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ORIGINAL ARTICLE

Clostridium difficile in the Intensive Care Unit: Epidemiology, Costs, and Colonization Pressure

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OBJECTIVE. To evaluate the epidemiology, outcomes, and importance of *Clostridium difficile* colonization pressure (CCP) as a risk factor for *C. difficile*–associated disease (CDAD) acquisition in intensive care unit (ICU) patients.

DESIGN. Secondary analysis of data from a 30-month retrospective cohort study.

SETTING. A 19-bed medical ICU in a midwestern tertiary care referral center.

PATIENTS. Consecutive sample of adult patients with a length of stay of 24 hours or more between July 1, 1997, and December 31, 1999.

RESULTS. Seventy-six (4%) of 1,872 patients were identified with CDAD; 40 (53%) acquired CDAD in the ICU, for an incidence of 3.2 cases per 1,000 patient-days. Antimicrobial therapy, enteral feeding, mechanical ventilation, vancomycin-resistant enterococci (VRE) colonization or infection, and CCP (5.5 vs 2.0 CDAD case-days of exposure for patients with acquired CDAD vs no CDAD; $P = .001$) were associated with CDAD acquisition in the univariate analysis. Only VRE colonization or infection (45% of patients with acquired CDAD vs 16% of patients without CDAD; adjusted odds ratio, 2.76 [95% confidence interval, 1.36-5.59]) and a CCP of more than 30 case-days of exposure (20% with acquired CDAD vs 2% with no CDAD; adjusted odds ratio, 3.77 [95% confidence interval, 1.14-12.49]) remained statistically significant in the multivariable analysis. Lengths of stay (6.1 vs 3.0 days; $P < .001$ by univariate analysis) and ICU costs ($11,353 vs $6,028; $P < .001$ by univariate analysis) were higher for patients with any CDAD than for patients with no CDAD.

CONCLUSIONS. In this nonoutbreak setting, the CCP was an independent risk factor for acquisition of CDAD in the ICU at the upper range of exposure duration. Having CDAD in the ICU was a marker of excess healthcare use.

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Clostridium difficile–associated disease (CDAD) is a nosocomial diarrheal illness associated with significant morbidity, excess healthcare costs, and prolonged hospital stay.[1] In developed countries, CDAD severity and incidence have increased, with recent estimates of 0.9-8.4 cases per 1,000 admissions or discharges, corresponding to the spread of a recently characterized hypervirulent strain of *C. difficile*.[2-6] Despite the high concentration of at-risk patients in intensive care units (ICUs), relatively little is known about the impact of CDAD in these settings. Two ICU outbreaks of CDAD have been described,[7,8] and 3 other studies have reported incidences of CDAD in the ICU of 0.4-100 cases per 1,000 patient-days per 1,000 admissions.[2,9,10] One analysis of the National Nosocomial Infections Surveillance database identified associations between CDAD and length of ICU stay, medical device use, and admission during the winter; however, other exposure data were limited, and costs were not assessed.[2]

For nosocomial infection, determination of the relative roles of endogenous risk factors, which affect host susceptibility to infection, versus exogenous risk factors related to increased pathogen exposure may aid in the design of targeted prevention measures.[11] Endogenous CDAD risk factors, such as advanced age, underlying comorbidities, and receipt of antimicrobial agents[12-15] and gastric acid suppression therapy,[16] alter the natural resistance to CDAD provided by the gut's microbial flora; however, many of these factors are not readily modifiable. Conversely, exogenous CDAD risk factors are related to exposure to *C. difficile* spores in the hospital environment. Epidemiologic and molecular typing studies have confirmed prolonged hospitalization, physical proximity to a patient with CDAD, and medical device use to be ex-

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ogenous risk factors.[2,17-21] Colonization pressure is a useful epidemiologic marker of exogenous risks that quantifies susceptible patients' pathogen exposure in terms of the number of infectious contacts and the duration of exposure. Colonization pressure is an independent risk factor for acquisition of other nosocomial pathogens in ICUs[22-25]; however, its role in CDAD has not been determined. The objectives of this study were to describe the epidemiology of CDAD in severely ill patients, to evaluate *C. difficile* colonization pressure (CCP) as a risk factor for CDAD acquisition in a contained area, and to estimate the effect of CDAD on ICU outcomes.

