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Original Article

Clostridioides difficile colonization and the frequency of subsequent treatment for *C. difficile* infection in critically ill patients

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Abstract

Objective: To determine risk factors for *Clostridioides difficile* colonization and *C. difficile* infection (CDI) among patients admitted to the intensive care unit (ICU).

Design: Retrospective observational cohort study.

Setting: Tertiary-care facility.

Patients: All adult patients admitted to an ICU from July 1, 2015, to November 6, 2019, who were tested for *C. difficile* colonization. Patients with CDI were excluded.

Methods: Information was collected on patient demographics, comorbidities, laboratory results, and prescriptions. We defined *C. difficile* colonization as a positive nucleic acid amplification test for *C. difficile* up to 48 hours before or 24 hours after intensive care unit (ICU) admission without evidence of active infection. We defined active infection as the receipt of an antibiotic whose only indication is the treatment of CDI. The primary outcome measure was the development of CDI up to 30 days after ICU admission. Logistic regression was used to model associations between clinical variables and the development of CDI.

Results: The overall *C. difficile* colonization rate was 4% and the overall CDI rate was 2%. Risk factors for the development of CDI included *C. difficile* colonization (aOR, 13.3; 95% CI, 8.3–21.3; $P < .0001$), increased ICU length of stay (aOR, 1.04; 95% CI, 1.03–1.05; $P < .0001$), and a history of inflammatory bowel disease (aOR, 3.8; 95% CI, 1.3–11.1; $P = .02$). Receipt of any antibiotic during the ICU stay was associated with a borderline increased odds of CDI (aOR, 1.9; 95% CI, 1.0–3.4; $P = .05$).

Conclusion: *C. difficile* colonization is associated with the development of CDI among ICU patients.

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Hospital-onset, healthcare-associated *Clostridioides difficile* infection (CDI) is an important cause of morbidity and mortality in the United States. In 2017, CDI caused >400,000 infections and >20,000 deaths in the United States.[1] Hospital-onset, healthcare-associated CDI has historically been attributed to healthcare exposure to another patient with active infection. However, genome-based sequencing suggests that this is true for only ~33% of healthcare-associated cases.[2] Up to 20% of hospitalized patients are colonized with *C. difficile* on admission and may be important sources of infection to other patients.[3] In addition, exposures during a patient's hospitalization, such as the use of antibiotics and proton pump inhibitors (PPIs), may put colonized patients at higher risk of developing CDI.[4]

Colonization with *C. difficile* has been studied primarily among general ward patients but may have implications for intensive care unit (ICU) patients as well. In the ICU, CDI is associated with increased healthcare costs, longer length of stay, and increased need for skilled nursing or rehabilitation on discharge.[5] Hospital mortality is also higher for ICU patients with CDI.[6] *C. difficile* colonization may play an important role in the pathogenesis of CDI in ICU patients given the frequent use of therapies associated with progression to active disease.[7] The relationship between *C. difficile* colonization and CDI in the ICU has been evaluated in several prior studies with mixed results.[8–10] Tschudin-Sutter et al[8] found that colonization with *C. difficile* was a risk factor for the development of CDI among ICU patients, although this risk factor was not identified in a similar study by Zhang et al.[9] Notably, the study by Zhang et al was performed at a referral hospital in western China, and a baseline *C. difficile* colonization rate of only 1.7% was

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reported, lower than that reported in the Tschudin-Sutter study (3.1%) and other studies in non-ICU populations.[8,9]

Our institution implemented a *C. difficile* screening protocol upon admission for hospitalized patients that began in targeted units in July 2015 and expanded to include all admitted patients in 2018.[11] The program initially began with select general ward units from 2015 to 2017. In 2017, the program was rolled out in additional units including all our hospital's ICUs. This screening program provides a unique opportunity to study *C. difficile* colonization across our entire ICU population. In this study, we assessed the prevalence of *C. difficile* colonization among ICU patients, determined risk factors for colonization, and assessed risk factors for the subsequent development of CDI.

