathogen

<table>
<thead>
<tr>
<th>Potential pathogen</th>
<th>Recommended antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen described in early onset HAP/VAP without MDR risk factor and</td>
<td>Antipseudomonal cephalosporin or Antipseudomonal carbapenem or Antipseudomonal β-lactam/β-lactam inhibitor plus</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Antipseudomonal fluoroquinolone or Aminoglycoside (amikacin, gentamicin, tobramycin) plus</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em> (ESBL)</td>
<td></td>
</tr>
<tr>
<td><em>Acinetobactor species</em></td>
<td></td>
</tr>
<tr>
<td>MRSA</td>
<td>Linezolid or vancomycin</td>
</tr>
</tbody>
</table>
IDAAT (initially delayed appropriate antibiotic treatment); a time of ≥24h between the point of suspected VAP and the administration of AAT

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IDAAT (+) (n=33)</th>
<th>IDAAT (-) (n=74)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality</td>
<td>23 (69.7)</td>
<td>21 (28.4)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Mortality attributed to VAP</td>
<td>13 (39.4)</td>
<td>8 (10.8)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Main factor leading to delays in appropriate therapy; presence of resistant organism
Treatment of HAP and VAP must be initiated as soon as the diagnosis is entertained.

Emphasis on the need to anticipate resistant organism in the selection of initial therapy in at-risk patients.
Adequate dosing

- Pharmacodynamic property
- Action mechanism
- Post-antibiotic effect

Time-dependent vs Concentration-dependent

Different tissue penetration

Toxicity
Adequate dosing

Initial IV adult dose with normal renal function for HAP, VAP and HCAP

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefepime</td>
<td>1-2 g q 8-12h</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2g q 8h</td>
</tr>
<tr>
<td>Imipenem</td>
<td>500mg q 6 or 1g 1 8h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1g q 8h</td>
</tr>
<tr>
<td>Piperacillin/tazobactam</td>
<td>4.5g q 6h</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15mg/kg q 12h</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600mg q 12h</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400mg q 8h</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>750mg per d</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>7mg/kg per d</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>7mg/kg per d</td>
</tr>
<tr>
<td>Amikacin</td>
<td>20mg/kg per d</td>
</tr>
</tbody>
</table>
For treatment of microbiologically proven cases of HAP do you use:

1. Broad spectrum monotherapy
2. Combination therapy
Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis

Nasia Safdar, Jo Handelsman, and Dennis G Maki

Gram-negative bacilli

Intrinsic & acquired resistance

Combination Antibiotics

Benefits?

Drug toxicity Increased cost Superinfection

Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis

Nasia Safdar, Jo Handelsman, and Dennis G Maki

Combination therapy vs monotherapy: mortality of Gram-negative bacteraemia

Summary odds ratio: 0.96

Does combination antimicrobial therapy reduce mortality in Gram-negative bacteremia? A meta-analysis

Nasia Safdar, Jo Handelsman, and Dennis G Maki

Combination therapy vs monotherapy: mortality of *P. aeruginosa* bacteremia

Summary odds ratio: 0.50
Indicating a mortality benefit with combination therapy

Combination therapy versus monotherapy: a randomised pilot study on the evolution of inflammatory parameters after ventilator associated pneumonia [ISRCTN31976779]
Pierre Damas, Christophe Garweg, Mehran Monchi, Monique Nys, Jean-Luc Canivet, Didier Ledoux and Jean-Charles Preiser

CRP revolution

K-M curve of mechanical ventilation duration

No clinical and biological benefit of combination therapy

Crit Care 2006;10:R52
Key Pad Question

What duration of antimicrobial therapy do you typically use to treat uncomplicated HAP?

