ORIGINAL ARTICLE

Evaluation of Hospital Room Assignment and Acquisition of *Clostridium difficile* Infection

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(See the commentary by Weber and Rutala, on pages 207–209.)

BACKGROUND AND OBJECTIVE. *Clostridium difficile* spores persist in hospital environments for an extended period. We evaluated whether admission to a room previously occupied by a patient with *C. difficile* infection (CDI) increased the risk of acquiring CDI.

DESIGN. Retrospective cohort study.

SETTING. Medical intensive care unit (ICU) at a tertiary care hospital.

METHODS. Patients admitted from January 1, 2005, through June 30, 2006, were evaluated for a diagnosis of CDI 48 hours after ICU admission and within 30 days after ICU discharge. Medical, ICU, and pharmacy records were reviewed for other CDI risk factors. Admitted patients who did develop CDI were compared with admitted patients who did not.

RESULTS. Among 1,844 patients admitted to the ICU, 134 CDI cases were identified. After exclusions, 1,770 admitted patients remained for analysis. Of the patients who acquired CDI after admission to the ICU, 4.6% had a prior occupant without CDI, whereas 11.0% had a prior occupant with CDI ($P = .002$). The effect of room on CDI acquisition remained a significant risk factor ($P = .008$) when Kaplan-Meier curves were used. The prior occupant's CDI status remained significant ($P = .01$; hazard ratio, 2.35) when controlling for the current patient's age, Acute Physiology and Chronic Health Evaluation III score, exposure to proton pump inhibitors, and antibiotic use.

CONCLUSIONS. A prior room occupant with CDI is a significant risk factor for CDI acquisition, independent of established CDI risk factors. These findings have implications for room placement and hospital design.

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Clostridium difficile infection (CDI) is a common cause of hospital-acquired diarrhea, ranging in severity from a mild diarrheal illness to pseudomembranous colitis, toxic megacolon, and death.[1] Asymptomatic colonization also occurs, with rates of 2%–3% among healthy individuals and 10%–25% among hospitalized patients.[1] CDI is an increasing cause of hospital morbidity and mortality, especially among elderly people, and in the last decade rates of CDI in the United States have at least tripled.[2] The financial burden of CDI is also increasing. Costs of hospitalization for patients with CDI are 54% higher than costs for patients whose hospital stay did not include the infection.[3] Annually, this cost has been estimated to exceed $1 billion, in part due to an extended length of stay.[3]

Multiple studies have confirmed that *C. difficile* can be cultured from the hospital environment and isolated for up to 5 months after inoculation.[2,4] *C. difficile* can be found on 49% of surfaces in rooms occupied by patients with CDI and on 29% of surfaces in rooms of asymptomatic carriers.[2]

Room assignment has been shown to be important in the acquisition of hospital-acquired infections, with a 40% increased risk of acquiring methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus infection when the previous room occupant was positive.[5] Specific to CDI, one study showed a 12% attributable risk of nosocomial CDI when patients were roommates, neighbors, or later occupants of a room occupied by a patient with CDI.[6] Another study, by Dubberke et al,[7] showed *C. difficile* colonization pressure to be a risk factor for acquiring CDI independent of demographic characteristics, severity of illness,

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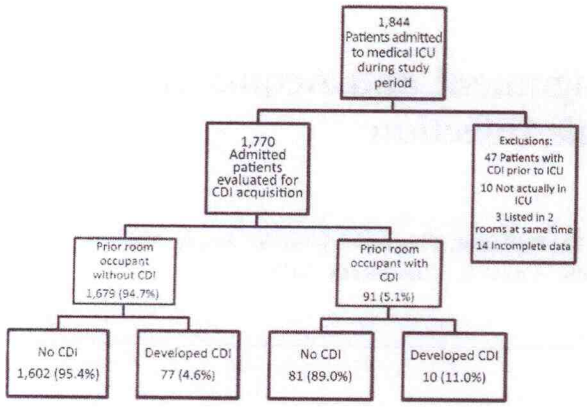

FIGURE 1. Acquisition of *Clostridium difficile* infection (CDI) after admission to a medical intensive care unit (ICU), January 1, 2005, through June 30, 2006. The difference in CDI acquisition between the group with a negative prior occupant and the group with a positive prior occupant was significant ($P = .002$).

medications received, and procedures or surgeries performed. Our study investigates whether the prior room occupant's CDI status is a risk factor for acquiring CDI.