Methods

Study design, definitions, and patient population

This retrospective observational cohort study included all patients 18 years of age and older who were admitted to an ICU between July 1, 2015, and November 6, 2019, at the University of Chicago Medicine, an 800-bed, tertiary-care facility with 104 adult ICU beds in southern Chicago. Patients were included in the analysis if they were admitted to an ICU within 72 hours of hospital admission, were screened for *C. difficile* colonization on ICU admission, and remained in the ICU for a minimum of 24 hours. For patients with multiple ICU stays during the study period meeting inclusion criteria, only the first ICU stay was included in the analysis. Patients who had evidence of CDI at the time of ICU admission were excluded from the study. The primary outcome measure was the development of CDI within 30 days after ICU admission. This study was approved by the institutional review board with a waiver of consent.

We defined patients as being colonized with *C. difficile* if they had a positive test for *C. difficile* on admission to the ICU but did not have evidence of active infection. Tests could be obtained up to 48 hours before or 24 hours after ICU admission. For patients who were admitted through the emergency room or the general wards, tests could be obtained in those locations. For patients who were screened more than once with discrepant results (eg, at least 1 positive and one negative result), the patient was classified as colonized. Tests could include a *C. difficile* nucleic acid amplification test performed on a perirectal swab or stool sample using the Xpert *C. difficile* assay (Cepheid, Sunnyvale, CA) or a *C. difficile* nucleic acid amplification test performed as part of the FilmArray Gastrointestinal Panel (BioFire Diagnostics, Salt Lake City, UT).

We defined active infection with *C. difficile* as the receipt of an antibiotic whose only indication is the treatment of CDI (eg, oral vancomycin, rectal vancomycin, or oral fidaxomicin) that was continued for at least 72 hours inpatient and/or was prescribed upon hospital discharge. We chose not to require a recent positive *C. difficile* test in our definition because our laboratory uses the same assay for both screening and testing for clinical disease and our hospital policy discourages repeat testing among colonized patients. Rather, patients who screen positive and develop clinical signs of CDI are treated based on clinical symptoms without repeated testing. We used a minimum treatment duration of 72 hours to exclude patients who were started empirically on *C. difficile*–directed therapy prior to confirmatory testing. Although metronidazole may also be used for CDI, we did not include this medication in our definition since metronidazole has other non-CDI indications and our hospital has a widely adopted treatment pathway for CDI that does not involve metronidazole monotherapy. Patients were considered to have active CDI and were excluded from the study if treatment was started up to 72 hours before or 48 hours after ICU admission. Patients were considered to have developed CDI if treatment was started between 48 hours and 30 days after ICU admission. Patients were followed for up to 30 days after ICU admission or until hospital discharge or death, whichever was sooner.

We elected to use antibiotic prescriptions as a surrogate for treating clinicians' impression of the patient's clinical symptoms rather than performing retrospective chart review given the variability in electronic medical record documentation of symptoms such as diarrhea. Our hospital has a robust antimicrobial stewardship program that reviews all prescriptions for oral vancomycin and fidaxomicin in real-time to help confirm appropriate use. We also reviewed the subset of cases identified during the study period by our infection control program as hospital-onset healthcare-associated CDI to ensure that these cases were also correctly classified in our study. This subset included patients who developed symptoms of CDI >3 days after hospital admission, had a positive test for *C. difficile*, and who were not known to be colonized on hospital admission. Similar to our stewardship personnel, our infection preventionists perform chart review and discuss patients' symptoms in real time with the treating clinicians.

Data collection

The following information was collected from the electronic medical record: patient demographics, comorbidities, hospital diagnoses, laboratory results, and prescription medications. Comorbidities known to be associated with development of *C. difficile*, including diabetes, chronic kidney disease (CKD), obesity, inflammatory bowel disease, human immunodeficiency virus (HIV), cancer, and transplant, were determined by a review of each patient's past medical history and hospital diagnoses. The electronic medical record was also reviewed for the receipt of relevant prescriptions in the prior 30 days and during the ICU stay, including antibiotics, CDI-directed therapy, histamine 2 (H2) receptor antagonists, and PPIs. We analyzed the receipt of any antibiotic as well as several specific antibiotic categories (ie, cephalosporins, β-lactam–β-lactamase inhibitor combinations, carbapenems, fluoroquinolones, and clindamycin) based on those that are known to be associated with CDI.[12,13] ICU length of stay was calculated using our hospital's bed assignment data.