METHODS

Study Design, Population, and Site

This study was a secondary analysis of a 30-month retrospective cohort study. All patients consecutively admitted to the Barnes-Jewish Hospital adult medical ICU with a length of stay of 24 hours or more between July 1, 1997, and December 31, 1999, were eligible for participation. Barnes-Jewish Hospital is a 1,287-bed midwestern tertiary care medical center with a 19-bed medical ICU that consists of 2 suites (with 10 and 9 private beds) separated by pass-through hallways and shared equipment rooms. For patients with multiple ICU admissions, only the first admission was counted if admissions were separated by 30 days or more. Multiple admissions within a 30-day period were aggregated. The study was approved by the Washington University Human Studies Committee and the Saint Louis University Institutional Review Board.

Study Definitions

CDAD was defined as detection of *C. difficile* toxin A or B in a clinical stool specimen, the collection of which was ordered by the treating ICU physician, by means of a cytotoxicity assay (Bartels). The daily CDAD point prevalence was calculated as the sum of patients with CDAD who were in the ICU during the 14-day period the disease was considered transmissible.

The CCP was calculated for each patient as the sum of the daily CDAD point prevalences for every day spent in the ICU while susceptible. For determination of the CCP, the following assumptions were made: (1) all patients with a positive result of a toxin test had CDAD, (2) patients with CDAD were infectious and contributed to the CCP for 14 days after the day the initial positive stool sample was collected, (3) patients with no CDAD were susceptible during their entire ICU stay, and (4) patients who had CDAD were susceptible again 14 days after the initial positive stool sample.

Patients with stool specimens collected during the period between 24 hours after ICU admission and 24 hours after ICU discharge that tested positive for toxins A or B were considered to have acquired CDAD. Patients with stool samples collected during the period between 14 days before and less than 24 hours after ICU admission that tested positive for toxins A or B were considered to have prevalent CDAD. Patients with subsequent positive stool samples collected more than 14 days after the initial positive result were defined as having a recurrent case of CDAD and were considered to be nonsusceptible until 14 days after collection of the subsequent positive stool sample.

Antimicrobial and Infection Control Practices

During the first 18 months of this study, preferred empirical gram-negative antimicrobial agents were cycled as described elsewhere.[25] For patients with CDAD, vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus,* or multidrug-resistant gram-negative colonization or infection, routine barrier precautions, which consisted of donning gowns and gloves before entering the rooms and removing gowns and gloves and performing hand hygiene after leaving the rooms, were in place during the first 12 months and last 6 months of the study.[23,25] During months 13-24, routine barrier precautions consisted of glove use only, without gowns, as previously reported.[23] All rooms were routinely cleaned by applying standard quaternary ammonium salt solution to hard surfaces. Cleaning was performed by 2 dedicated housekeepers during the first 10 months of the study and by 4 patient service representatives, who also performed patient-related duties, during the final 20 months of the study. Rooms occupied by patients with CDAD did not undergo enhanced cleaning.

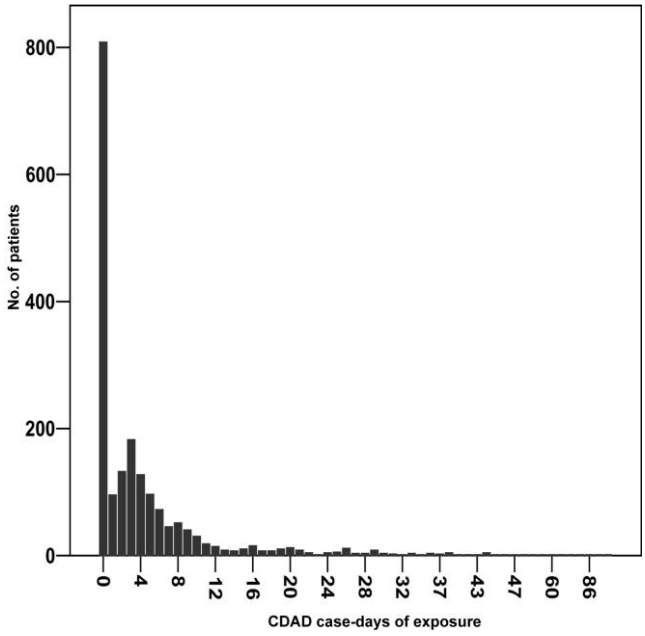

FIGURE 1. Frequency distribution of *Clostridium difficile* colonization pressure among patients hospitalized in the medical intensive care unit of a large midwestern tertiary care center, July 1997 through December 1999. CDAD, *C. difficile*–associated disease.

