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

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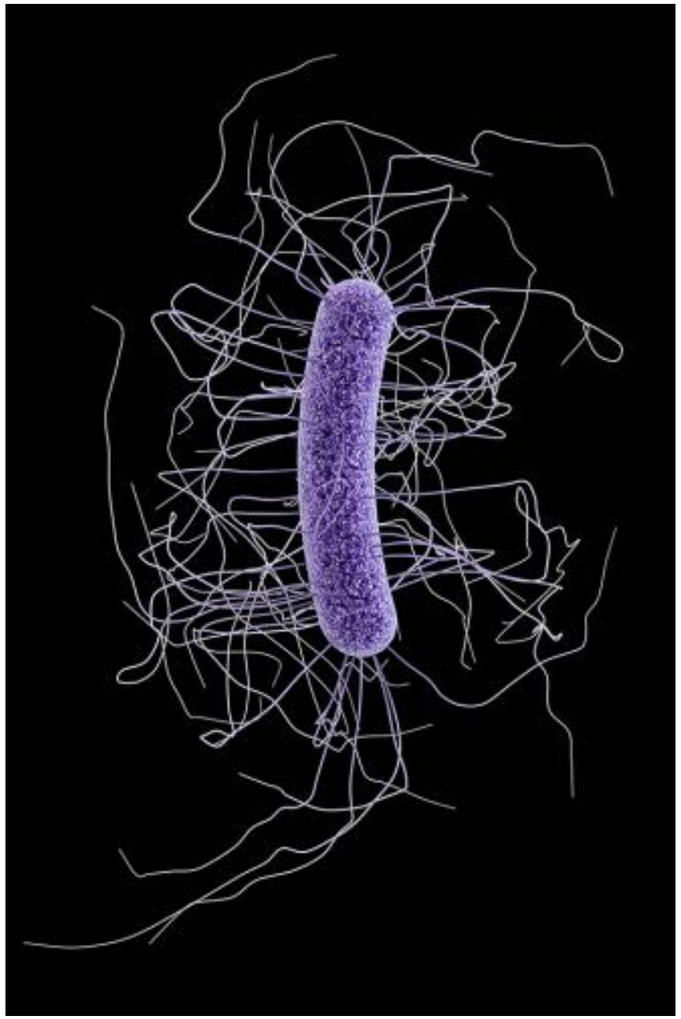
Transparency declaration

- 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

1. Balsells E, et al. *J Glob Health* 2019;9(1):010407; **2.** NICE, https://www.nice.org.uk/advice/esmpb1/chapter/Key-points-from-the-evidence 2015;
3. Slimings C, et al. *J Antimicrob Chemother* 2014;69(4):881–91; **4.** Brown KA, et al. *Antimicrob Agents Chemother* 2013;57(5):2326–32;
5. Deshpande A, et al. *J Antimicrob Chemother* 2013;68(9):1951–61; **6.** Bender M and Niederman M. *Ann Res Hosp* 2018;2:6.

CAP, community-acquired pneumonia; CDI, *Clostridioides difficile* infection; CTX+M, ceftriaxone plus macrolide

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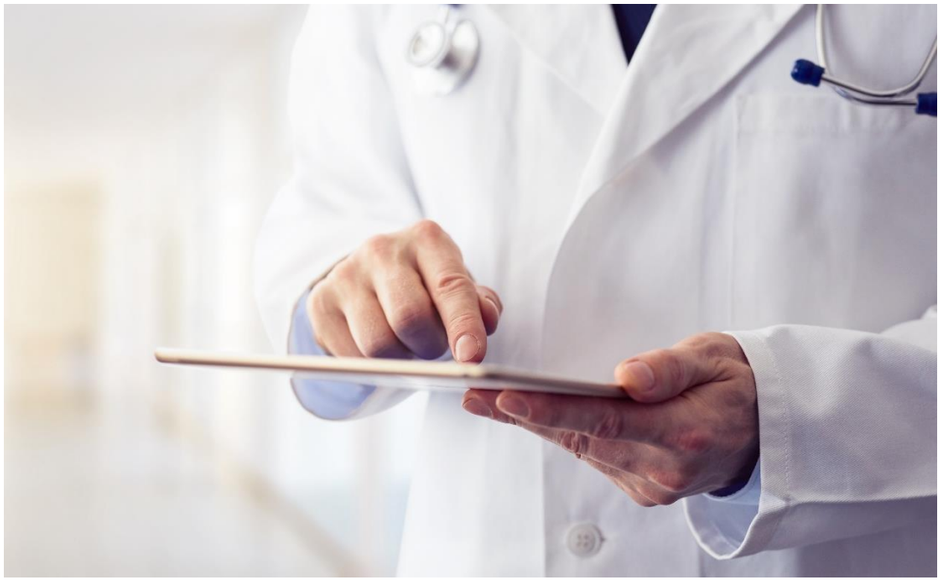
Aim