Statistical analysis

Baseline characteristics were evaluated using descriptive statistics. Discrete data were reported as frequencies and percentages. Continuous data were reported as medians and interquartile ranges. Significance testing was performed using χ^2 tests for categorical variables, and t tests were used for continuous variables. Logistic regression was used to model associations between CDI and demographics, comorbidities, ICU treatment characteristics, and medication exposures. A multivariable model was created using variables with $P < .10$ from significance testing. Odds ratios (ORs) and adjusted odds ratios (aORs) with accompanying 95% confidence intervals (95% CIs) are presented. All tests were done in Stata version 15.0 software (StataCorp, College Station, TX).

Results

In total, 18,883 patients were admitted to the ICU during the study period (Fig. 1). Among them, 14,033 patients were excluded from the study. Reasons for exclusion included ICU admission lasting <24 hours (n = 3,822), ICU admission starting >72 hours after

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Table 1. Baseline Characteristics of the Study Population

Variable	All Patients (n = 4,850), No. (%)[a]	Not *C. difficile* Colonized (n = 4,658, 96.0%), No. (%)[a]	*C. difficile* Colonized (n = 192, 4.0%), No. (%)[a]	*P* Value
Demographics				
Age, median y [IQR]	62 [49–72]	61 [49–72]	64.5 [51–76]	.06
Sex, male	2,581 (53.2)	2,495 (53.6)	86 (44.8)	.02
Race/Ethnicity				
Black non-Hispanic	2,751 (56.7)	2,629 (56.4)	122 (63.5)	.11
White non-Hispanic	1,493 (30.8)	1,441 (30.9)	52 (27.1)	
Hispanic	256 (5.3)	245 (5.3)	11 (5.7)	
Other/Unknown	350 (7.2)	343 (7.4)	7 (3.7)	
Comorbidities				
Diabetes	1,516 (31.3)	1,438 (30.9)	78 (40.6)	.004
Chronic kidney disease	1,224 (25.2)	1,158 (24.9)	66 (34.4)	.003
Cancer	922 (19.0)	888 (19.1)	34 (17.7)	.64
HIV	51 (1.1)	48 (1.0)	3 (1.6)	.48
Transplant	138 (2.9)	133 (2.9)	5 (2.6)	.84
IBD	65 (1.3)	62 (1.3)	3 (1.6)	.79
Cirrhosis	157 (3.2)	148 (3.2)	9 (4.7)	.25
Obesity	725 (15.0)	694 (14.9)	31 (16.2)	.64
Exposures				
Hospitalization in past 90 d	850 (17.5)	787 (16.9)	63 (32.8)	<.001
CDI treatment in past 30 d	11 (0.2)	6 (0.1)	5 (2.6)	<.001
Use of antibiotics in past 30 d				
Any antibiotic	1,019 (21.0)	960 (20.6)	59 (30.7)	.001
Cephalosporin	728 (15.0)	692 (14.9)	36 (18.8)	.14
β-lactamase inhibitor combination	156 (3.2)	150 (3.2)	6 (3.1)	.94
Carbapenem	14 (0.3)	14 (0.3)	0 (0.0)	.45
Fluoroquinolone	118 (2.4)	108 (2.3)	10 (5.2)	.01
Clindamycin	83 (1.7)	78 (1.7)	5 (2.6)	.33
Use of PPI or H2 blocker in past 30 d	618 (12.7)	586 (12.6)	32 (16.7)	.10

Note. IQR, interquartile range; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; CDI, *Clostridioides difficile* infection; PPI, proton pump inhibitor; H2, histamine 2.
[a]Units unless otherwise stated.

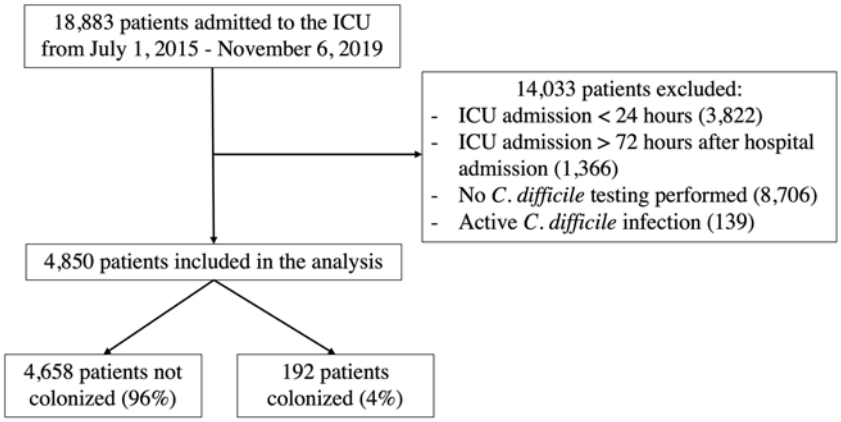

Fig. 1. Flow diagram of patients included in the analysis. We evaluated all patients who were admitted to the intensive care unit (ICU) from July 1, 2015, to November 6, 2019. Patients were excluded if their ICU admission was <24 hours, if they were admitted to the ICU >72 hours after hospital admission, if they did not have *C. difficile* testing performed, or if they had active *C. difficile* infection at the time of ICU admission.

