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Concise Communication

Impact of infectious diseases consultation for hospitalized patients with *Clostridioides difficile* infection

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Abstract

Clostridioides difficile infection (CDI) is associated with substantial morbidity and mortality. This study described outcomes associated with mandatory infectious diseases (ID) consultation in hospitalized patients with CDI. ID consultation was associated with increased appropriate concomitant antibiotic use, however longer courses of concomitant antibiotics were administered.

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Introduction

The Centers for Disease Control and Prevention (CDC) 2019 report of antibiotic resistant threats in the United States classified *Clostridioides difficile* infection (CDI) as an urgent health threat with 462,100 cases and an estimated 12,800 deaths in 2017.[1,2] CDI is associated with substantial morbidity and mortality and strategies to improve management and outcomes are urgently needed.

Interventions by antimicrobial stewardship teams have led to improved adherence to guideline recommended CDI processes, but improvements in important clinical outcomes such as mortality and recurrence are lacking.[3] To our knowledge, no previous studies have evaluated the role of mandatory infectious diseases (ID) consultation for CDI. The value of ID consultation in improving quality of care and clinical outcomes of infections including *Staphylococcus aureus* bacteremia, Gram-negative bacteremia, and candidemia is well established.[4–6] The current study investigated outcomes associated with mandatory ID consultation for all hospitalized patients with CDI.

Methods

Study designs and population

We conducted a retrospective cohort study of all adult patients hospitalized with CDI between July 1, 2018 and December 31, 2019 at a 548-bed community teaching hospital. Study approval was obtained through the hospital's institutional review board. Prior to the implementation of mandatory ID consultation for patients with CDI, management and treatment including need for ID consultation were determined by the primary team. Beginning in July 2019, all patients with positive laboratory CDI testing required ID consultation. Consultation was determined by an ID consult note in the electronic medical record.

Patient demographic and clinical information was abstracted manually and electronically through the health-system data warehouse. Manually abstracted data included CDI symptoms, days of therapy (DOTs) of concomitant antibiotic use, 30-day CDI-associated mortality, and CDI treatment. Variables abstracted electronically included demographics, an internal prediction rule for patient mortality,[7] Charlson Comorbidity Index, CDI test type, 30-day readmission, length of stay (LOS), intensive care unit (ICU) LOS, CDI recurrence, 30-day mortality, colectomy and post-acute care discharge.

Definitions

CDI testing consisted of an enzyme immunoassay (EIA) for glutamate dehydrogenase (GDH) and an EIA for detection of toxin A/B (C. diff Quik Check Complete®, Alere). If testing for GDH was positive and the EIA for toxin A/B was negative, then a confirmatory polymerase chain reaction (PCR) assay (Xpert® *C. difficile*, Cepheid) was performed. CDI was diagnosed using the National Health Safety Network definition for laboratory surveillance and reporting.[8]

Outcomes

The primary outcomes were appropriateness and DOTs of non-CDI concomitant antibiotic therapy, defined as the aggregate sum of DOTs administered as inpatients and prescribed as outpatients following positive testing results for CDI. Outpatient DOTs were determined from discharge documentation. Appropriateness of concomitant antibiotics was determined by investigators' chart review for confirmation of infectious diagnoses warranting

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Table 1. Demographics and clinical characteristics by cohort

Variable[a]	Historical cohort ($N = 109$)	Intervention cohort ($N = 104$)	P value	PS weighted P value
Age, years[b]	67.5 (17)	68.2 (16.7)	.76	.904
Gender			.716	.475
Female	56 (51.4)	57 (54.8)		
Male	53 (48.6)	47 (45.2)		
Race			.465	.358
Non-white	13 (11.9)	17 (16.4)		
White	96 (88.1)	87 (83.7)		
Comorbidities				
Congestive heart failure	35 (32.1)	28 (26.9)	.497	.804
Hypertension	66 (60.6)	74 (71.2)	.137	.329
Diabetes Mellitus	32 (29.4)	30 (28.9)	>.999	.933
COPD	23 (21.1)	17 (16.4)	.476	.981
Respiratory failure	33 (30.3)	20 (19.2)	.088	.65
Renal	55 (50.5)	51 (49)	.944	.663
Pneumonia	18 (16.5)	8 (7.7)	.079	.751
Sepsis	44 (40.4)	50 (48.1)	.32	.782
Gastrointestinal bleed	9 (8.3)	2 (1.9)	.075	.351
Cancer	28 (25.7)	21 (20.2)	.43	.702
Inflammatory bowel disease	4 (3.7)	3 (2.9)	>.999	.953
Prospective mortality risk score[b,c,7]	2.6 (1.1)	2.6 (1.1)	.93	.875
Retrospective mortality risk score[b,d,7]	2.4 (1.1)	2.4 (1.1)	.985	.952
Charlson Comorbidity Index[b,e]	2.3 (1.8)	2 (1.7)	.332	.474
CDI severity			.178	.654
Non-severe	54 (49.5)	41 (39.4)		
Severe	55 (50.5)	63 (60.6)		
CDI testing			.121	
GDH+/Toxin+	31 (28.4)	40 (38.5)		
GDH+/PCR+	78 (71.6)	64 (61.5)		