TABLE 1. Results of Univariate Analysis of Patient Characteristics to Determine Risk Factors for *Clostridium difficile*–Associated Disease (CDAD) Acquisition in the Medical Intensive Care Unit (ICU) of a Large Midwestern Tertiary Care Center

Characteristic	Patient group			
	Prevalent CDAD (n = 36)	Acquired CDAD (n = 40)	No CDAD (n = 1,796)	P[a]
Age, mean y (range)	68.9 (34-93)	58.7 (16-91)	59.3 (16-95)	.84
Female sex	18 (50)	17 (42)	943 (52)	.21
Nonwhite race	14 (39)	12 (30)	797 (44)	.07
APACHE II score, mean ± SD	22.7 ± 5.4	23.4 ± 6.1	21.1 ± 7.5	.06
Dedicated housekeeping	12 (33)	11 (28)	622 (35)	.35
Gowns used for contact precautions	19 (53)	26 (65)	1,123 (62)	.75
Duration of susceptibility, median ICU-days (range)[b]	0	9.0 (2-58)	4.0 (1-123)	<.001
Nosocomial exposure				
Antimicrobial therapy, type[b]				
Anti–gram positive	31 (86)	40 (100)	1,518 (84)	.007
Anti–gram negative	29 (81)	39 (98)	1,522 (85)	.02
Antianaerobic	25 (69)	32 (80)	935 (52)	<.001
Antifungal	9 (25)	17 (42)	327 (18)	<.001
Gastric acid suppression therapy[b]	25 (69)	38 (95)	1,525 (85)	.08
Mechanical ventilation	20 (56)	34 (85)	991 (55)	<.001
Enteral tube feeding	14 (39)	26 (65)	533 (30)	<.001
P. aeruginosa bacteremia[b]	0	4 (10)	31 (2)	.006
MRSA bacteremia[b]	8 (22)	5 (12)	169 (9)	.42
VRE colonization or infection[b]	12 (33)	18 (45)	281 (16)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. See Methods for definitions of prevalent CDAD and acquired CDAD. APACHE, Acute Physiology and Chronic Health Evaluation; MRSA, methicillin-resistant *Staphylococcus aureus; P. aeruginosa, Pseudomonas aeruginosa;* VRE, vancomycin-resistant enterococci.

[a] P values for comparison of acquired CDAD versus no CDAD were calculated by means of the χ^2 or Fisher exact test (for variables expressed as proportions), the Student t test (for variables expressed as means), or the Mann-Whitney U test (for variables expressed as medians).

[b] For patients with any CDAD, data were recorded before the first test positive for *C. difficile* toxin.

Data Collection

Clinical, laboratory, and cost data were obtained from hospital informatics and clinical databases and included demographic characteristics, nosocomial exposures, comorbid nosocomial pathogens, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and antimicrobial exposures, which were classified into previously described categories on the basis of their activity against gut flora.[26,27] As part of an ongoing VRE surveillance program, all stool specimens collected for *C. difficile* toxin detection were screened for VRE, and rectal swab specimens were obtained from all patients to screen for VRE on ICU admission and weekly until discharge.[23,25]

Outcomes

The CDAD incidence density was calculated as the number of acquired cases of CDAD during the study period per 1,000 ICU patient-days of susceptibility. Lengths of stay were defined as days elapsed from admission until discharge or until death if the patient died. Total hospital costs were obtained from the hospital's financial accounting system and converted to 2002 US dollars.[28] The ICU costs were estimated by dividing total hospital costs by the length of hospital stay and multiplying the dividend by the length of ICU stay.

Statistical Analysis

All patients in the cohort were used in the calculation of the daily point prevalence of CDAD, but prevalent CDAD cases were excluded for the risk factor analysis. For all univariate analyses, categorical variables were compared using the χ^2 test or the Fisher exact test, and continuous variables were compared by the Student t test or the Mann-Whitney U test if nonnormally distributed. Logistic regression models were used to evaluate risk factors for the dependent variables of CDAD acquisition and ICU mortality (ie, death from any cause while in the ICU). Age, sex, and exposure variables with a univariate P value of less than .10 for the association with CDAD acquisition or mortality were selected for the regression models. Because of the unusual frequency distribution of the CCP (Figure 1), multiple dichotomous variables were created (categories of 0 [reference], 1-3, 4-7, 8-14, 15-30, and more than 30 case-days of exposure) in the CDAD