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

Study details

- 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 calculated[1]:
  - 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

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

Statistical analysis

- Bivariate analysis was conducted to identify variables associated with CDI
- CDI incidence tabulated across CCI/PSI categories

- 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

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

Characteristic	Number (%)
Female	17,174 (51.8)
Age ≥65	21,615 (65.2)
CCI score	
0	7436 (22.4)
1	9139 (27.5)
2	6321 (19.1)
≥3	10,277 (31.0)
PSI risk class	
2	11,728 (35.4)
3	11,200 (33.8)
4	9366 (28.2)
5	879 (2.6)

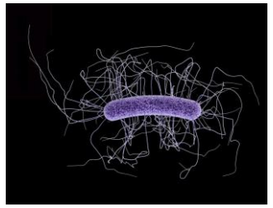
- 273 (0.8%) had CDI diagnosis

Characteristic	Number (%)
Female	159 (57.2)
Age ≥65	219 (78.8)
CCI score	
0	35 (12.6)
1	60 (21.6)
2	62 (22.3)
≥3	121 (43.5)
PSI risk class	
2	50 (18.0)
3	101 (36.3)
4	108 (38.8)
5	19 (6.8)

- 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



Patients with CDI = 0.8%
n=273

Age ≥65	Prior CAP	Cancer	Dementia	Acute respiratory failure
Yes = 1.0% No = 0.8%	Yes = 1.3% No = 0.8%	Yes = 1.5% No = 0.7%	Yes = 1.2% No = 0.8%	Yes = 1.5% No = 0.7%

Coronary heart disease	Congestive heart failure	Renal failure	Immuno-compromised	Prior hospitalization in previous year
Yes = 1.1% No = 0.6%	Yes = 1.4% No = 0.7%	Yes = 1.4% No = 0.7%	Yes = 1.4% No = 0.9%	Yes = 1.5% No = 0.8%

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

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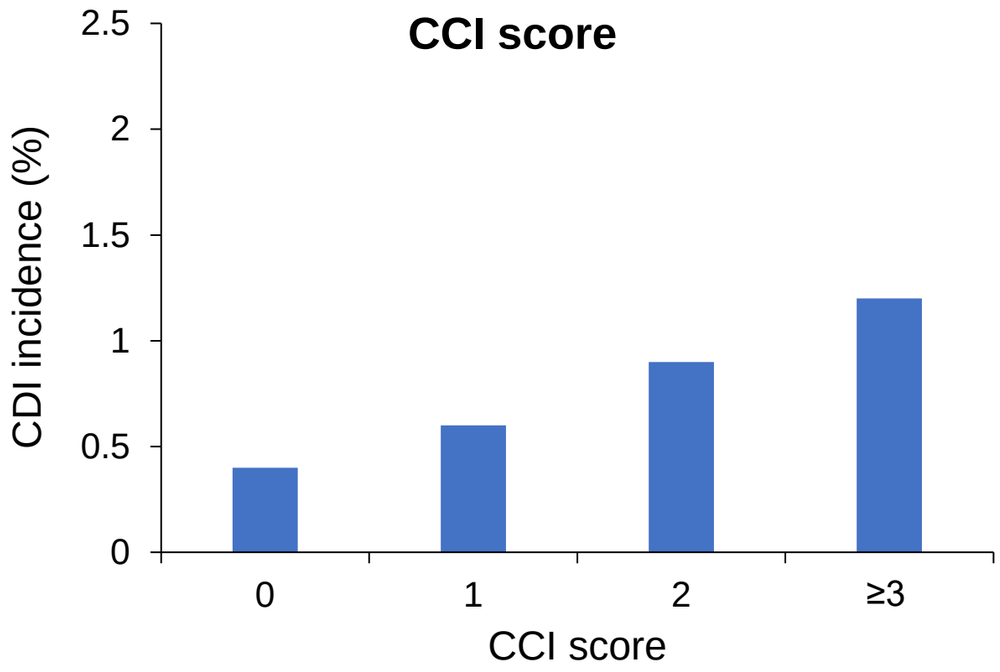
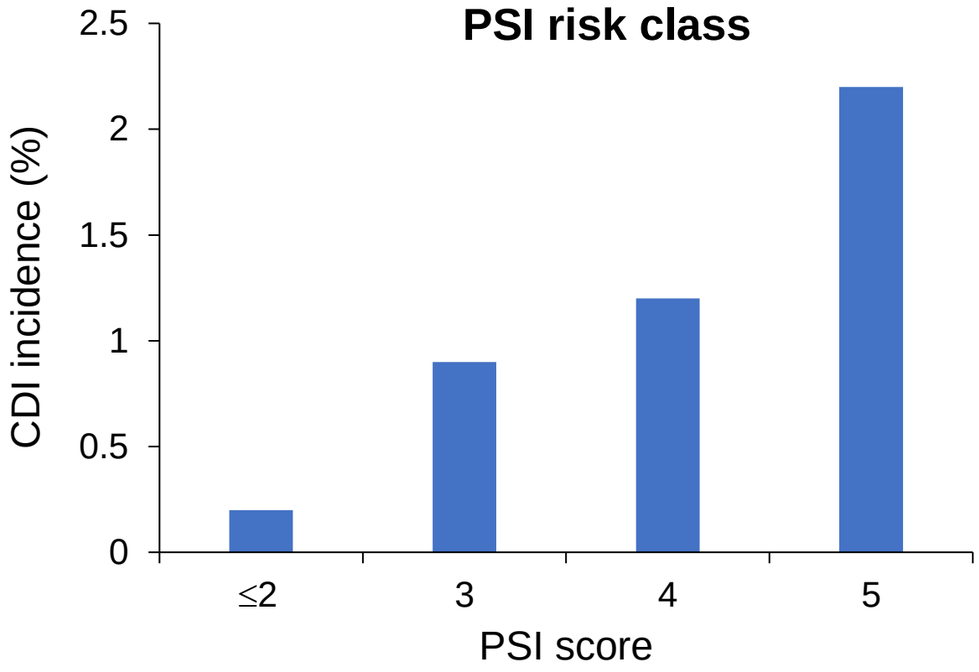
CDI incidence in CTX+M patients with CAP

