Management of Hospital-acquired Pneumonia

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Introduction

• Definitions:
  • **Hospital-acquired pneumonia (HAP)** refers to the development of parenchymal lung infection after at least 48 hours of hospitalization.
  • **Ventilator-associated pneumonia (VAP)** refers to the development of parenchymal lung infection after the patient has undergone intubation and received mechanical ventilation after at least 48 hours.
  • **Health-care-associated pneumonia (HCAP)** refers to pneumonia that develops inside or outside the hospital in the presence of risk factors for multi-drug-resistant pathogens because of prior contact with health-care environment.

Niederman M, CID 2010

http://www.infectiologie.org.tn
Epidemiology of HAP

- HAP is the second most common nosocomial infection and accounts for approximately 25% of all infection in the Intensive Care Unit (ICU)
Epidemiology of HAP

• The incidence of VAP is 10-30% among patient who require mechanical ventilation for more than 48 hours
Epidemiology of HAP

• Probability to develop VAP is directly related to duration of mechanical ventilation and intubation
Probability of development of ventilator-associated pneumonia and duration of mechanical ventilation

Odds ratio

Days intubation

Day 5  Day 10  Day 15  Day 20

HAP Introduction

- The risk of VAP is highest early in the course of hospital stay, and estimated to be 3% per day during the first 5 days of ventilation, 2% per day during 5-10 days of ventilation, 1% per day during days afterwards.

Epidemiology of HAP

• Time of onset: Early vs. Late

  • For HAP-early onset: Diagnosed 2-5 day after hospitalization
  • For HAP-late onset: Diagnosed ≥ 5 days after hospitalization
HAP Introduction

• Usually HAP will increase hospital stay by 7-9 days per patient, and has been reported to produce an excess cost of more than 49,000$ per patient.
Introduction:
Risk Factors for Development of HAP

• Patient related in:
  • Male sex
  • Pre-existing pulmonary disease
  • Multiple organ system failure

• Treatment related in:
  • Intubation
  • Enteral feeding
Mortality among patients with pneumonia
(Percentage of hospital mortality by classification)

Mortality Rate (% Patients)

- CAP (n=2221): 10%
- HCAP (n=988): 19.8%
- HAP (n=835): 18.8%
- VAP (n=499): 29.3%

P-values:
- P < 0.0001
- P < 0.0001
- P = NS

http://www.infectiologie.org.tn
### Mortality Associated with Ventilator-Associated Pneumonia (VAP) in Unmatched Studies

VAP related mortality has been demonstrated by Muscedere et al

<table>
<thead>
<tr>
<th>Study (year)</th>
<th># of patients</th>
<th>Population</th>
<th>Mortality in group without VAP, no (%)</th>
<th>Mortality in group with VAP, no (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrahim et al (2001)</td>
<td>880</td>
<td>Medical-surgical</td>
<td>283 (32.2)</td>
<td>400 (45.5)</td>
</tr>
<tr>
<td>Tejada et al (2001)</td>
<td>103</td>
<td>Trauma</td>
<td>19 (18.8)</td>
<td>45 (43.5)</td>
</tr>
<tr>
<td>Moine et al (2002)</td>
<td>764</td>
<td>Medical-surgical</td>
<td>168 (22.0)</td>
<td>359 (47.0)</td>
</tr>
<tr>
<td>Kanafani et al (2003)</td>
<td>70</td>
<td>Medical-surgical</td>
<td>21 (30.0)</td>
<td>27 (39.0)</td>
</tr>
<tr>
<td>Warren et al (2003)</td>
<td>819</td>
<td>Medical-surgical</td>
<td>278 (34.0)</td>
<td>410 (50.0)</td>
</tr>
<tr>
<td>Alp et al (2004)</td>
<td>2402</td>
<td>Medical-surgical</td>
<td>288 (12.0)</td>
<td>1561 (65.0)</td>
</tr>
<tr>
<td>Myny et al (2005)</td>
<td>287</td>
<td>Medical-surgical</td>
<td>57 (20.0)</td>
<td>89 (31.0)</td>
</tr>
<tr>
<td>Noor et al (2005)</td>
<td>250</td>
<td>Medical-surgical</td>
<td>80 (32.0)</td>
<td>143 (57.1)</td>
</tr>
<tr>
<td>Moreno et al (2006)</td>
<td>2172</td>
<td>Medical-surgical</td>
<td>391 (18.0)</td>
<td>760 (35.0)</td>
</tr>
<tr>
<td>Hyllienmark et al (2007)</td>
<td>221</td>
<td>Medical-surgical</td>
<td>35 (16.0)</td>
<td>73 (33.0)</td>
</tr>
<tr>
<td>Suka et al (2007)</td>
<td>8892</td>
<td>Medical-surgical</td>
<td>889 (10.0)</td>
<td>1823 (20.5)</td>
</tr>
<tr>
<td>Valles et al (2007)</td>
<td>101</td>
<td>Medical-surgical</td>
<td>27 (27.0)</td>
<td>45 (45.0)</td>
</tr>
<tr>
<td>Van Der Kooi et al (2007)</td>
<td>1533</td>
<td>Medical-surgical</td>
<td>353 (23.0)</td>
<td>399 (26.0)</td>
</tr>
<tr>
<td>Cuellar et al (2008)</td>
<td>1290</td>
<td>Medical-surgical</td>
<td>181 (14.0)</td>
<td>497 (38.5)</td>
</tr>
<tr>
<td>Da Rocha et al (2008)</td>
<td>275</td>
<td>Medical-surgical</td>
<td>128 (46.5)</td>
<td>88 (32.1)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>20,059</strong></td>
<td>...</td>
<td><strong>3200 (16.0)</strong></td>
<td><strong>6719 (33.5)</strong></td>
</tr>
</tbody>
</table>

