The safety and effectiveness of an antibiotic stewardship intervention in hospitalized patients with community-acquired pneumonia: a stepped wedge cluster randomized trial

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Conflicts of interest

No conflicts of interest
“A strategy of preferred empirical treatment with β-lactam monotherapy was noninferior to strategies with a β-lactam–macrolide combination or fluoroquinolone monotherapy with regard to 90-day mortality.”

Wim G. Boersma, M.D., Ph.D., Clara J. Compaïjen, M.D., Eva van der Wall, M.D., Jan M. Prins, M.D., Ph.D., Jan J. Oosterheert, M.D., Ph.D., and Marc J.M. Bonten, M.D., Ph.D., for the CAP-START Study Group

1. Postma et al. NEJM. 2015
Introduction

• Dutch recommendation CAP patients hospitalized to non-ICU ward:
  – Benzylpenicillin or amoxicillin

• Guideline adherence in clinical practice was low
  – 22% in β-lactam monotherapy strategy received penicillin or amoxicillin

1. Postma et al. NEJM. 2015
Introduction

• Antibiotic stewardship may improve guideline adherence

• Yet, uncertain whether a strategy with narrow-spectrum β-lactam is safe
  – Only 15% had documented pneumococcal CAP¹
  – Risk for undertreatment

1. Postma et al. NEJM. 2015
Study aim

1. To reduce broad-spectrum antibiotics by a multifaceted antibiotic stewardship intervention

2. Demonstrate that a strategy with increased use of narrow-spectrum β-lactam is safe
Study population

Inclusion criteria:

– Clinical diagnosis of CAP
– Admitted to a non-intensive care ward
– Received antibiotic therapy on day of admission
Study population

Exclusion criteria:

– <18 years
– Resident of long-term care facility
– Previous hospitalization within 14 days
– Cystic fibrosis
– Immunocompromised
  • HIV infection with a last CD4 count of <300/μL
  • Cytotoxic chemotherapy or radiotherapy in the previous 3 months
  • Chronic hemodialysis > 3 months
  • History of receiving an organ or bone marrow transplant
  • Using immunosuppressive therapy
Study design

- Pre-intervention period
- Intervention period

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<tr>
<th>A</th>
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Hospitals

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- B
- C
- D
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- I

**Intervention bundle**

**Education**
- Clinical lessons
- E-learning

**Prospective Audit and Feedback**
- Empirical therapy
- Pneumococcal urine antigen test

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### Clinical lessons
- Jan
- Feb
- Mar
- Apr
- May
- Jun
- Jul
- Aug
- Sept
- Oct
- Nov
- Dec

### E-learning
- Jan
- Feb
- Mar
- Apr
- May
- Jun
- Jul
- Aug
- Sept
- Oct
- Nov
- Dec
Outcomes and statistical analyses

Primary effectiveness outcome
1. Broad-spectrum Days of therapy (DOT)

**Narrow-spectrum DOTs:**
- Benzylpenicillin monotherapy
- Amoxicillin monotherapy
- Doxycyclin monotherapy

**Broad-spectrum DOTs:**
- All other antibiotic regimens
Outcomes and statistical analyses

Amoxicillin

Ciprofloxacin

BS DOT

BS DOT

BS DOT

NS DOT

NS DOT

5 days
Outcomes and statistical analyses

Primary effectiveness outcome
1. Broad-spectrum Days of therapy (DOT)
   – Superiority analysis for differences in mean
Outcomes and statistical analyses

Primary safety outcome
2. All-cause 90-day mortality
   – Intention-to-treat analysis
   – Assumed mortality 10%
   – Non-inferiority margin of 3%
   – One-sided alpha of 0.05
5,683 patients with pneumonia admitted to non-ICU ward

Pre-intervention period:
3,145 patients screened

1,047 (33.3%) not eligible:
- 292 (9.3%) Resident in LTCF
- 208 (6.6%) Previous hospitalization
- 28 (0.9%) Cystic Fibrosis
- 519 (16.5%) Immunocompromised

2,240 included in study

Intervention period:
3,145 patients screened

822 (32.4%) not eligible:
- 254 (10.0%) Resident in LTCF
- 187 (7.7%) Previous hospitalization
- 13 (0.5%) Cystic Fibrosis
- 368 (14.5%) Immunocompromised