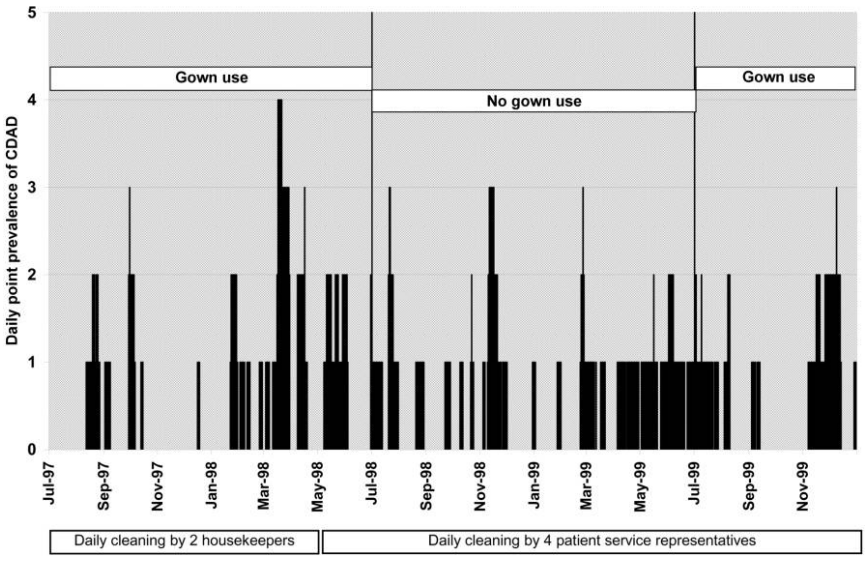

FIGURE 2. Daily point prevalence of *Clostridium difficile*–associated disease (CDAD) and infection control practices in the medical intensive care unit of a large midwestern tertiary care center, July 1997 through December 1999.

acquisition regression model. To further examine CCP as a risk factor for CDAD acquisition, successive regression models were created by varying the hypothetical cutoff values for CCP. Starting with the observed median used in the original model, the binary CCP was increased successively. Multiple linear regression was used to evaluate the association of CDAD with ICU costs and ICU lengths of stay, using log-transformed dependent variables and the same independent variable selection method used for the mortality logistic regression model. Regression diagnostic analyses were performed to identify outliers. A 2-tailed *P* value of less than .05 was considered to be statistically significant. All analyses were performed using SPSS statistical software, version 12.0 for Windows (SPSS).

RESULTS

Cohort Description

During the 30-month study period, 2,631 patients were treated in the ICU; 748 (28%) were excluded because their ICU stay was less than 24 hours, and 11 (0.4%) were excluded because data were missing, leaving 1,872 evaluable cohort patients. The mean age was 59.5 years, 978 (52%) were women, 1,813 (97%) were white or African American, and the mean APACHE II score was 21.1.

Epidemiology of CDAD

Seventy-six patients (4%) had confirmed CDAD, based on positive results of toxin tests during their ICU stay (Table 1). Thirty-six (47%) of these patients had prevalent CDAD on ICU entry, whereas 40 (53%) had acquired CDAD, for an incidence density of 3.2 cases per 1,000 patient-days. The median duration spent in the ICU before acquisition was 9.0 days (range, 2-58 days). The pattern of CDAD appearance was sporadic, reflecting intermittent introductions by patients with prevalent cases and onset of acquired cases. The highest CDAD daily point prevalence was 4 cases, which occurred on 5 consecutive days (Figure 2). On 517 days (57% of the study period), the CDAD point prevalence was 0 cases. Twenty (56%) of the 36 prevalent cases were introduced into the ICU on one of those days. Nine (22%) of the 40 acquired cases occurred within 14 days of one of these CDAD introductions. Twenty-three acquired cases (58%) occurred on a day when the CDAD point prevalence was 0 cases. Two patients developed recurrent episodes.

Risk Factor Analysis

Patients who acquired CDAD were demographically similar to those with no CDAD (Table 1). Antimicrobial use was widespread, with 1,653 cohort patients (88%) receiving at least 1 agent during their ICU stay. Receipt of antimicrobial agents from any class, number of susceptible days spent in the ICU, mechanical ventilation, enteral feeding, VRE colonization or infection, and *Pseudomonas aeruginosa* bacteremia were associated with CDAD acquisition in the univariate analysis. Gown use and housekeeping practices were similar for patients with acquired CDAD and those without CDAD. Other than the CCP, only VRE colonization or infection was associated with CDAD acquisition, after adjusting for confounders (adjusted odds ratio [aOR], 2.76 [95% confidence interval (CI), 1.36-5.59]).

