The appropriateness of community-acquired pneumonia guideline recommendations for treatment of healthcare-associated pneumonia in countries with low antibiotic resistance

Valentijn A. Schweitzer¹, Rinck Smits¹, Inger van Heijl², Cornelis H. van Werkhoven¹, Douwe F. Postma¹,³, C.H. Edwin Boel⁴, Jan J. Oosterheert³, Marc J.M. Bonten¹,⁴

¹Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, The Netherlands
²Department of Clinical Pharmacy, Tergooi Hospital, Hilversum/Blaricum, The Netherlands
³Departments of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, The Netherlands
⁴Department of Medical Microbiology, University Medical Center Utrecht, The Netherlands
Conflicts of interest

- No conflicts of interest
## Introduction

- Healthcare associated pneumonia (HCAP) introduced\(^1\)

### HCAP definition

<table>
<thead>
<tr>
<th>Residence of</th>
<th>- Nursing home</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Long-term care facility</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Within last 90 days</th>
<th>- Hospitalization ≥2 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within last 30 days</td>
<td>- i.v. antibiotic therapy</td>
</tr>
<tr>
<td></td>
<td>- Woundcare</td>
</tr>
<tr>
<td></td>
<td>- Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>- Attended hospital/hemodialysis clinic</td>
</tr>
</tbody>
</table>

\(^1\) IDSA, Am J Respir Crit Care Med 2005
Introduction

– In spectrum of hospital-acquired pneumonia (HAP)
Introduction

– HCAP ≠ resistant pathogens$^1$
– HCAP removed from HAP guideline$^2$

$^1$ Chalmers et al, CID 2014
$^2$ Kalil et al, CID 2016
Introduction

- HCAP ≠ resistant pathogens\(^1\)
- HCAP removed from HAP guideline\(^2\)
- Suggestion: implement in CAP guideline\(^2\)

\(^1\) Chalmers et al, CID 2014
\(^2\) Kalil et al, CID 2016
Introduction

– HCAP ≠ resistant pathogens

• Resistant pathogens:
  – MRSA
  – Gram-negative Enterobacteriaceae
  – *Pseudomonas aeruginosa*

• However:
  – Resistance to empiric treatment more relevant
  – Low resistant countries: narrow-spectrum beta-lactam (amoxicillin or penicillin)

1 Chalmers et al, CID 2014
2 Kalil et al, CID 2016
Introduction

Research objective:

Investigate whether HCAP criteria predict pneumonia caused by amoxicillin resistant pathogens in moderate-severe CAP patients

1 Chalmers et al, CID 2014
2 Kalil et al, CID 2016
Method

• Data from the CAP-START trial\(^1\)
  – Multicentre cluster randomized trial

  – Patients hospitalized for moderate-severe CAP

  – 7 hospitals in the Netherlands

  – February 2011 – August 2013

\(^1\) Postma et al. NEJM. 2015
Methods – data collection

• HCAP criteria

• Microbiology results
  – Sputum cultures
  – Blood cultures
  – Susceptibility patterns
  – Pneumococcal urine antigen tests
  – Legionella urine antigen tests
Methods – data analysis

• In case of missing susceptibility:
  – Intrinsically resistant → resistant
  – Pathogen with resistance to amoxicillin >95% → resistant
  – Pathogen with resistance to amoxicillin <5% → susceptible
Methods – sensitivity analysis

Best-case scenario

Worst-case scenario
# Results – baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>CAP</th>
<th>HCAP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>77% (1756)</td>
<td>23% (527)</td>
<td></td>
</tr>
<tr>
<td>Age (y, median, range)</td>
<td>70 (18-99)</td>
<td>72 (19-100)</td>
<td>&lt;0.01&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Male</td>
<td>57%</td>
<td>61%</td>
<td>0.07&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smoking</td>
<td>21%</td>
<td>19%</td>
<td>0.12&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>18%</td>
<td>40%</td>
<td>&lt;0.01&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>PSI-score (mean)</td>
<td>132</td>
<td>137</td>
<td>0.08&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1. Mann-Whitney U test  
2. Pearson Chi-Square test  
3. Independent T-test
## Results – microbiology

<table>
<thead>
<tr>
<th>Test</th>
<th>CAP</th>
<th>HCAP</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sputum culture</td>
<td>46%</td>
<td>44%</td>
<td>0,50¹</td>
</tr>
<tr>
<td>Blood culture</td>
<td>76%</td>
<td>76%</td>
<td>0,99¹</td>
</tr>
<tr>
<td>Pneumococcal urine antigen test</td>
<td>79%</td>
<td>77%</td>
<td>0,29¹</td>
</tr>
<tr>
<td>Legionella urine antigen test</td>
<td>77%</td>
<td>72%</td>
<td>0,03¹</td>
</tr>
</tbody>
</table>

1. Pearson Chi-Square test
<table>
<thead>
<tr>
<th>Pathogen</th>
<th>CAP</th>
<th>HCAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>15,4%</td>
<td>12,1%</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>7,5%</td>
<td>6,5%</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>2,4%</td>
<td>4,6%</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>2,1%</td>
<td>6,1%</td>
</tr>
<tr>
<td><em>Pseudomonas</em> species</td>
<td>1,8%</td>
<td>4,4%</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>1,5%</td>
<td>1,5%</td>
</tr>
<tr>
<td><em>Klebsiella</em> species</td>
<td>1,3%</td>
<td>1,9%</td>
</tr>
<tr>
<td><em>Legionella pneumophila</em></td>
<td>1,0%</td>
<td>0,2%</td>
</tr>
<tr>
<td>No bacterial pathogen</td>
<td>66,6%</td>
<td>65,5%</td>
</tr>
</tbody>
</table>
Results

Amoxicillin resistance

Best-case scenario
10.1% CAP, 15.0% HCAP, *p* < 0.01

Worst-case scenario
15.2% CAP, 20.3% HCAP, *p* < 0.01

1. Pearson Chi-Square test
Discussion

• Majority no bacterial pathogen $\rightarrow$ uncultured resistance?

• Consequences of resistance for empirical treatment unknown

• Other factors better predictors?
  – Previous cultures with resistant bacteria
  – Co-morbidities
    • Chronic obstructive pulmonary disease
    • Immunosuppression
Conclusion

- Amoxicillin resistance 5% higher in HCAP patients
- HCAP more frequently caused by:
  - *Staphylococcus aureus*
  - *Pseudomonas* species
  - *Escherichia coli*
- Absolute risks are low
- Focus on identifying better predictors for resistance
Acknowledgments CAP-START

UMC Utrecht
Henri van Werkhoven
Douwe Postma
Ferdinand Teding-van Berkhout
Andy Hoepelman
Jan Jelrik Oosterheert
Marc Bonten

Diakonessenhuis Utrecht
Sanjay Sankatsing
Steven Thijsen
Leontine van Elden

AMC Amsterdam
Rene Jonkers
Jan Prins

Amphia Hospital Breda
Jan Kluytmans
Joachim Aerts

Medical Centre Alkmaar
Wim Boersma

Kennemer Gasthuis
Robin Soetekouw
Anne Claire Compaijen

Spaarne Hospital
Reinier Veenhoven†
Ivo van der Lee
Eva van der Wall
Method

CAP-START

- β-lactam monotherapy (BL) n= 656
- β-lactam macrolide (BLM) n= 739
- Fluoroquinolone monotherapy (FQL) n= 888

1 Postma et al. NEJM. 2015