Source: Muscedere J, et al. CID, 2010
HAP and VAP can be caused by a wide variety of bacteria that originate from the patient flora as well as the health care bacteria.
Microbiology

In several studies, a consistent organisms caused nearly 80% of HAP and VAP episodes:

1. *Staphylococcus aureus* 28%
2. *Pseudomonas aeruginosa* 21.8%
3. *Klebsiella spp* 9.8%
4. *E.coli* 6.9%
5. *Acinetobacter spp* 6.8%, and
6. *Enterobacter spp* 6.3%
The rest of HAP episodes with positive bacterial culture (>20% of all cases) are caused by *Serratia* spp, *Stenotrophomonas maltophilia*, and community-acquired pathogens (*Pneumococci, Haemophilus influenzae*).
# Risk factors for MDR pathogens in HAP

Risk Factors for multidrug-resistant pathogens causing hospital-acquired pneumonia, healthcare-associated pneumonia, and ventilator-associated pneumonia

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

## Regional Incidence of Pathogens Isolated from Patients Hospitalized with Pneumonia in the Last 5 Years of the SENTRY Antimicrobial Surveillance Program (31,436 Cases)

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All regions</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>28.0</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>21.8</td>
</tr>
<tr>
<td><em>Klebsiella species</em></td>
<td>9.8</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>6.9</td>
</tr>
<tr>
<td><em>Acinetobacter species</em></td>
<td>6.8</td>
</tr>
<tr>
<td><em>Enterobacter species</em></td>
<td>6.3</td>
</tr>
<tr>
<td><em>Serratia species</em></td>
<td>3.5</td>
</tr>
<tr>
<td><em>Stenotrophomonas maltophilia</em></td>
<td>3.1</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>2.9</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>2.7</td>
</tr>
</tbody>
</table>

[Jones R, CID, 2010](http://www.infectiologie.org.tn)
Variations in Drug Susceptibility Rates between Hospital-Acquired Bacterial Pneumonia (HABP) and Ventilator-Associated Bacterial Pneumonia (VABP) Isolates from All SENTRY Antimicrobial Surveillance Program Regions, 2004-2008

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Susceptibility, % (HABP / VABP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>41/49&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>87/78</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>42/52&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cefepime</td>
<td>41/49</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>41/49</td>
</tr>
<tr>
<td>Meropenem</td>
<td>41/49</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>41/49</td>
</tr>
</tbody>
</table>

**NOTE.** Boldface indicated >5% decrease in susceptibility for VABP isolates, compared with HABP isolates. More than a 10% lower susceptibility occurred with 3 drug-pathogen analyses.