CCP

The median CCP experienced by each patient in the cohort was 2.0 CDAD case-days of exposure (range, 0-109 case-days;

TABLE 2. Results of Univariate and Multivariate Analyses of *Clostridium difficile* Colonization Pressure (CCP) as a Risk Factor for *C. difficile*–Associated Disease (CDAD) Acquisition in the Medical Intensive Care Unit of a Large Midwestern Tertiary Care Center

Risk factor	Patient group: Acquired CDAD (n = 40)	Patient group: No CDAD (n = 1,796)	Adjusted OR (95% CI)	P[a]
Univariate analysis only				
CCP, median (range)	5.5 (0-103)	2.0 (0-109)	…	.001
Logistic regression model				
CCP >0	28 (70)	1,031 (57)	0.88 (0.42-1.85)	.11
CCP >2	27 (68)	808 (45)	1.27 (0.61-2.64)	.005
CCP >4	21 (52)	505 (28)	1.39 (0.69-2.80)	.001
CCP >9	15 (38)	207 (12)	1.81 (0.86-3.78)	<.001
CCP >10	15 (38)	177 (10)	2.17 (1.04-4.56)	< .001

NOTE. Data are no. (%) of patients, unless otherwise indicated. The CCP was calculated for each patient as the sum of the daily CDAD point prevalences for every day spent in the ICU while susceptible. Multiple dichotomous variables were created for the CCP because of its unusual frequency distribution. See Methods for additional assumptions made in determining the CCP. CI, confidence interval; OR, odds ratio.

[a] P values are for univariate analyses calculated by the Mann-Whitney U test (for median CCP) or the χ^2 test (for categorized CCP variables).

Figure 1). Notably, 808 patients (43%) experienced no CCP and had a shorter median ICU length of stay than patients who experienced any CCP (2.5 vs 4.0 days; $P < .001$). Five patients acquired CDAD less than 24 hours after ICU discharge. The remaining 71 patients with CDAD contributed 555 case-days of risk to the CCP (median, 6.0 case-days; range, 1-33 case-days). The median CCP for all 40 patients who acquired CDAD was 5.5 case-days of exposure (range, 0-103 case-days); however, 12 (30%) experienced no CCP while in the ICU. The remaining 28 patients experienced a median CCP of 13.0 case-days. In univariate analysis, the CCP was associated with acquiring CDAD (median CCP, 5.5 case-days for acquired CDAD vs 2.0 case-days for no CDAD; $P = .001$) (Table 2). In the logistic regression model that evaluated risk factors for CDAD acquisition, other than VRE colonization or infection, only the highest category of CCP (ie, more than 30 case-days of exposure) was significant (20% for acquired CDAD vs 2% for no CDAD; aOR, 3.77 [95% CI, 1.14-12.49]) (Figure 3). With sequential logistic regression modeling, a threshold CCP of 10 was necessary for CCP to become an independent risk factor for CDAD acquisition (aOR, 2.17 [95% CI, 1.04-4.56]) (Table 2). Acquisition of CDAD occurred in 15 (8%) of the 192 susceptible patients who experienced more than 10 case-days of CCP and in only 25 (2%) of 1,619 susceptible patients with a CCP of 10 case-days or less.

Impact of CDAD on Outcomes and Costs

Outcomes for patients with any CDAD, acquired CDAD only, and no CDAD are presented in Table 3. In total, 378 patients (20%) died in the ICU, and 308 (16%) required transfer to a long-term care facility. The median length of ICU stay was 3.0 days, and the median ICU costs were $6,137 for the 1,835 patients for whom cost data were available. Although mortality was not significantly different, lengths of hospital and ICU stay were approximately twice as long for patients with any CDAD, compared with patients without CDAD. Hospital and ICU costs were similarly higher for patients with any CDAD, compared with patients without CDAD. Having any CDAD was also associated with discharge to a long-term care facility. The increased costs and lengths of stay were even more pronounced for patients who acquired CDAD while in the ICU. In the logistic regression model, APACHE II score, nonwhite race, methicillin-resistant *S. aureus* bacteremia, VRE colonization or infection, enteral feeding, mechanical ventilation, and receipt of an antifungal agent were independently associated with ICU mortality, although CDAD was not. By multivariable linear regression modeling to adjust for confounding, having any CDAD was significantly associated