METHODS

This retrospective cohort study took place at an 809-bed tertiary care hospital that has a 20-bed medical intensive care unit (ICU), more than 1,200 ICU admissions per year, and a mean ICU length of stay of 5.1 days. From January 1, 2005, through June 30, 2006, medical ICU patients were evaluated for a diagnosis of CDI 48 hours after admission to the ICU and within 30 days after transfer from the ICU. The medical ICU was chosen because of its high-risk population and the presence of single rooms. CDI cases were reviewed to ensure that patients had not been given a CDI diagnosis within the previous 3 months, to distinguish between patients with recurrent infection and primary infection. Patients who had been given a diagnosis of CDI before their ICU stay were included as potential sources of room exposure but were excluded from the analysis of CDI acquisition. Time at risk for acquiring CDI was considered to be the duration of the ICU stay and 30 days after transfer out of the ICU. To determine the CDI status of the prior room occupant, the patient in the room immediately before the current occupant was evaluated for positive *C. difficile* toxin results up to 30 days before the current occupant's ICU admission date.

ICU visits were identified using billing records and were verified by cross-referencing ICU and medical records. CDI cases were identified using infection control, medical, and microbiology records. CDI testing was done by enzyme-linked immunoabsorbent assay (ELISA) for toxins A and B (Premier Toxin A/B assay; Meridian Bioscience). Stool for CDI testing was sent on the basis of the clinical discretion of the ICU physicians. At the time of the study, body substance isolation was used for all patients with and without CDI. Routine cleaning practices were applied to all rooms, which included cleaning of frequently touched areas and bathrooms daily and terminal cleaning of the entire room with a low-level quaternary disinfectant.

ICU patients who did not acquire CDI during the study period served as control patients. ICU, pharmacy, and medical records were used to identify the presence of established CDI risk factors, including age, Acute Physiology and Chronic Health Evaluation (APACHE) III score, and proton pump inhibitor and antibiotic use. The patient's age and APACHE III score was determined at the time of ICU admission. Patients were evaluated for administration of proton pump inhibitors and antibiotics from the start of their hospitalization to the date on which they tested positive for CDI or were transferred out of the ICU. If CDI was diagnosed after discharge from the ICU, the end date of proton pump inhibitor and antibiotic exposure remained the day the patient transferred out of the ICU. Patients were given a categorical yes-or-no value for any receipt of a proton pump inhibitor. For analysis, antibiotics were grouped as follows: norfloxacin, levofloxacin, ciprofloxacin, the fluoroquinolones combined, clindamycin, third- and fourth-generation cephalosporins, carbapenems, piperacillin-tazobactam, other penicillins (including nafcillin and aminopenicillins), metronidazole, vancomycin, and aminoglycosides. Route of administration (intravenous vs oral) was defined only for vancomycin. These antibiotics were chosen because of their documentation in the literature as a significant risk factor for CDI and/or because of their high prevalence in our medical ICU. First- and second-generation cephalosporins were not evaluated because of infrequent use. Metronidazole and oral vancomycin were evaluated because of their potential for treatment or protec-