<sup>a</sup>VABP *S. aureus* isolates were generally more susceptible to oxacillin and fluoroguinolones.
Comparison of Abx susceptibility of GNRs in KAMC Riyadh on 1998, 2007 and 2010

<table>
<thead>
<tr>
<th>GNRs</th>
<th>Ceftazidime %</th>
<th>Ciprofloxacin %</th>
<th>Pip-Tazo %</th>
<th>Imipenem %</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.Coli</td>
<td>93</td>
<td>70</td>
<td>88</td>
<td>87</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>68</td>
<td>69</td>
<td>69</td>
<td>91</td>
</tr>
<tr>
<td>Pseudomonas spp</td>
<td>91</td>
<td>75</td>
<td>68</td>
<td>89</td>
</tr>
<tr>
<td>Acinetobacter spp</td>
<td>43</td>
<td>17</td>
<td>25</td>
<td>52</td>
</tr>
</tbody>
</table>
Diagnosis of HAP and VAP

• Niederman. ATS + IDSA Guidelines, AJRCCM, 2005

Diagnosis

The diagnosis of HAP is suspected if the patient has a radiographic infiltrate that is new or progressive, along with clinical findings suggesting infection, which include the new onset of fever, leukocytosis, and decline in oxygenation. When fever, leukocytosis, purulent sputum, and a positive culture of sputum or tracheal aspirate are present without a new lung infiltrate, the diagnosis of nosocomial tracheobronchitis should be considered.

Microbiologic Diagnosis of HAP

- Blood culture
- Samples of lower respiratory tract secretion should be obtained including:
  - Endotracheal aspirate
  - BAL, or
  - Protected specimen brush sample
- If there a complicating empyema, a pleural aspirate should be obtained.

Treatment of HAP

Once the clinical decision has been made to initiate therapy, the overall approach to therapy is summarized in the following algorithm.

Empiric Antibiotic Therapy for HAP

- HAP, VAP or HCAP Suspected (All Disease Severity)

  - Late Onset (> 5 days) or Risk Factors for Multi-drug Resistant (MDR) Pathogens

  - Limited Spectrum Antibiotic Therapy

  - YES
    - Broad Spectrum Antibiotic Therapy For MDR Pathogens

  - NO
    - Niederman M. et al. AJRCCM, 2005

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Niederman M. et al. AJRCCM, 2005
American Thoracic Society Documents

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia
IDSA Initial empiric AB therapy for HAP/VAP in patients with late-onset disease or risk factors from multidrug-resistant pathogens and all disease severity.

- **B-Lactam/B-lactamase inhb.**
  - Piperacillin/tazobactam
  - 4 × 4.5 g

- **Antipseudomonal ceph.**
  - Cefepime 2-3 × 1-2g
  - Ceftazidime 3 × 2g

- **Antipseudomonal carb.**
  - Imipenem 4×500mg or 3×1g
  - Meropenem 3 × 1g

**PLUS**

- **Antipseudomonal fluoroquinolone**
  - Ciprofloxacin 3 × 400 mg
  - Levofloxacin 1 × 750 mg

**OR**

- **Aminoglycoside**
  - Gentamicin 7 mg/kg per day
  - Tobramycin 7 mg/kg per day
  - Amikacin 20 mg/kg per day

**Addition of coverage for MRSA if suspected**

- **PLUS/ MINUS**
  - Vancomycin
  - 2 × 15mg/ kg

  **OR**

  - Linezolid
  - 2 × 600 mg

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IDSA Initial empiric AB therapy for HAP/VAP in patients with NO risk factors for multidrug-resistant pathogens, early onset, and any disease severity

Ampicillin-Sulbactam
4 × 3g

OR

Ceftriaxone 1 × 2g

OR

Levofloxacin 1 × 750 mg
Moxifloxacin 1 × 400 mg
Ciprofloxacin 3 × 400 mg

OR

Ertapenem 1 × 1g

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EUROPEAN GUIDELINES FOR HOSPITAL ACQUIRED PNEUMONIA

Defining, treating and preventing hospital acquired pneumonia: European perspective

1. European Respiratory Society (ERS),
2. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and
3. European Society of Intensive Care Medicine (ESICM)
ESCMID 2009 Antimicrobial treatment of early onset pneumonia without any additional risk factors.

Aminopenicillin plus β-lactamase-inhibitor
Amoxi-Clav 3 × 2.2g
Amp-Sulb 3 × 3g

2nd G. Cep.
Cefuroxime 3 × 1.5g

OR

3rd G. Cep.
Cefotaxime 3 × 2g
Ceftriaxone 1 × 2g

OR

Respiratory quinolone
(not ciprofloxacin)
Levofloxacin 1 × 750 mg
Moxifloxacin 1 × 400 mg

OR

Levofloxacin 1 × 750 mg
Moxifloxacin 1 × 400 mg

OR

Cefotaxime 3 × 2g
Ceftriaxone 1 × 2g

OR

Levofloxacin 1 × 750 mg
Moxifloxacin 1 × 400 mg

OR

Cefotaxime 3 × 2g
Ceftriaxone 1 × 2g

OR

http://www.infectiologie.org.tn
http://www.infectiologie.org.tn
ESCMID Antimicrobial treatment of late onset pneumonia