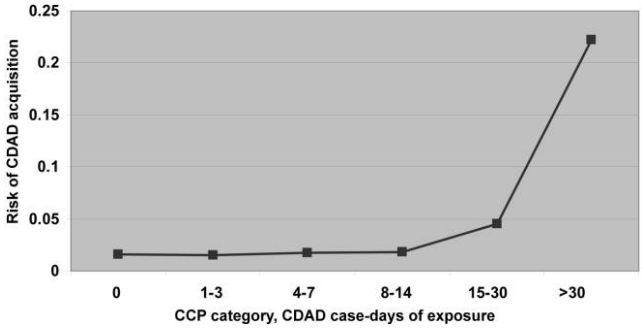

FIGURE 3. Risk of *Clostridium difficile*–associated disease (CDAD) acquisition in the medical intensive care unit of a large midwestern tertiary care center, according to *C. difficile* colonization pressure (CCP) category, July 1997 through December 1999.

TABLE 3. Outcomes and Costs for Patients in the Medical Intensive Care Unit (ICU) of a Large Midwestern Tertiary Care Center, Stratified by *Clostridium difficile*– Associated Disease (CDAD) Status

Variable	Patient group			P[a]
	Any CDAD (n = 76)	Acquired CDAD only (n = 40)	No CDAD (n = 1,796)	
Mortality				
During ICU stay	15 (20)	7 (18)	363 (20)	.92
During non-ICU hospital stay	27 (36)	13 (32)	495 (28)	.13
Discharge to long-term care facility	21 (28)	9 (22)	287 (16)	.007
Length of stay, median d (range)				
ICU	6.1 (1-86)	14.9 (1-86)	3.0 (1-106)	<.001
Hospital	24.5 (2-184)	38.3 (4-184)	10.1 (1-397)	<.001
Costs, median $US (range)[b]				
During ICU stay	11,353 (2,061-175,878)	25,092 (2,497-175,878)	6,028 (987-255,941)	<.001
During entire hospital stay	45,910 (5,936-271,024)	68,036 (7,991-271,024)	18,620 (1,668-334,523)	<.001

NOTE. Data are no. (%) of patients, unless otherwise indicated. See Methods for the definition of acquired CDAD.

[a] P values for univariate comparison between patients with any CDAD and patients with no CDAD were calculated by the χ^2 test (for variables expressed as proportions) or the Mann-Whitney U test (for variables expressed as median values).

[b] Cost data were available for 1,835 patients: 75 had any CDAD, 39 had acquired CDAD only, and 1,760 had no CDAD.

with a greater length of ICU stay (aOR, 1.24 [95% CI, 1.07-1.44]) and trended toward higher ICU costs (aOR, 1.18 [95% CI, 0.995-1.39]). In both of these models, the following variables were also associated with increased ICU costs and lengths of ICU stay: age; APACHE II score; receipt of antimicrobials with activity against gram-negative, anaerobic, or fungal organisms; concomitant nosocomial bacteremia; VRE colonization; enteral feeding; and mechanical ventilation.

DISCUSSION

The results of this large cohort study confirmed CDAD to be a sporadic ICU nosocomial infection in the absence of a recognized outbreak, with an observed incidence similar to that reported elsewhere for ICUs at large teaching hospitals.[2] As others have reported in ICU and non-ICU populations, we observed an association between CDAD and markedly increased lengths of stay[2] and a subsequent trend toward higher costs,[1] particularly for patients who acquired CDAD in the ICU. Many nosocomial infections have been reported to be markers of increased use of ICU resources,[29-31] and our findings suggest that CDAD is another important ICU infection.

Efforts to prevent CDAD in vulnerable ICU patients are now more imperative than ever, because a *C. difficile* strain with enhanced virulence has recently emerged in North America and Europe. This strain, characterized by the presence of a binary toxin, hyperproduction of toxins A and B, and universal resistance to fluoroquinolones, has caused multiple severe CDAD outbreaks with higher attributable mortality.[3-5] A number of molecular epidemiology studies have previously confirmed that exogenous transmission of *C. difficile* from other patients and contaminated hospital environments occurs but is not necessarily sufficient for the development of CDAD.[12,18,19,32-34] After exposure, endogenous risk factors that affect the normal colonic flora or the host immune response probably determine whether CDAD will develop or whether asymptomatic, and possibly protective, colonization occurs.[12,14,21,35] Prevention strategies usually consist of reducing exogenous risk with barrier infection control policies and bleach disinfection or of reducing endogenous risk through restrictions on the use of high-risk antimicrobials.[36-39]