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Table 2. Risk Factors for the Development of *C. difficile* Infection

Variable	All Patients (n = 4,850), No. (%)[a]	No CDI (n = 4,751, 98.0%), No. (%)[a]	CDI (n = 99, 2.0%), No. (%)[a]	*P* Value
Demographics				
Age, median y [IQR]	62 [49–71]	61 [49–71]	63 [42–74]	.68
Sex, male	2,581 (53.2)	2,527 (53.2)	54 (54.6)	.79
Race/Ethnicity				
Black non-Hispanic	2,751 (56.7)	2,699 (56.8)	52 (52.5)	.30
White non-Hispanic	1,493 (30.8)	1,464 (30.8)	29 (29.3)	
Hispanic	256 (5.3)	247 (5.2)	9 (9.1)	
Other/Unknown	350 (7.2)	341 (7.2)	9 (9.1)	
Comorbidities				
Diabetes	1,516 (31.3)	1,486 (31.3)	30 (30.3)	.84
Chronic kidney disease	1,224 (25.2)	1,198 (25.2)	26 (26.3)	.81
Cancer	922 (19.0)	910 (19.2)	12 (12.1)	.08
HIV	51 (1.1)	51 (1.1)	0 (0.0)	.30
Transplant	138 (2.9)	136 (2.9)	2 (2.0)	.62
IBD	65 (1.3)	61 (1.3)	4 (4.0)	.02
Cirrhosis	157 (3.2)	153 (3.2)	4 (4.0)	.65
Obesity	725 (15.0)	715 (15.1)	10 (10.1)	.17
C. difficile colonized	192 (4.0)	163 (3.4)	29 (29.3)	<.001
Features of ICU illness				
ICU length of stay, median d [IQR]	2.6 [1.6–4.9]	2.6 [1.6–4.9]	4.8 [2.4–13.6]	.0008
Use of antibiotics				
Any antibiotic	3,663 (75.5)	3,577 (75.3)	86 (86.9)	.008
Cephalosporin	3,106 (64.0)	3,027 (63.7)	79 (79.8)	.001
β-Lactamase inhibitor combination	409 (8.4)	401 (8.4)	8 (8.1)	.90
Carbapenem	108 (2.2)	105 (2.2)	3 (3.0)	.58
Fluoroquinolone	229 (4.7)	227 (4.8)	2 (2.0)	.20
Clindamycin	214 (4.4)	208 (4.4)	6 (6.1)	.42
Use of PPI or H2 blockers	2,990 (61.7)	2,920 (61.5)	70 (70.7)	.06
Mortality with 30 d of ICU admission	489 (10.1)	479 (10.1)	10 (10.1)	.96

Note. CDI, *Clostridioides difficile* infection; IQR, interquartile range; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; ICU, intensive care unit; PPI, proton pump inhibitor; H2, histamine 2.
[a]Units unless otherwise stated.

hospital admission (n = 1,366), *C. difficile* testing not performed at the time of ICU admission (n = 8,706), and active CDI at the time of ICU admission (n = 139). The remaining 4,850 patients were included in the final analysis, of whom 4,658 (96%) were not *C. difficile* colonized and 192 (4%) were *C. difficile* colonized. Overall, 90.3% of patients had testing performed on a rectal swab, 7.0% had testing performed on a stool sample, and 2.8% had testing performed on both a rectal swab and a stool sample.