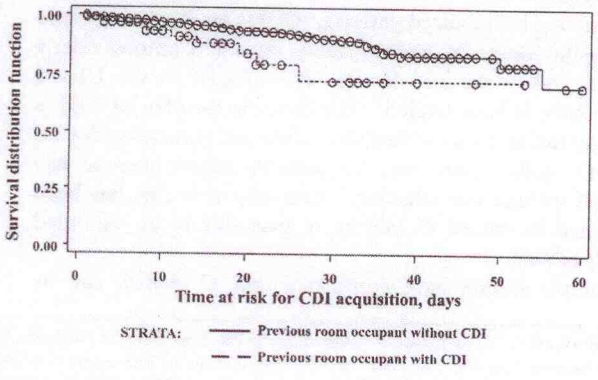

FIGURE 2. Kaplan-Meier curve of *Clostridium difficile* infection (CDI) development. The survival distribution function indicates the absence of the development of CDI. The group with a prior room occupant with CDI was more likely to develop CDI ($P = .008$).

TABLE 1. Characteristics of 1,770 Patients Admitted to a Medical Intensive Care Unit (ICU)

Characteristic	Patients with CDI (n = 87)	Patients without CDI (n = 1,682)	P for patient status	Patients with previous occupant with CDI (n = 91)	Patients with previous occupant without CDI (n = 1,677)	P for previous occupant status
Age, median (range), years	57 (19–90)	56 (15–96)	.73	60 (18–85)	56 (15–96)	.19
Male	57 (65.5)	854 (50.1)	.01	61 (67)	850 (50.7)	.002
APACHE III score, median (range)	74 (15–139)	64 (6–196)	.001	66 (18–158)	65 (6–196)	.33
ICU LOS, median (range), days	7 (1–72)	4 (1–121)	<.001	4 (1–53)	4 (1–121)	.12
Hospital LOS, median (range), days	27 (4–164)	11 (1–358)	<.001	13 (1–164)	11 (1–358)	.75
ICU mortality	11 (12.6)	297 (17.7)	.31	13 (14.3)	294 (17.5)	.48
Hospital mortality	22 (25.3)	395 (23.5)	.70	18 (19.8)	398 (23.7)	.45

NOTE. Data are no. (%) of patients, unless otherwise indicated. APACHE, Acute Physiology and Chronic Health Evaluation; CDI, *Clostridium difficile* infection; LOS, length of stay.

tive effects against CDI. Antibiotic use was recorded as a yes-or-no value for exposure and as quantity of antibiotics received. The quantity of antibiotics received for each group was determined by calculating the defined daily dose according to World Health Organization guidelines.[8]

Statistical analysis was performed using SAS for Windows software, version 9.1.3 (SAS Institute). Differences in patient characteristics were evaluated using the independent-samples t test and the Wilcoxon rank-sum test. The 2-tailed χ^2 test and the Fisher exact test were used to evaluate the significance of differences between CDI acquisition among patients with and those without a prior room occupant with CDI. The 2 groups were also evaluated using Kaplan-Meier curves to account for the time at risk for CDI acquisition. Finally, multivariate analysis was performed using Cox proportional hazards models to control for established CDI risk factors. Differences with a P value of less than .05 were considered significant.

The study was approved by the Institutional Review Board of the University of Michigan.

RESULTS

During the study period, 1,844 patients admitted to the medical ICU were recognized on the basis of hospital billing records. A total of 134 cases of CDI were identified. After exclusions, 1,770 patients were available for analysis, who were divided into 2 groups depending on the CDI status of the previous occupant. As seen in Figure 1, the difference in CDI acquisition between the group with a negative prior occupant and the group with a *C. difficile*–positive prior occupant (4.6% vs 11.0%) was significant (P = .002). To account for the time at risk for CDI acquisition, the 2 groups were evaluated further using Kaplan-Meier curves, with survival considered the absence of CDI development. Figure 2 shows that the group with a prior room occupant with CDI was more likely to develop CDI, with a P value of .008 by the log-rank test. The mean time from ICU admission to development of CDI was 12.5 days.