- 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

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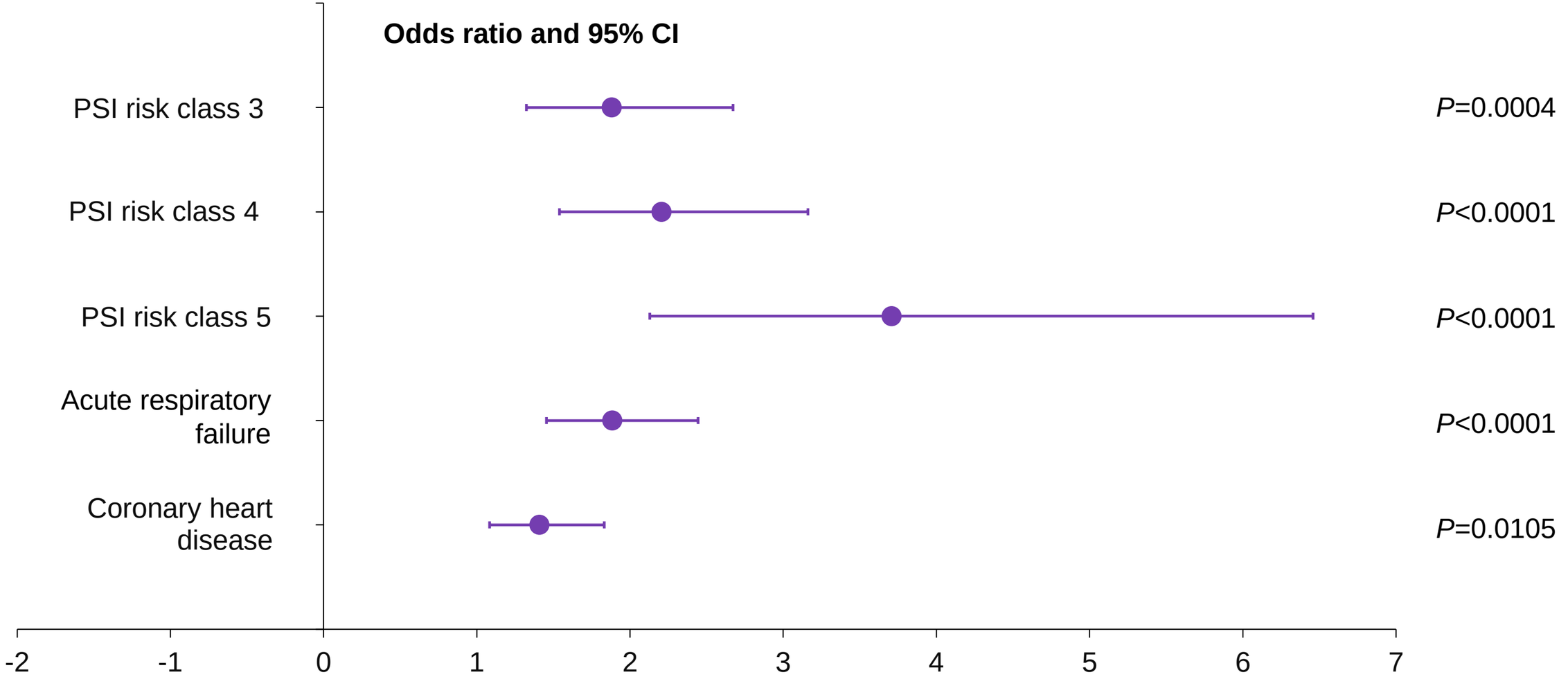
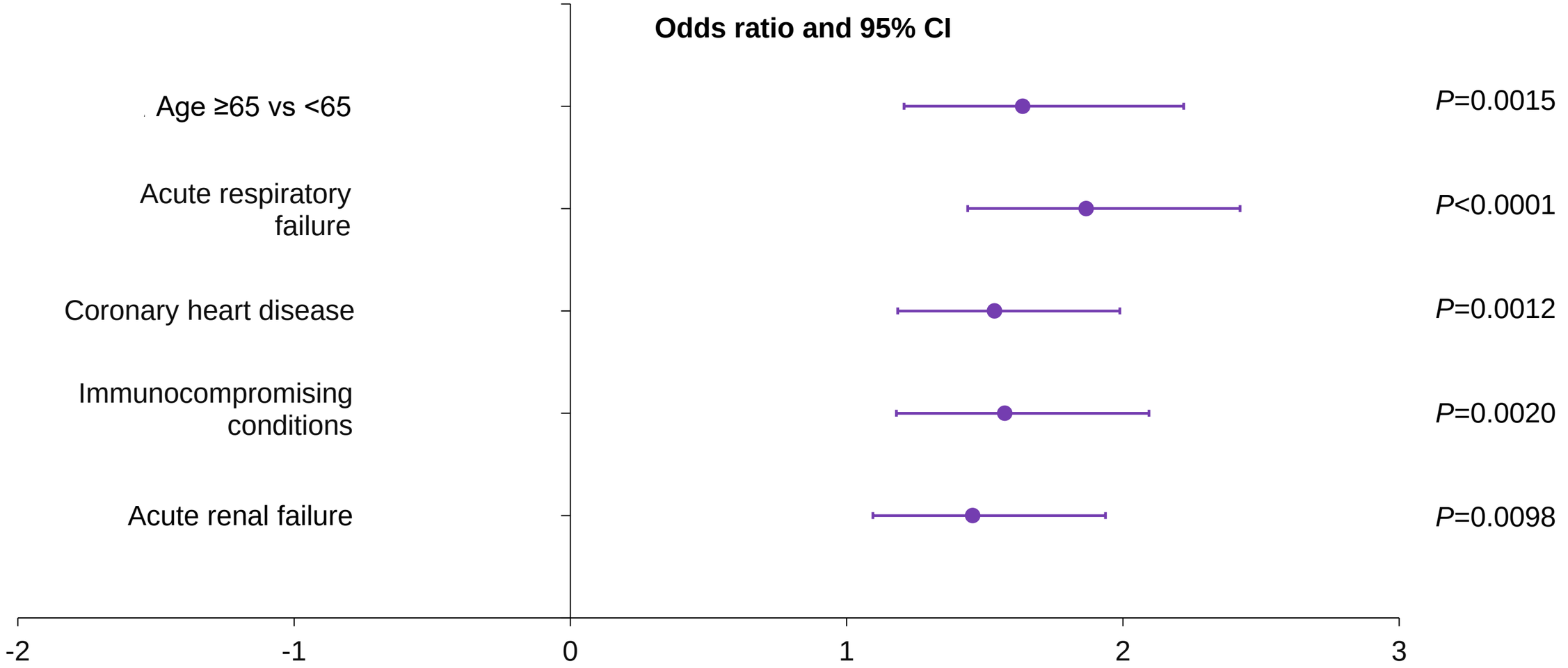
Factors independently associated with CDI risk (multivariate model with PSI)



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

Conclusions

- 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[1-4]
- 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

1. Eze P, et al. *J Glob Health* 2017;7(1):010417; **2.** Garey KW, et al. *J Hosp Infect* 2008;70(2):142–7; **3.** Chmielewska M, et al. *Adv Exp Med Biol* 2017;955:59–63; **4.** Ziakas PD, et al. *Medicine (Baltimore)* 2016;95(31):e4187.

CAP, community-acquired pneumonia; CDI, *Clostridioides difficile* infection; CTX+M, ceftriaxone plus macrolide; ICD-9-CM, international classification of diseases, 9th revision, clinical modification code;

Acknowledgments

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Thank you