Baseline characteristics of the study population stratified by *C. difficile* colonization status are shown in Table 1. Overall, the median age was 62 years and most patients (56.7%) were Black non-Hispanic. Also, 53.2% of patients in the study were male, but male patients were slightly less likely than female patients to be colonized with *C. difficile* on admission (44.8% vs 53.6%; $P = .02$). Patients with *C. difficile* colonization were more likely to have diabetes (40.6% vs 30.9%; $P = .004$) and chronic kidney disease (34.4% vs 24.9%; $P = .003$), but there were no significant differences with respect to other comorbidities. Patients who were colonized with *C. difficile* were more likely to have been hospitalized in the past 90 days (32.8% vs 16.9%; $P < .001$) and to have been treated for CDI in the past 30 days (2.6% vs 0.1%; $P < .001$). Receipt of an antibiotic in the past 30 days was also associated with *C. difficile* colonization (30.7% vs 20.6%; $P = .001$), although of all antibiotic classes investigated, only receipt of fluoroquinolones was significantly associated with colonization (5.2% vs 2.3%; $P = .01$). We did not detect any significant difference between groups with regard to use of PPIs or H2 receptor antagonists.

Table 2 shows risk factors for the development of CDI. Overall, 99 patients (2.0%) in the study developed CDI. When comparing CDI classification between our study and the infection control

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Table 3. Multivariable Regression Analysis for the Development of *C. difficile* Infection

	Bivariate Analysis		Multivariable Analysis	
Variable	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
C. difficile colonized	11.7 (7.4–18.5)	<.0001	13.3 (8.3–21.3)	<.0001
Cancer	0.6 (0.3–1.1)	.08	0.6 (0.3–1.2)	.14
IBD	3.2 (1.2–9.1)	.03	3.8 (1.3–11.1)	.02
ICU length of stay	1.04 (1.03–1.05)	<.0001	1.04 (1.03–1.05)	<.0001
Use of any antibiotic	2.2 (1.2–3.9)	.01	1.9 (1.0–3.4)	.05
Use of PPI or H2 blocker	1.5 (1.0–2.3)	.06	1.26 (0.8–2.0)	.34

Note. OR, odds ratio; CI, confidence interval; IBD, inflammatory bowel disease; ICU, intensive care unit; PPI, proton pump inhibitor; H2, histamine 2.

subset, we found an overall high level of agreement (36 of 38, 94.7%). We did not detect significant demographic differences between those who developed CDI and those who did not. Unlike with *C. difficile* colonization, there was no significant association between CDI and diabetes or chronic kidney disease. However, CDI was more common among patients with inflammatory bowel disease (4.0% vs 1.3%; $P = .02$). Patients who were colonized with *C. difficile* were significantly more likely to develop CDI (29.3% vs 3.4%; $P < .001$). The ICU length of stay was >2 days longer for patients who developed CDI compared to those who did not (2.6 days vs 4.8 days; $P = .0008$). The use of antibiotics was common in the study population overall; 75.5% of patients received at least 1 antibiotic during their ICU stay. Patients who developed CDI were more likely to have received an antibiotic while in the ICU (86.9% vs 75.3%; $P = .008$), particularly cephalosporin antibiotics (79.8% vs 63.7%; $P = .001$). We detected modestly increased use of PPIs or H2 receptor antagonists in the CDI group, although this did not reach statistical significance (70.7% vs 61.5%; $P = .06$). The median time to CDI onset was 8 days after ICU admission, and 43.4% of patients developed CDI while in the ICU. All patients in the study were treated with vancomycin. We did not detect a significant difference between groups with regard to mortality.

Table 3 summarizes the results of a multivariable regression analysis for the development of CDI. Of all the variables included in the model, *C. difficile* colonization was associated with the greatest increased odds of developing CDI (aOR, 13.3; 95% CI, 8.3–21.3; $P < .0001$). Other factors associated with an increased odds of developing CDI included a longer ICU length of stay (aOR, 1.04; 95% CI, 1.03–1.05; $P < .0001$) and a history of inflammatory bowel disease (aOR, 3.8; 95% CI, 1.3–11.1; $P = .02$). Receipt of any antibiotic during the ICU stay was associated with a borderline increased odds of CDI (aOR, 1.9; 95% CI, 1.0–3.4; $P = .05$). Other variables included in the model, including a history of cancer and the use of PPIs or H2 receptor antagonists, were not significantly associated with the development of CDI.

