Epidemiology of *Clostridioides difficile* infections among hospitalized community-acquired pneumonia patients who received empiric treatment with ceftriaxone plus a macrolide

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Transparency declaration

- Thomas P. Lodise is a consultant to Paratek Pharmaceuticals, Inc.
- Kenneth T. LaPensee is a Paratek Pharmaceuticals, Inc. employee and shareholder
- Hoa V. Le was an employee of PAREXEL at the time of the study, and is a Harry Guess-Merck Award recipient, a GlaxoSmithKline shareholder, and a BMS employee
- Stephen Villano is a consultant to and shareholder in Paratek Pharmaceuticals, Inc.
Background: *Clostridioides difficile* infections (CDI)

- Estimated global rate of healthcare-associated CDI is 2.24 per 1000 admissions/year\(^1\)
- Antibiotics most commonly linked with CDI:
  - Clindamycin, cephalosporins, quinolones\(^2-5\)
  - 2nd, 3rd, and 4th generation cephalosporins are associated with 2- to 3-fold increased risk of CDI\(^3-5\)
- Ceftriaxone plus a macrolide (CTX+M):
  - Often recommended for community-acquired pneumonia (CAP)\(^6\)
  - Epidemiology of CDI among hospitalized CAP patients receiving CTX+M is not well described

Aim

To determine the rate of antibiotic-specific CDI infection among CAP patients treated with CTX+M in a large-scale US hospital database study.

CAP, community-acquired pneumonia; CDI, Clostridioides difficile infection; CTX+M, ceftriaxone plus macrolide
Retrospective study (2012–2015)

• Hospitalized adults in Vizient (formerly MedAssets) database

Vizient clinical data:

• Inpatient and hospital-based outpatient data
• Over 400 hospitals across 42 US states (59% South, 17% West, 13% Midwest, 12% Northeast)
• Large and small hospitals in urban (87%) and rural (13%) locations

Data on episodes of case with daily detail linked to ICD-9-CM diagnosis and procedure codes

ICD-9-CM, international classification of diseases, 9th revision, clinical modification code
Patients

**Inclusion criteria**

- Hospitalized patients
- Age ≥18 years
- Primary discharge ICD-9-CM code for CAP
- ≥1-year enrollment before index date
- Received CTX+M on Days 1–2
- No CDI admitting diagnosis

**Data elements**

- Demographics, comorbidities, healthcare exposure history were collected
- Disease severity was calculated¹:
  - Charlson Comorbidity Index (CCI)
  - Pneumonia Severity Index (PSI)
- Outcome: Patients with ICD-9-CM code for CDI ≤60 days of index CAP admission for CAP

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¹ Lodise T, LaPensee K. ID Week, October 2018, San Francisco, CA.

CAP, community-acquired pneumonia; CCI, Charlson comorbidity index; CDI, Clostridioides difficile infection; CTX+M, ceftriaxone plus macrolide; ICD-9-CM, international classification of diseases, 9th revision, clinical modification code; PSI, pneumonia severity index
Multivariate analysis (2 models) conducted using stepwise logistic regression

- Variables present in >5% of study population entered into the models if associated with CDI ($P<0.10$) at model entry
- Variables were retained in final model if $P>0.05$

Bivariate analysis was conducted to identify variables associated with CDI

CDI incidence tabulated across CCI/PSI categories

CCI, Charlson comorbidity index; CDI, *Clostridioides difficile* infection; PSI, pneumonia severity index
## CDI incidence in CTX+M patients with CAP

