Risk factors associated with *Clostridioides difficile* infection in hospitalized patients with community-acquired pneumonia

W. Justin Moore, PharmD[1,2]; Caroline C. Jozefczyk, PharmD[3]; Paul Yarnold, PhD[4]; Karolina Harkabuz[2]; Valerie Widmaier, MBA, MLS (ASCP)CM[1,5]; Christina Silkaitis, CIC, FAPIC, MBA[1]; Sarah Sutton, MD[1,6]; Chao Qi, PhD[1,5]; Richard G. Wunderink, MD[1,7]; Teresa R. Zembower, MD, MPH, FIDSA[1,6]; Nathaniel J. Rhodes, PharmD, MSc, BCPS-AQID[1,2]

[1]Northwestern Memorial Hospital, Chicago, IL, USA; [2]Midwestern University Chicago College of Pharmacy, Downers Grove, IL, USA; [3]OhioHealth, Mansfield, OH, USA; [4]Optimal Data Analysis, LLC, Chicago, IL, USA; [5]Department of Pathology, Northwestern Memorial Hospital, Chicago, IL, USA; [6]Division of Infectious Diseases, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [7]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

W. Justin Moore, PharmD
Northwestern Medicine
251 E Huron Street
Chicago, IL 60611
William.moore@nm.org

Abstract, Modified

Background: Adults hospitalized with community-acquired pneumonia (CAP) typically receive antibiotics and thus are at increased risk of developing *Clostridioides difficile* infection (CDI), a disease of significant morbidity.
Methods: We developed and validated a CAP-specific clinical decision algorithm to facilitate optimal diagnostic stewardship of *C. difficile* polymerase chain reaction (PCR) testing. The study was a single-center retrospective, case-control analysis of hospitalized adult patients empirically treated for CAP between January 1, 2014 and May 29, 2018. A series of predictive models and validity assessments were used to evaluate demographic and post-admission patient-specific risk factors as predictors of CDI case status among patients with CAP.
Results: Thirty-two PCR confirmed CDI cases were identified and 232 randomly selected controls were drawn from the total CAP population. After propensity score weighting, hospital-onset (HO) CDI was significantly associated with broad-spectrum Gram-negative antibiotic use (P=0.002) as was subsequent community-onset (CO) CDI (P=0.005). Modified-APACHE II > 8.5 (P=0.003) and broad-spectrum Gram-negative antibiotic use (P=0.002) were associated with healthcare-associated CDI and were robust in multiple validity analyses. Patients with m-APACHE II ≤ 8.5 who received broad-spectrum Gram-negative antibiotics were more likely (odds=1:2) to experience healthcare-associated CDI compared to those who did not receive these broad-spectrum agents (odds=1:125) and compared to those with m-APACHE II > 8.5 irrespective of treatment (odds=5:27).
Conclusions: Broad-spectrum Gram-negative antibiotic use was the common factor in development of CDI in patients with CAP in all settings. Prospective validation studies are needed to confirm our model's validity and clinical utility for diagnostic test stewardship.

Background

- Patients hospitalized for community-acquired pneumonia (CAP) are often treated with antibiotics and may carry an increased risk for developing *Clostridioides difficile* infections (CDI).
- Risk estimation tools are needed to guide monitoring and reduce CDI.

Purpose

- To develop and validate CAP-specific decision models that support diagnostic and antimicrobial stewardship in hospitalized pneumonia patients.

Methods

Design: retrospective, single-center, case-control study

Included: hospitalized patients with CAP admitted to general medicine wards between 1/1/2014 and 5/29/2018

- **Case**: Received antibiotics for CAP, and subsequently developed CDI within 90 days of index admission
- **Control**: Random sampling of patients who received antibiotics for CAP without developing CDI within 90 days

Excluded: patients with cystic fibrosis, ≥3 admissions within 30 days, CAP requiring ICU admission, and death within 48 hours

Data Points:

- Comorbidities, baseline demographics, laboratory values, vital signs, severity of illness, prior hospitalization, and previous antibiotic use

Analysis:

- Univariate Optimal Data Analysis (ODA) was used to evaluate differences in demographic and post-admission risk factors to classify CDI case or control status with maximum accuracy
- Propensity-score weights: identified via structural decomposition analysis of pre-treatment variables
- Classification Tree Analysis (CTA) was used to predict 1) community onset (CO) CDI, 2) hospital-onset (HO) CDI, 3) CO healthcare facility-associated (HFCA) CDI, and 4) healthcare-associated (HA) CDI (HO+CO-HFCA)
- Models evaluated according to Percent Accuracy in Classification (PAC), Effect Strength for Sensitivity (ESS), positive predictive value (PPV), negative predictive value (NPV), and the D statistic
- Parsimonious model selection was guided by lowest D and highest ESS; Novometric bootstrap validity assessment was used to judge the generalizability of the model to an independent sample
- Modeling completed via ODA package (v1.1.1) for R (v3.5.1) http://doi.org/10.5281/zenodo.4075245