Discussion

In this retrospective observational cohort of adult patients admitted to the ICU, we found an overall *C. difficile* colonization rate of 4% and an overall CDI rate of 2%. The treatment of CDI among colonized patients was 15.1% versus 1.5% in noncolonized patients. In multivariable analysis, patients with a history of *C. difficile* colonization had a significantly higher odds of receiving treatment for CDI compared to patients who were not *C. difficile* colonized (aOR, 13.3; 95% CI, 8.3–21.3; $P < .0001$), even after adjustment for potential confounders. Thus, *C. difficile* colonization may be an important factor for ICU clinicians and antimicrobial stewardship personnel to consider when making therapeutic decisions for these patients.

Overall, the *C. difficile* colonization rate in our study, 4%, is similar to the overall colonization rate of 4.2% at our institution that has been previously reported.[11] Our colonization rate is also similar to rates reported in the literature for both hospitalized patients in general and ICU patients in particular. Prevalence rates for hospitalized patients range from 3% to 21% in various studies.[3] Similarly, rates in the ICU have been reported to range from 1.7% to 19%.[8–10] The risk factors for *C. difficile* colonization included female sex, a history of diabetes, and a history of chronic kidney disease. We also detected higher rates of *C. difficile* colonization among patients with recent hospitalization, recent CDI treatment, or recent use of antibiotics, similar to what has been reported in the literature.[3] Fluoroquinolones are known to be a strong risk factor for the development of CDI.[14] In our study, fluoroquinolones were the only antibiotic class associated with *C. difficile* colonization.

Overall, 2% of the patients in our study developed CDI within the 30-day follow-up period. In multivariable analysis, colonization with *C. difficile* was associated with the development of CDI and had a higher adjusted OR than any other variable in the model, including a history of cancer or inflammatory bowel disease, ICU length of stay, or the use of antibiotics, PPIs or H2 receptor antagonists. The use of antibiotics in the ICU bordered on significance in multivariable analysis. Receipt of antibiotics has been consistently demonstrated to be a risk factor for CDI in other studies.[12] In our study, antibiotic use was highly prevalent, with 75.5% of patients overall receiving at least one antibiotic during their ICU stay. We were not able to evaluate the intensity of exposure (number of doses or days) to antibiotics, PPIs or H2 receptor antagonists. This, in addition to the high rate of antibiotic prescribing, may have limited our ability to assess this effect.

Patients colonized with *C. difficile* are increasingly recognized as an important target for infection control programs, and the isolation of these patients results in a decreased incidence of hospital acquired CDI.[15] In hospitals where universal *C. difficile* screening is not feasible, ICU patients could be targeted as a higher risk population for screening and isolation, which may be more cost-effective.[16] *C. difficile* colonization in the ICU could have implications for antimicrobial stewardship programs as well.

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These programs have been highly effective in reducing the incidence of CDI and other multidrug-resistant infections among hospitalized patients.[17,18] However, stewardship programs face challenges in the ICU, where patients have a higher acuity of illness and clinicians may be hesitant to de-escalate antibiotic therapy.[19,20] Patients colonized with *C. difficile* could be targeted as a key group for stewardship efforts and could help ICU clinicians consider adverse effects when making decisions about the use of antibiotics.

Our study had several limitations. It was a retrospective study performed at a single institution, so the results may not be generalizable to other settings. In addition, our center routinely screens all admitted patients for *C. difficile* colonization, but universal screening may not be available at all centers without a significant increase in the use of microbiology laboratory resources. In addition, many patients were excluded from our study due to lack of screening on ICU admission, likely due to the phased rollout of our screening program. We elected to include patients admitted prior to the ICU screening rollout to maximize the number of patients included in the study. We used the receipt of oral vancomycin or fidaxomicin as a surrogate marker for the presence of CDI. However, some colonized patients who did not meet clinical criteria for CDI may have been erroneously treated by the clinical team and therefore incorrectly categorized as having CDI. In addition, as our hospital does not routinely perform cytotoxin assay testing, colonized patients who developed diarrhea for other, non-CDI reasons may have also been incorrectly categorized. We addressed this by comparing our classification to our infection control program's classification and overall found a high level of agreement. Although our infection control program does not review all CDI cases, based on the high level of agreement, the impact of any erroneous CDI classification to our results is likely small. We were only able to analyze medications that were prescribed by a provider within our healthcare system, so we may have missed external prescriptions that patients received. Finally, we limited the analysis to patients who were admitted to the ICU within 72 hours of hospital admission, so the results may not apply to patients who are transferred to the ICU later during their hospital stay.