- **33,173 patients met the inclusion criteria**
- **273 (0.8%) had CDI diagnosis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Female</strong></td>
<td>17,174 (51.8)</td>
<td><strong>Female</strong></td>
<td>159 (57.2)</td>
</tr>
<tr>
<td><strong>Age ≥65</strong></td>
<td>21,615 (65.2)</td>
<td><strong>Age ≥65</strong></td>
<td>219 (78.8)</td>
</tr>
<tr>
<td><strong>CCI score</strong></td>
<td></td>
<td><strong>CCI score</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7436 (22.4)</td>
<td>0</td>
<td>35 (12.6)</td>
</tr>
<tr>
<td>1</td>
<td>9139 (27.5)</td>
<td>1</td>
<td>60 (21.6)</td>
</tr>
<tr>
<td>2</td>
<td>6321 (19.1)</td>
<td>2</td>
<td>62 (22.3)</td>
</tr>
<tr>
<td>≥3</td>
<td>10,277 (31.0)</td>
<td>≥3</td>
<td>121 (43.5)</td>
</tr>
<tr>
<td><strong>PSI risk class</strong></td>
<td></td>
<td><strong>PSI risk class</strong></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>11,728 (35.4)</td>
<td>2</td>
<td>50 (18.0)</td>
</tr>
<tr>
<td>3</td>
<td>11,200 (33.8)</td>
<td>3</td>
<td>101 (36.3)</td>
</tr>
<tr>
<td>4</td>
<td>9366 (28.2)</td>
<td>4</td>
<td>108 (38.8)</td>
</tr>
<tr>
<td>5</td>
<td>879 (2.6)</td>
<td>5</td>
<td>19 (6.8)</td>
</tr>
</tbody>
</table>

CDI incidence in CTX+M patients was similar to that in patients who received a fluoroquinolone on Days 1–2 of hospitalization (1.1%)

CCI, Charlson comorbidity index; CDI, *Clostridioides difficile* infection; CTX+M, ceftriaxone plus macrolide; PSI, pneumonia severity index
Multiple CDI risk factors were identified in bivariate analysis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Yes (%)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65</td>
<td>1.0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Prior CAP</td>
<td>1.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.5%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Dementia</td>
<td>1.2%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>1.5%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.1%</td>
<td>0.6%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1.4%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Immuno-compromised</td>
<td>1.4%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Prior hospitalization in previous year</td>
<td>1.5%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

n refers to number of patients with CDI by diagnosis factor. “Yes” refers to patients with the risk factor, “no” refers to patients without the risk factor. CDI, *Clostridioides difficile* infection.
CDI incidence in CTX+M patients with CAP

- CDI incidence in CTX+M patients increased with increasing CCI and PSI scores

CCI, Charlson comorbidity index; CDI, *Clostridioides difficile* infection; CTX+M, ceftriaxone plus macrolide; PSI, pneumonia severity index
Factors independently associated with CDI risk (multivariate model with PSI)

PSI risk class 3
- Odds ratio and 95% CI
- $P=0.0004$

PSI risk class 4
- Odds ratio and 95% CI
- $P<0.0001$

PSI risk class 5
- Odds ratio and 95% CI
- $P<0.0001$

Acute respiratory failure
- Odds ratio and 95% CI
- $P<0.0001$

Coronary heart disease
- Odds ratio and 95% CI
- $P=0.0105$

PSI scores compared with PSI ≤ 70.
Other factors compared presence vs non-presence.
All risk factors in the model affected ≥5% of the sample.
CDI, *Clostridioides difficile* infection; PSI, pneumonia severity index
Factors independently associated with CDI risk (multivariate model without PSI)

Factors compared presence vs non-presence. All risk factors in the model affected ≥5% of the sample.

CDI, *Clostridioides difficile* infection; PSI, pneumonia severity index
Some patient populations empirically receiving CTX+M may be at elevated risk for CDI:

- Aged ≥65
- Prior CAP
- Cancer
- Coronary heart disease
- Congestive heart failure
- Acute respiratory failure
- Dementia
- Immunocompromising conditions
- Renal failure
- Prior hospitalization in the past year

High-risk populations identified in this analysis are consistent with those identified in prior CDI risk-factor studies. Limitations: Use of ICD-9-CM codes to identify CDI; no comparator group

Future studies are needed to determine if alternative antibiotics with a lower propensity to cause CDI can reduce the risk of CDI observed in this study.

We wish to thank the Parexel Real World Evidence Team (Canter Martin, Chi Truong, MD, PhD, et al.) for data analysis and assistance with specifying the coding for PSI score development.

Thank you.