Although our findings provide further evidence that CDAD transmission probably occurs indirectly between patients in close proximity,[19] they also suggest that endogenous risk factors may be the more important targets for prevention when the incidence of CDAD is sporadic. First, most acquired CDAD cases occurred when there was no detectable CDAD in the ICU. Second, most imported cases were not temporally associated with subsequent acquired cases. Third, unlike with VRE, the infection control policy of donning gowns with gloves in this same cohort was not associated with a reduced risk of CDAD acquisition, compared with a gloves-only policy.[23] Perhaps most importantly, overall exposure to *C. difficile* experienced by susceptible patients, as quantified by the CCP, was an independent risk factor for CDAD only when the duration of exposure exceeded 10 case-days. Indeed, nearly one third of patients with acquired CDAD experienced no CCP before CDAD onset.

Thus, in a setting of sporadic CDAD incidence, it seems prudent to focus on mitigation of modifiable endogenous risk factors by emphasizing judicious use of antimicrobial agents and gastric acid suppression agents. Although it is often not feasible to restrict use of these drugs in critically ill patients, when treatment with broad-spectrum antimicrobial agents is necessary, substituting cephalosporins and fluoroquinolones with potentially lower-risk drugs, such as piperacillin-tazobactam, may be preferable.[40,41] Our findings

suggest that use of gloves alone may be equivalent to concomitant use of gloves and gowns for preventing transmission; however, this hypothesis would need to be formally tested before changes in barrier infection control guidelines can be recommended. Furthermore, intensive environmental disinfection with sodium hypochlorite should be considered early in a suspected CDAD outbreak.[37,42] Prospective molecular epidemiology studies are needed to confirm the efficacy of such a prevention strategy.

To our knowledge, we describe the first large-scale study that investigated the epidemiology of CDAD in an ICU setting and the first study that evaluated colonization pressure as a risk factor for CDAD acquisition. Strengths of this study include a well-characterized cohort, availability of thorough outcomes data, and a multiyear duration to minimize the effect of minor spikes or decreases in CDAD incidence.

As with most observational investigations, our study has several limitations. First, our model for calculating the CCP was based on the assumptions that (1) the onset of diarrhea occurred rapidly after exposure to *C. difficile* in critically ill patients, (2) patients with CDAD shed epidemiologically significant amounts of *C. difficile* in their stools for 14 days after diagnosis, and (3) patients without laboratory-confirmed *C. difficile* toxin are not at risk to transmit *C. difficile*. Use of a different cutoff time for distinguishing prevalent from acquired CDAD (eg, 48 hours instead of 24 hours) would have had little impact on our estimates, because the number of acquired cases that occurred 24-48 hours after ICU admission was similar to the number that occurred 24-48 hours after discharge. Although it is known that asymptomatic inpatients are frequently colonized with *C. difficile*,[14,21] their importance as reservoirs is not clear. Second, the model was unable to account for the CCP experienced in the hospital before ICU admission. Third, it is possible that some of the patients with a positive result of a *C. difficile* toxin test did not have CDAD; however, this misclassification bias was likely to be infrequent, given the high specificity of the cytotoxicity assay and because stool toxin tests were not routinely ordered unless clinically compatible symptoms were present. Fourth, because this study was a secondary analysis, the primary data on specific drugs or drug classes were not available to more completely characterize antimicrobial exposure. In addition, direct ICU-specific cost data were unavailable and were likely underestimated by our method. Although we observed associations between CDAD and increased lengths of ICU stay and costs, we cannot conclude that these increases are attributable solely to CDAD. Indeed, our multivariable analyses suggest that many of the measured exposure variables were associated with these complex outcomes. Our hypothesis is that having CDAD in the ICU is one of many markers for increased use of healthcare resources. Finally, the reported data predated the emergence of the recently recognized hypervirulent strain, which may exhibit transmission dynamics that differ from those of the strains recovered from patients in our study.

CDAD is an important ICU infection and has considerable implications for resource use. Colonization pressure becomes an important exogenous risk factor for CDAD transmission only at high levels of exposure. In addition to use of traditional barrier infection control methods, mitigation of endogenous risk factors should be emphasized.

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