In summary, our study shows that colonization with *C. difficile* upon admission to the ICU is strongly associated with the development of CDI independent of other risk factors. Future studies should assess the impact of colonization status on the development of CDI in a prospective manner.

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

References

1. Guh AY, Mu Y, Winston LG, *et al.* Trends in US burden of *Clostridioides difficile* infection and outcomes. *N Engl J Med* 2020;382:1320–1330.
2. Eyre DW, Cule ML, Wilson DJ, *et al.* Diverse sources of *C. difficile* infection identified on whole-genome sequencing. *N Engl J Med* 2013;369:1195–1205.
3. Crobach MJT, Vernon JJ, Loo VG, *et al.* Understanding *Clostridium difficile* colonization. *Clin Microbiol Rev* 2018;31:e00021–17.
4. Caroff DA, Yokoe DS, Klompas M. Evolving insights into the epidemiology and control of *Clostridium difficile* in hospitals. *Clin Infect Dis* 2017;65:1232–1238.
5. Prechter F, Katzer K, Bauer M, Stallmach A. Sleeping with the enemy: *Clostridium difficile* infection in the intensive care unit. *Crit Care* 2017;21:260.
6. Gao T, He B, Pan Y, *et al.* Association of *Clostridium difficile* infection in hospital mortality: a systematic review and meta-analysis. *Am J Infect Control* 2015;43:1316–1320.
7. Bobo LD, Dubberke ER, Kollef M. *Clostridium difficile* in the ICU: the struggle continues. *Chest* 2011;140:1643–1653.
8. Tschudin-Sutter S, Carroll KC, Tamma PD, *et al.* Impact of toxigenic *Clostridium difficile* colonization on the risk of subsequent *C. difficile* infection in intensive care unit patients. *Infect Control Hosp Epidemiol* 2015;36:1324–1329.
9. Zhang X, Wang X, Yang J, Liu X, Cai L, Zong Z. Colonization of toxigenic *Clostridium difficile* among ICU patients: a prospective study. *BMC Infect Dis* 2016;16:397.
10. Mi H, Bao R, Xiao Y, *et al.* Colonization of toxigenic *Clostridium difficile* among intensive care unit patients: a multicentre cross-sectional study. *Front Cell Infect Microbiol* 2020;10:12.
11. Collison M, Murillo C, Marrs R, *et al.* Universal screening for *Clostridioides difficile* at an urban academic medical center. *Infect Control Hosp Epidemiol* 2021;42:351–352.
12. Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of *Clostridium difficile* infection. *Clin Infect Dis* 2011;53:42–48.
13. Hebert C, Du H, Peterson LR, Robicsek A. Electronic health record-based detection of risk factors for *Clostridium difficile* infection relapse. *Infect Control Hosp Epidemiol* 2013;34:407–414.
14. McCusker ME, Harris AD, Perencevich E, Roghmann MC. Fluoroquinolone use and *Clostridium difficile*–associated diarrhea. *Emerg Infect Dis* 2003;9:730–733.
15. Longtin Y, Paquet-Bolduc B, Gilca R, *et al.* Effect of detecting and isolating *Clostridium difficile* carriers at hospital admission on the incidence of *C difficile* infections: a quasi-experimental controlled study. *JAMA Intern Med* 2016;176:796–804.
16. Meltzer E, Smollan G, Huppert A, *et al.* Universal screening for *Clostridioides difficile* in a tertiary hospital: risk factors for carriage and clinical disease. *Clin Microbiol Infect* 2019;25:1127–1132.
17. Feazel LM, Malhotra A, Perencevich EN, Kaboli P, Diekema DJ, Schweizer ML. Effect of antibiotic stewardship programmes on *Clostridium difficile* incidence: a systematic review and meta-analysis. *J Antimicrob Chemother* 2014;69:1748–1754.
18. Baur D, Gladstone BP, Burkert F, *et al.* Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and *Clostridium difficile* infection: a systematic review and meta-analysis. *Lancet Infect Dis* 2017;17:990–1001.
19. Pickens CI, Wunderink RG. Principles and practice of antibiotic stewardship in the ICU. *Chest* 2019;156:163–171.
20. Wunderink RG, Srinivasan A, Barie PS, *et al.* Antibiotic stewardship in the intensive care unit: an official American Thoracic Society workshop report in collaboration with the AACN, CHEST, CDC, and SCCM. *Ann Am Thorac Soc* 2020;17:531–540.

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