Note. PS, propensity score; COPD, chronic obstructive pulmonary disease; ICU, Intensive care unit; CDI, *Clostridioides difficile* infection; GDH, glutamate dehydrogenase; PCR, polymerase chain reaction.
[a]Data are no. (%) unless otherwise specified.
[b]Data are summarized with mean (standard deviation).
[c]Analysis performed on encounters with available data ($n = 100$ historical cohort; $n = 99$ intervention cohort).
[d]Analysis performed on encounters with available data ($n = 104$ historical cohort; $n = 102$ intervention cohort).

antibiotic treatment based on institutional guidelines. Secondary outcomes included LOS, recurrence, 30-day mortality, 30-day CDI-associated mortality, and 30-day readmission. Recurrence was defined as meeting all three of the following criteria within 4 weeks after successful completion of CDI treatment: reappearance of symptoms (>3 unformed stools in 24 hour period), positive stool testing for *C. difficile*, and need for CDI re-treatment.

Analysis

The analysis compared the observations from July 1, 2018 to December 31, 2018 (historical cohort) and July 1, 2019 to December 31, 2019 (intervention cohort), with the intervention defined as establishment of mandatory ID consults (beginning July 2019). Baseline demographic and clinical variables were summarized using means and standard deviations or medians and inter-quartile ranges (IQR) for continuous variables with counts and percentages for categorical variables. Chi-squared tests, *t*-tests, and Wilcoxon tests were performed to test for differences between the groups. Propensity score weighting was used to create a balanced pseudo-population between the historical and intervention cohorts. After weighting, comparisons between demographics and comorbidities were repeated to check for balance.

Propensity scores were calculated from a Gradient Boosting Machine regression model. Propensity scores were converted to inverse probability of treatment weights, and outcomes were then compared using weighted versions of the Chi-squared test or Fisher's exact test for categorical variables or a weighted version of the *t* test or Wilcoxon rank-sum test for continuous variables. Both unadjusted and adjusted comparisons were made between the historical and intervention groups across all outcomes. Analyses were performed using SPSS, version 26.0 (IBM Corp) and

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Table 2. Outcomes by cohort

Variable[a]	Historical cohort ($N = 109$)	Intervention cohort ($N = 104$)	P value	PS weighted P value
ID consultation	43 (39.5)	102 (98.1)	<.001	<.001
Concomitant antibiotic use	49 (45)	43 (41.4)	.694	.692
Appropriate concomitant antibiotic use[b]	42 (85.7)	43 (100)	.013	.01
Antibiotic days of therapy[b,c]	4 (2, 8)	9 (6, 13)	<.001	<.001
Length of stay	7 (3, 12)	7 (4, 12)	.617	.464
ICU visit	17 (15.6)	15 (14.4)	.962	.784
ICU length of stay, days[c,d]	6 (3, 12)	3 (2, 11)	.354	.282
Recurrence	5 (4.6)	5 (4.8)	>.999	.888
Colectomy	1 (0.9)	3 (2.9)	.36	.332
Mortality				
30-d mortality[e]	16 (15)	8 (7.7)	.149	.424
30-d CDI-related mortality[f]	4 (3.9)	0 (0)	.058	.052
30-d readmission	22 (20.2)	22 (21.2)	.996	.92
Discharge to post-acute care	65 (59.6)	64 (61.5)	.885	.875
CDI antibiotic treatment				
Oral vancomycin	106 (97.3)	96 (92.3)	.187	.121
Oral metronidazole	4 (3.7)	1 (1)	.37	.057
Fidaxomicin	1 (0.9)	7 (6.7)	.032	.083
Rectal vancomycin	4 (3.7)	9 (8.7)	.218	.147
IV metronidazole	14 (12.8)	17 (16.4)	.596	.656
Combination treatment	14 (12.8)	17 (16.4)	.596	.656