A comparison of patient characteristics is displayed in Table 1. The groups were similar with the exception of a larger proportion of male patients who developed CDI and had a previous room occupant with CDI. Table 2 shows the percentage of patients who received proton pump inhibitors or antibiotics. The most frequent antibiotics received were fluoroquinolones (particularly levofloxacin), piperacillin-tazobactam, and intravenous vancomycin.

Next we performed multivariate analysis using Cox proportional hazards models to control for established CDI risk factors, as seen in Table 3. The risk factor of room remained significant with a P value of .01 and a hazard ratio of 2.35, whereas greater age, higher APACHE III score, and proton pump inhibitor and antibiotic exposure did not reach significance. The one exception was the other penicillin group, which reached significance with a P value of .04 and a hazard ratio of 0.47, corresponding to a protective effect against CDI. Antibiotic use was further evaluated using defined daily doses

TABLE 2. Medication Use among 1,770 Patients in a Medical Intensive Care Unit

Medication(s) used	Percentage of patients
Proton pump inhibitor	87.8
Norfloxacin	2.2
Levofloxacin	53.7
Ciprofloxacin	4.1
Fluoroquinolones	55.7
Clindamycin	6.1
Third- or fourth-generation cephalosporins	32.4
Carbapenems	12.6
Piperacillin-tazobactam	46.7
Other penicillin	13.9
Metronidazole	22.8
Vancomycin	
Oral	0.9
Intravenous	56.0
Aminoglycosides	13.9
At least 1 antibiotic	83.6
3 or more antibiotics	46.7

TABLE 3. Multivariate Analysis of Risk Factors for Acquisition of *Clostridium difficile* Infection (CDI)

Risk factor	HR (95% CI)	*P*
Prior room occupant with CDI	2.35 (1.21–4.54)	.01
Greater age	1.00 (0.99–1.01)	.71
Higher APACHE III score	1.00 (1.00–1.01)	.06
Proton pump inhibitor use	1.11 (0.44–2.78)	.83
Antibiotic exposure		
Norfloxacin	0.38 (0.05–2.72)	.33
Levofloxacin	1.08 (0.67–1.73)	.75
Ciprofloxacin	0.49 (0.15–1.67)	.23
Fluoroquinolones	1.17 (0.72–1.91)	.53
Clindamycin	0.45 (0.14–1.42)	.17
Third- or fourth-generation cephalosporins	1.17 (0.76–1.79)	.48
Carbapenems	1.05 (0.63–1.75)	.84
Piperacillin-tazobactam	1.31 (0.82–2.10)	.27
Other penicillin	0.47 (0.23–0.98)	.04
Metronidazole	1.31 (0.83–2.07)	.24
Vancomycin		
Oral	1.38 (0.32–5.89)	.67
Intravenous	1.55 (0.88–2.73)	.13
Aminoglycosides	1.27 (0.78–2.06)	.35
Multiple (≥3 antibiotic classes)	1.28 (0.75–2.21)	.37

NOTE. APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; HR, hazard ratio.

to determine the quantity of antibiotics received, as shown in Table 4. Again, the amount of antibiotic received was not significant, with the exception of the other penicillin group.

DISCUSSION

CDI has received increased attention in the last 10 years as outbreaks of CDI associated with a hypervirulent strain and more severe disease have occurred in many locations, including Maine,[9] Pittsburgh,[10] and Quebec.[11,12] The BI/NAP1 strain has binary toxin genes and a partial deletion in the *tcdC* gene, resulting in an estimated 16–23-fold increase in toxin A and B production, as well as fluoroquinolone resistance and increased sporulation capacity.[11] A predominant risk factor in these outbreaks was increasing fluoroquinolone use.[9-12]