- Piperacillin/tazobactam
  - 3 × 4.5 g
- Ceftazidime
  - 3 × 2 g
- Imipenem/ cilistatin
  - 3 × 1 g
- Meropenem
  - 3 × 1 g

OR

- Ciprofloxacin
  - 3 × 400 mg
- Levofloxacin
  - 1 × 750 mg

PLUS

Addition of coverage for MRSA if suspected

PLUS/ MINUS

- Vancomycin
  - 2 × 1g
- Linezolid
  - 2 × 600 mg
## Initial Empirical Antimicrobial Treatment

### Initial Empirical Antimicrobial Treatment for Patient with Hospital-Acquired, Ventilator-Associated, or Health Care-Associated Pneumonia, according to the 2005 American Thoracic Society and Infectious Disease Society of America Guidelines

<table>
<thead>
<tr>
<th>Potential Pathogen</th>
<th>Recommended antibiotic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No risk factors for MDR, early onset, and any disease severity</strong></td>
<td>Ceftriaxone; levofloxacin, moxifloxacin, ciprofloxacin; ampicillin-sulbactam; or ertapenem</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>…</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>…</td>
</tr>
<tr>
<td>MSSA</td>
<td>…</td>
</tr>
<tr>
<td>Antibiotic-susceptible, enteric gram-negative bacilli</td>
<td>…</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>…</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>…</td>
</tr>
<tr>
<td><em>Enterobacter species</em></td>
<td>…</td>
</tr>
<tr>
<td><em>Proteus species</em></td>
<td>…</td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>…</td>
</tr>
<tr>
<td><strong>Late onset disease or risk factors for MDR pathogens and all disease severity</strong></td>
<td>Combination antibiotic therapy: antipseudomonal cephalosporin (cefepime or ceftazidime), antipseudomonal carbapenem (imipenem or meropenem), or β-lactam or β-lactamase inhibitor (piperacillin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) plus linezolid or vancomycin (if risk factors present)</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>…</td>
</tr>
<tr>
<td><em>K. pneumoniae</em> (ESBL)</td>
<td>…</td>
</tr>
<tr>
<td><em>Acinetobacter species</em></td>
<td>…</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>…</td>
</tr>
<tr>
<td>MRSA</td>
<td>…</td>
</tr>
</tbody>
</table>

**NOTE.** ESBL, extended-spectrum β-lactamase; MDR, multidrug resistant, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*
## Initial Intravenous Adult doses of Antibiotics

Initial Intravenous, adult doses of antibiotics for empiric therapy of hospital-acquired pneumonia, including ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens.

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Dosage*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipseudomonal cephalosporin</strong></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>1-2g every 8-12h</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>2g every 8h</td>
</tr>
<tr>
<td><strong>Carbapenems</strong></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>500mg every 6h or 1g every 8h</td>
</tr>
<tr>
<td>Meropenem</td>
<td>1g every 8h</td>
</tr>
<tr>
<td><strong>β-Lactam/β-lactamase inhibitor</strong></td>
<td></td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
<td>4.5g every 6h</td>
</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>5-7mg/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>
<tr>
<td><strong>Antipseudomonal quinolones</strong></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>750mg every d</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400mg every 8h</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>15mg/kg every 12h‡</td>
</tr>
<tr>
<td>Linezolid</td>
<td>600mg every 12h‡</td>
</tr>
</tbody>
</table>

*Doses are based on normal renal and hepatic function/ +Trough levels for gentamicin and tobramycin should be less than 1µg/ml, and for amikacin they should be less than 4-5µg/ml/ ‡Trough levels for vancomycin should be 15-20µg/ml
Duration of Antibiotic Therapy

Pugh R. et al., have done a meta-analysis for 8 studies (1703 patients) to compare short (7 days) and prolonged antibiotic therapy for HAP and VAP.

They concluded that, for patients with HAP and VAP not due to non-fermenting gram-negative bacilli (particularly *P. aeruginosa* and *Acinetobacter* species) a short fixed course (7-8 days) antibiotic therapy may be more appropriate than prolonged course (10-15 days).
Other Therapeutic modalities

- Although promising, antibiotics aerosolization for treatment of VAP has not yet entered the armamentarium for daily practice.

- The results of recent investigations emphasize its potential contribution as an interesting adjunctive therapy to intravenous antibiotics, but the clinical impact of such strategy has not yet been definitely established.


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Thank You

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