Note. PS, propensity score; ID, infectious diseases; ICU, intensive care unit; CDI, *Clostridioides difficile* infection; IV, intravenous.
[a]Data are no. (%) unless otherwise specified.
[b]Analysis performed on encounters with concomitant antibiotic use.
[c]Data are median (interquartile ratio).
[d]Analysis performed on encounters with ICU stay.
[e]Analysis performed on subset of encounters with available data ($n = 107$, historical cohort; $n = 104$, intervention cohort).
[f]Analysis performed on subset of encounters with available data ($n = 102$, historical cohort; $n = 104$, intervention cohort).

R version 3.6.0 (R Project for Statistical Computing). A P value of ≤ .05 was considered statistically significant.

Results

Study population

A total of 213 CDI cases were identified during the study period; 109 in the historical cohort and 104 in the intervention cohort (Table 1). The study population had a mean age of 67.8 years with 113 (53.1%) females. There were no significant demographic or comorbidity differences between groups before or after propensity score weighting.

Clinical outcomes

The rate of ID physician consultations increased from 39.5% to 98.1% ($P < .001$) (Table 2). For specific CDI-related treatments, there was less prescribing of oral metronidazole (3.7% vs 1%; $P = .057$) and higher use of oral fidaxomicin (0.9% vs 6.7%; $P = .083$) in the intervention cohort, although these differences were not statistically significant. There was no difference in non-CDI concomitant antibiotic use between cohorts (45% vs 41.4%; $P = .692$); however, patients in the mandatory ID consult group were more likely to receive appropriate antibiotic therapy (85.7% vs 100%; $P = .01$). Patients received non-CDI antibiotics for longer duration in the mandatory ID consultation cohort (4 days vs 9 days; $P < .001$).

There was no difference in all-cause 30-day mortality (15% vs 7.7%; $P = .424$). CDI-related 30-day mortality was lower in the intervention cohort (3.9% vs 0%; $P = .052$), however this difference did not reach statistical significance. There were no differences in LOS, ICU stay, ICU LOS, 30-day readmission, CDI recurrence, or discharge to post-acute care facility.

Discussion

This study found the rate of ID physician consultations increased from 39.5% to 98.1% ($P < .001$) after implementation of mandatory ID consultation for all hospitalized patients with CDI. Patients in the mandatory ID consult group were more likely to receive appropriate antibiotic therapy (100% vs 85.7%; $P = .01$), similar to others that have reported improvement in adherence to antimicrobial guidelines with ID consultation.[4,5] However, DOTs in the intervention cohort were longer (4 vs 9 days; $P < .001$), likely reflecting variability in the underlying treated infection. Mandatory ID consultation was associated with lower 30-day CDI-related mortality (3.9% vs 0%; $P = .052$), although the difference was not statistically significant. These results collectively

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demonstrate benefit to the involvement of ID consultation for hospitalized patients with CDI.

While the IDSA Clinical Practice Guidelines outline standards for testing and treatment of CDI, there is no discussion or recommendation regarding consultation of ID specialists.[9] A study by Olmedo et al found that a rapid bedside intervention by an ID physician for CDI patients reduced the use of unnecessary non-CDI antibiotics by 19%.[10] Our study corroborates this finding. There was no statistical difference in prescribing of specific CDI-related treatments in the cohorts, however there was increased administration of fidaxomicin (0.9% vs 6.7%; $P = .083$) and decreased use of oral metronidazole (3.7% vs 1%; $P = .057$) in the intervention cohort.

Limitations of this analysis include small sample sizes and the retrospective single center design. Similar time periods (July–December) were analyzed, eliminating seasonality as a potential confounder. However, the short six month study periods may have led to sampling bias with rare CDI-associated outcomes such as mortality and colectomies. Additionally, chart reviews were not blinded and may have introduced potential bias for improved outcomes associated with ID consultation.

This study adds to the growing literature demonstrating improved outcomes associated with ID consultation.[4–6] ID consultation was associated with increased appropriate concomitant antibiotic use. Given the high morbidity and mortality associated with CDI and the expansion of CDI therapeutics, future studies are urgently needed to further examine the role of ID consultation for patients with CDI.

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