The most important risk factor for CDI is antibiotic use because of the disruption of the normal colon flora that allows *C. difficile* to overgrow. Antibiotics of particular concern include β-lactams, clindamycin, and fluoroquinolones, although almost all classes have been implicated in disease.[9-15] Prolonged use as well as use of multiple antibiotics conveys increased risk, although infection can occur after a single preoperative dose of antibiotics.[14] Additional medications that have been implicated in increased CDI risk include antimotility agents, chemotherapies, laxatives, proton pump inhibitors, and H2 blockers.[9,13,16,17] Other reported risk factors for CDI are greater age, greater severity of illness, greater length of stay, certain comorbidities (including congestive heart failure, cerebrovascular accidents, renal disease, hepatic disease, chronic obstructive pulmonary disease, leukemia, and lymphoma), low albumin level, mechanical ventilation, gastrointestinal procedures, and tube feeding.[9,11-13,18]

In our study, CDI was a frequent complication among patients admitted to the medical ICU, with an infection rate of 49 cases per 1,000 patients discharged. Our study further confirmed the important role the hospital environment plays in transmission of infections such as CDI because placement in a room of a prior occupant with CDI was a significant risk factor for CDI acquisition independent of other risk factors, including age, severity of illness, and proton pump inhibitor and antibiotic use. The Kaplan-Meier curve suggested that the time of greatest risk of developing CDI when exposed by the prior room occupant may be within the first 30 days, although this would be clarified with a longer period of post-ICU follow-up. Not surprisingly, patients in our study who acquired CDI had longer ICU and total hospital lengths of stay. Men had higher CDI rates, but they also had higher APACHE III scores. Although higher APACHE III scores did not reach significance as a risk factor for CDI ($P = .06$), there was a trend toward higher APACHE III scores among these patients, potentially accounting for the higher rate of infected men.

This study has important implications for determination of room placement. Many hospitals currently contain rooms meant for multiple occupants who shared a bathroom. Our findings further support recommendations for the future of hospital design, as it is recommended in the American Institute of Architects' *Guidelines for Design and Construction of Healthcare Facilities*[19] from 2006 that the maximum number of beds per hospital room be limited to one unless other functional reasons are present that necessitate more occupants.

Many prior studies have shown antibiotic and proton pump inhibitor exposure to be a risk factor for CDI acquisition. In our study, antibiotic use among patients who did develop CDI was not statistically significantly different than that among patients who did not. This is likely because the majority of patients in the medical ICU during the study period received antibiotics. The only antibiotic class that showed significance was the other penicillin group. Only a small percentage of patients in the ICU actually received antibiotics from this group, with an even smaller fraction receiving large amounts, making the result of unclear significance. Given the number of variables evaluated, it is possible that the result is due to chance alone. No association between proton pump inhibitor use and CDI was observed in our study, also likely due to their prevalence in the study population.

Limitations of this study include lack of evaluation for antibiotic exposure before hospitalization (either at home, at

outside hospitals before the transfer, or in the emergency department before admission), given that it has been noted that CDI can occur up to 8 weeks after antibiotic exposure.[1] We stopped evaluating for antibiotic exposure after patients were transferred out of the ICU, and it is feasible that a patient did not receive antibiotics until after he or she left the ICU but still obtained the *C. difficile* spores during the ICU stay, the combination of which led to the development of CDI within 30 days of transfer out of the ICU. Because *C. difficile* spores can remain in the environment for up to 5 months, another limitation is evaluating the prior room occupant for a CDI diagnosis for only 30 days before the current patient's ICU admission date.

Other potential risk factors were not addressed in our study. Given the preference for proton pump inhibitor use in our ICU, we did not consider H_2 blocker use. We did not evaluate tube feeding as a risk factor for CDI because of the inability to determine it accurately from our records. Although we did not officially control for gastrointestinal procedures during the ICU stay, the 20 patients who did undergo such a procedure (comprising 10 patients with CDI who occupied a room initially and the 10 patients who developed CDI after them) were evaluated individually. Only 1 of these patients, who underwent upper and lower endoscopy, went on to develop CDI, which was determined to be too minor to be of significance. We also did not evaluate individual medical conditions and instead used the APACHE III score to indicate the patient's degree of illness.