1,844 included in study
<table>
<thead>
<tr>
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<th>Pre-intervention (n= 2,240)</th>
<th>Intervention (n= 1,844)</th>
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<tbody>
<tr>
<td><strong>Age (y, median, IQR)</strong></td>
<td>73 (63 - 81)</td>
<td>74 (64 - 82)</td>
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<tr>
<td><strong>Male gender (n, %)</strong></td>
<td>1,193 (53.3)</td>
<td>970 (53.6)</td>
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<td><strong>Co-morbidities (n, %)</strong></td>
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<tr>
<td>COPD/asthma</td>
<td>964 (43.0)</td>
<td>878 (47.6)</td>
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<tr>
<td>Cardiovascular disease</td>
<td>300 (13.4)</td>
<td>259 (14.0)</td>
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<td>Diabetes mellitus</td>
<td>388 (17.3)</td>
<td>316 (17.1)</td>
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<tr>
<td>Malignancy</td>
<td>212 (9.5)</td>
<td>169 (9.2)</td>
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<td><strong>Smoking (current)</strong></td>
<td>515 (27.3)</td>
<td>409 (27.5)</td>
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<tr>
<td><strong>Antibiotic use before admission (n, %)</strong></td>
<td>743 (31.5)</td>
<td>568 (30.0)</td>
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<td><strong>Radiologically confirmed CAP (n, %)</strong></td>
<td>1689 (75.4)</td>
<td>1370 (74.3)</td>
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<tr>
<td><strong>PSI score (median, IQR)</strong></td>
<td>90 (71 - 111)</td>
<td>90 (69 - 111)</td>
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<tr>
<td><strong>CURB score (median, IQR)</strong></td>
<td>2 (1 - 2)</td>
<td>2 (1 - 2)</td>
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<tr>
<td><strong>Pneumococcal urine antigen test (n, %)</strong></td>
<td>967 (43.2)</td>
<td>1171 (63.5)</td>
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**DOT (median, IQR)**

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<tr>
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<tbody>
<tr>
<td>Narrow-spectrum</td>
<td>0 (0 – 6)</td>
<td>5 (0 – 8)</td>
</tr>
<tr>
<td>Broad-spectrum</td>
<td>6 (2 – 9)</td>
<td>3 (0 – 8)</td>
</tr>
<tr>
<td>Any antibiotic</td>
<td>8 (7 – 10)</td>
<td>8 (7 – 11)</td>
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Adjusted Days on Therapy

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<tr>
<td>Broad-spectrum</td>
<td>6.6</td>
<td>4.8</td>
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</table>

Adjusted relative reduction in broad-spectrum DOTs:
26.9% (95% CI: 14.5%-37.5%)
90-day mortality

- Pre-intervention: 10.8 (242/2223)
- Intervention: 10.8 (199/1836)
90-day mortality
Intention-to-treat analysis
Risk difference

Mortality pre-intervention higher
Mortality intervention higher

Crude

Adjusted

0.0% (90% CI: -1.9% – 2.0%)
0.2% (90% CI: -2.6% – 2.4%)
Conclusions

• A multifaceted antibiotic stewardship intervention to stimulate narrow-spectrum β-lactam antibiotics in patients hospitalized with non-severe CAP
  – reduced the days of broad-spectrum antibiotics with 27%...
  – ... and was non-inferior to previous standard of care for day-90 mortality
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Empirical antimicrobial therapy

- Narrow-spectrum antibiotics
- Other beta-lactam therapy
- Beta-lactam + fluoroquinolone
- Fluoroquinolone monotherapy
- Beta-lactam + macrolide
- Other

% of patients

Pre-intervention vs. Intervention
# Diagnostics CAP-PACT study

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-intervention (n= 2,240)</th>
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<tr>
<td>Sputum culture (n, %)</td>
<td>887 (39.6)</td>
<td>782 (42.4)</td>
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<tr>
<td>Blood culture (n, %)</td>
<td>1605 (71.7)</td>
<td>1384 (75.1)</td>
</tr>
<tr>
<td>Pneumococcal urine antigen test (n, %)</td>
<td>967 (43.2)</td>
<td>1171 (63.5)</td>
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<tr>
<td>Legionella urine antigen test (n, %)</td>
<td>1298 (57.9)</td>
<td>1254 (68.0)</td>
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