1. ≤ 5 days
2. ≤ 7 days
3. ≤ 14 days
4. ≤ 21 days
Resolution of Infectious Parameters after Antimicrobial Therapy in Patients with Ventilator-associated Pneumonia

PAUL J. W. DENNESEN, ANDRÉ J. A. M. van der VEN, ALPHONS G. H. KESSELS, GRAHAM RAMSAY, and MARC J. M. BONTEN

**Mean log CFU/mL of Bacteria**

- Decreased 0.2 cfu/ml/day p<0.01
- Decreased 0.15 * 10^3/mm^3/day p<0.01
- Decreased 0.05 /day p<0.01

**Leukocyte count**

- Increased 0.8 kPa/day p<0.01

**Highest temperature**

- Decreased 0.05 /day p<0.01

**P/F ratio**
Mean duration to resolution of these parameters
Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults
A Randomized Trial

Beta-lactam + AG or FQ
±
Vancomycin (38%)

8 days vs 15 days

No disadvantage of short-8-day duration therapy for microbiologically proven VAP in mortality
Less emergence of multi-resistant pathogens in short-8-day duration therapy
Key Pad Question

Do you use a de-escalation strategy in the treatment of HAP?

1. Never
2. Seldom
3. Sometimes
4. Always
De-escalation

- Broad spectrum, empirical antimicrobial agents
- Delaying the initiation of targeted therapy pending bacteriologic results

Clinical balance: de-escalation

- Patient response
- Culture results
- Procalcitonin?

Fostering organism resistance

Adverse outcome
740 patients, all received empirical broad-spectrum antibiotics
TT group; tailoring or discontinuing antibiotics in response to culture results
No TT group; did not receive TT

28-day mortality (%)

- TT patients with positive cultures: 17.2% (N=320)
- No TT patients with positive culture: 14.1% (N=92)

*P=0.53*
Targeted therapy is associated with less antibiotic use and no evidence of harm in the management of VAP
Mortality rates among patients with VAP according to whether therapy was escalated or de-escalated

- De-escalated (n=88): 17.0%
- No change (n=245): 23.7%
- Escalated (n=61): 42.6%

P = 0.001
Guide group: Initial Imipenem based regimen with either Amikacin or Ciprofloxacin ± Vancomycin or Azithromycin → De-escalation on D3 based on the microbiological results

Adequate treatment(%)
Very broad-spectrum initial therapy did not result in the emergence of antibiotic resistance as long as duration of antibiotic use was limited.
Clinical outcome in HCAP and HAP

<table>
<thead>
<tr>
<th></th>
<th>HCAP</th>
<th>HAP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=49)</td>
<td>(n=81)</td>
<td></td>
</tr>
<tr>
<td>Invasive MV</td>
<td>5 (10.2)</td>
<td>9 (11.1)</td>
<td>0.872</td>
</tr>
<tr>
<td>LOS for survivors</td>
<td>14.0 ± 9.7</td>
<td>17.3 ± 15.1</td>
<td>0.210</td>
</tr>
<tr>
<td>Mortality</td>
<td>14 (28.6)</td>
<td>28 (34.6)</td>
<td>0.479</td>
</tr>
</tbody>
</table>
## Comparison of microbiological data between HCAP and HAP

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>HCAP (n=49)</th>
<th>HAP (n=81)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram negative pathogens</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosae</em></td>
<td>4 (8.2)</td>
<td>13 (16.1)</td>
<td>0.196</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>1 (2.0)</td>
<td>4 (4.9)</td>
<td>0.405</td>
</tr>
<tr>
<td><em>Klebsiellae pneumoniae</em></td>
<td>5 (10.2)</td>
<td>0 (0.0)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Gram positive pathogens</strong></td>
<td>8 (16.3)</td>
<td>24 (29.6)</td>
<td>0.088</td>
</tr>
<tr>
<td><em>MRSA</em></td>
<td>2 (4.1)</td>
<td>18 (22.2)</td>
<td>0.006</td>
</tr>
<tr>
<td><em>MSSA</em></td>
<td>2 (4.1)</td>
<td>1 (1.2)</td>
<td>0.295</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>4 (8.2)</td>
<td>5 (6.2)</td>
<td>0.665</td>
</tr>
<tr>
<td><strong>Multidrug resistant pathogens</strong></td>
<td>8 (16.3)</td>
<td>35 (43.2)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Resistance rates of *Pseudomonas aeruginosae* (%)
Antibiotic therapy for HAP should commence within 24h

Patient risk stratification schema based on clinical presentation, time of onset, and potential for resistant pathogens based on antibiotic exposure

Initiation of appropriate therapy and dosing in HAP will produce improved clinical outcomes
Combination therapy was not found to be superior to monotherapy.

A short course of therapy of seven to eight days should suffice for most cases of HAP.

Guidelines can be further refined after the analysis of local resistance patterns.