The use of defined daily doses in determining the amount of antibiotics received has limitations because it may underestimate antibiotic exposure for patients with renal failure, particularly those receiving renal replacement therapy. It also may be inaccurate if the administered dose differed from the defined daily dose. A future direction to correct this problem is evaluation using the number of days of therapy, although this approach has been shown to have limitations as well.[20]

A toxin ELISA was used to diagnose CDI, which was the standard method at our institution during the study period. These assays do have limitations, with studies showing decreased sensitivity compared with other methods, such as cell cytotoxicity assays and culture.[1] Typing of *C. difficile* strains was not done at the time of our study; therefore, it is unknown whether the BI/NAP1 strain was present. Lack of culture data and typing also prevents evaluating whether the ICU patient who developed CDI after occupying the room of a CDI patient carried the same *C. difficile* strain. Patients were not screened for the possibility of being an asymptomatic *C. difficile* carrier capable of contaminating the environment. This may be most relevant for a patient with a long hospital stay before their ICU admission because they would be more likely to be a carrier. Evaluating ICU staff as a source of *C. difficile* transmission and infection was beyond the scope of this study, but the staff in the medical ICU rotate among patients with sufficient variety to potentially negate any effect.

TABLE 4. Multivariate Analysis of Quantity of Antibiotic Exposure Using Defined Daily Doses (DDDs) as a Risk Factor in Acquisition of *Clostridium difficile* Infection

Antibiotic use (DDDs)	HR (95% CI)	*P*
Norfloxacin	0.96 (0.79–1.17)	.69
Levofloxacin	0.99 (0.96–1.02)	.47
Ciprofloxacin	0.93 (0.78–1.11)	.44
Fluoroquinolones	0.99 (0.96–1.02)	.35
Clindamycin	0.78 (0.52–1.17)	.23
Third- or fourth-generation cephalosporin	0.99 (0.96–1.03)	.58
Carbapenems	0.99 (0.94–1.06)	.84
Piperacillin-tazobactam	1.02 (0.98–1.05)	.38
Other penicillin	0.84 (0.71–0.98)	.03
Metronidazole	0.98 (0.93–1.03)	.42
Vancomycin		
Oral	0.72 (0.23–2.27)	.57
Intravenous	1.00 (0.96–1.04)	.96
Aminoglycosides	0.98 (0.94–1.03)	.50

NOTE. CI, confidence interval; HR, hazard ratio.

Although during the study period all patients were treated equally from an isolation and room cleaning standpoint, our study potentially raises questions regarding the importance of diligent isolation practices and proper environmental cleaning. Disinfection with a 1 : 10 dilution of bleach has been effective in reducing the frequency of environmental contamination with *C. difficile*.[1] This, combined with hand washing with soap and water, contact precautions, and isolation of patients, can limit the spread of CDI.[10] In an effort to decrease CDI transmission, starting in April 2007 the policies at the study institution changed to include cleaning every patient room with bleach after discharge regardless of the patient's CDI status. Contact precautions were also initiated for all patients with CDI. Future directions of our investigations include reevaluating the effect of a prior room occupant's CDI status with the new cleaning and isolation methods in place. The effect of other room decontamination options could also be explored, such as the use of hydrogen peroxide vapor, which has been shown to reduce the incidence of nosocomial CDI.[21] Other future directions include evaluating whether asymptomatic colonized patients contribute to increased risk to the next room occupant and determining the relationship between the duration of spores in the environment and the likelihood that they could cause disease.

In conclusion, the CDI status of a prior room occupant in this study was a statistically significant risk factor for acquisition of CDI in the medical ICU, independent of such known CDI risk factors as greater age, greater severity of illness, and proton pump inhibitor and antibiotic use. This finding further highlights the importance of the hospital environment in transmission of serious infections and the need for improved hospital design that incorporates single-patient rooms and bathrooms.

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