Results

Table 1. Select Demographics and Risk Factors for any CDI case or control status

Select Demographics	Total, n=264	Case, n=32	Control, n=232	P-value
Age (years), mean (SD)	63.1 (17.9)	68.5 (17.6)	62.4 (17.8)	0.071
Female, n (%)	135 (51.1)	16 (50.0)	119 (51.3)	>0.99
Weight (kg)	84.4 (27.5)	84.8 (28.6)	84.4 (27.4)	0.945
Modified APACHE II, mean (SD)	8.5 (4.5)	11.2 (4.2)	8.1 (4.4)	<0.001
PSI, mean (SD)	80.5 (32.0)	105 (26.3)	77.1 (31.2)	<0.001
Select Risk Factors, n (%)				
Hospitalization > 2 days in last 90 days	56 (21.2)	18 (56.2)	38 (16.4)	<0.001
Antibiotic use in last 90 days	83 (31.4)	19 (59.4)	64 (27.6)	<0.001
BUN > 29 mg/dl	35 (13.3)	12 (37.5)	23 (9.9)	<0.001

Table 2. Attributes predictive of CDI cases in training and validity ODA analysis

	Training Model			Validity (Leave-one-out) Model	
Model: IF attribute = "yes" THEN predict CDI	**PAC** %	**ESS** %	**M.C.** Exact P-value	**ESS** %	**M.C.** Exact P-value
Hospitalization > 48 hr in last 90 days	80.3	39.9	<0.001	39.9	0.000003
Modified-APACHE II > 8.5	57.6	32.9	0.0016	32.9	0.000382
Antibiotic use in the last 90 days	70.8	31.8	0.0004	31.8	0.000466
Chronic comorbidities	72.6	28.5	0.0019	28.5	0.001287
BUN > 29 (mg/dL)	83.7	27.6	0.0002	27.6	0.000165
History of acid-suppressant use	66.7	24.4	0.0103	24.4	0.006898

Table legend: PAC = overall percent accuracy in classification or the sum of those correctly classified divided by the total; ESS = Effect Strength for Sensitivity = 100 x [((Sens+Spec)/2)-50/(100-50)] or accuracy normed for chance; M.C. = exact P-value from 10,000 Monte Carlo simulations

Results Continued

Figure 1. Propensity score CTA model and metrics

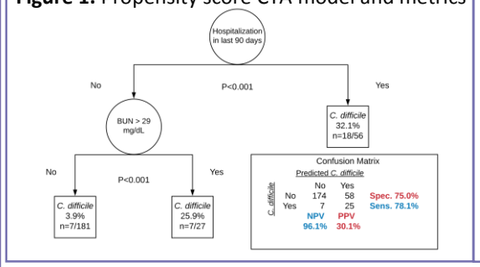


Figure 2. Final HA-CDA CTA model and metrics

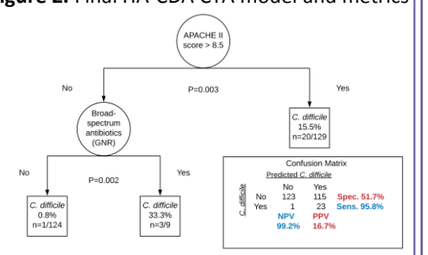
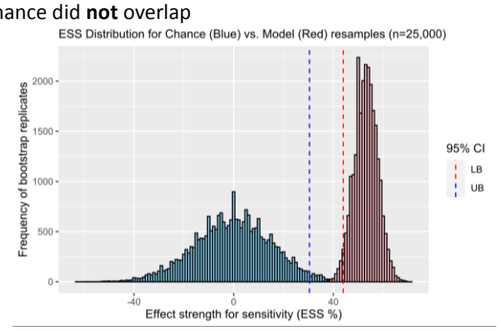


Table 3. Weighted CTA models of CDI in patients with CAP

Outcome: Predictor(s)	ESS	wESS	Sensitivity	Specificity	P-value
CO-CDI: Broad Abx	13.7%	20.7%	100%	13.7%	0.005
HO-CDI: Broad Abx	48.7%	56.3%	58.8%	89.9%	0.002
HA-CDI: Broad Abx + m-APACHE II score	47.5%	49.3%	95.8%	51.7%	0.003 0.002

Figure 3. Novometric bootstrap analysis of the final weighted CTA model of HA CDI found that the exact discrete 95% CIs for model and chance did **not** overlap

Percentile	Model ESS (%)	Chance ESS (%)
0%	32.8	-63.5
2.5%	44.0	-31.5
5%	45.4	-26.2
25%	50.0	-10.4
50%	53.0	-0.1
75%	56.1	10.4
95%	60.7	25.3
97.5%	62.1	**30.4**
100%	71.1	56.6



Conclusion and Limitations

Conclusions:

- Broad-spectrum Gram-negative antibiotic use was significantly associated with subsequent development of community-onset (CO) and HO CDI.
- Bootstrap reproducible models of healthcare-associated CDI (CO-HCFA or HO) were identified. These models had high negative predictive value and were weighted by propensity score defined via structural decomposition.
- Electronic decision support systems could utilize models like these to increase visibility of hospitalized patients' risk for developing CDI due to modifiable risk factors including spectrum of antibiotic received.

Limitations:

- Cases are likely under-reported and causality cannot be inferred, though propensity scoring reduces threats to causal inference attributable to baseline individual-difference risk factors.
- Additional unmeasured variables may further improve classification of CDI in this population.

References & Disclosures

Included authors have reported disclosures available at https://idweek.org/abstracts.