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Environmental transmission of *Clostridium difficile*: association between hospital room square footage and *C. difficile* infection

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Abstract

Background—The hospital environment is important in the transmission of *Clostridium difficile*, with *C. difficile* frequently contaminating environmental surfaces. Our objective was to evaluate the association between hospital room square footage and acquisition of nosocomial *C. difficile* infection (CDI).

Methods—A case-control study was conducted at a university hospital during the calendar year of 2011. Case patients were adult inpatients with nosocomial CDI. Control patients were hospitalized patients without CDI, and were randomly selected and matched to cases in a 2:1 ratio based on hospital length of stay in 3-day strata. A multivariate model was developed using conditional logistic regression to evaluate risk factors for nosocomial CDI.

Results—A total of 75 case patients and 150 control patients were included. On multivariate analyses, greater square footage of the hospital room was associated with a significantly increased risk of acquiring CDI (odds ratio [OR] for every 50 ft^2, 3.00; 95% confidence interval [CI], 1.75-5.16; $P<0.001$). Other factors associated with an increased risk of CDI were location in a single room (OR, 3.43; 95% CI, 1.31-9.05; $P=0.01$), malignancy (OR, 4.56; 95% CI, 1.82-11.4; $P=0.001$), and receipt of cefepime (OR, 2.48; 95% CI, 1.06-5.82; $P=0.04$) or immunosuppressants (OR, 6.90; CI, 2.07-23.0; $P=0.002$) within the previous 30 days.

Potential conflicts of interest. None to report.

Conclusions—Greater room square footage increased the risk of acquisition of CDI in the hospital setting, likely due to increased environmental contamination and/or difficulty in effective disinfection. Future studies are needed to determine feasible and effective cleaning protocols based on patient and room characteristics.

Keywords

Clostridium difficile; risk factors; rooms, patients; infection control

INTRODUCTION

Clostridium difficile has rapidly emerged as the leading cause of healthcare-associated infectious diarrhea [1, 2]. Infections due to *C. difficile* are associated with significant morbidity and mortality, with clinical presentation ranging from diarrhea to pseudomembranous colitis, toxic megacolon, and sepsis [3]. Established risk factors for *C. difficile* infection (CDI) include advanced age [4, 5], prolonged hospital stay [6], immunosuppression [7, 8], and exposure to various classes of antibiotics [9, 10].

Multiple studies have demonstrated that *C. difficile* is capable of frequently contaminating the hospital environment, including patient skin sites, hands of healthcare workers, and hospital room surfaces [11-15] such that transmission can occur directly via healthcare worker-patient contact or indirectly from contaminated surfaces [16, 17]. In addition, *C. difficile* is capable of forming endospores that are resistant to many sterilization and disinfection measures including heat, 70% ethanol (i.e., the main component in hand sanitizers), and quaternary ammonium compounds, thus facilitating its persistence on environmental surfaces [15, 18]. Along these lines, studies have shown that room assignment is important in the acquisition of *C. difficile*, with patients placed in a room with a previous occupant with CDI having a significantly increased risk of CDI [19, 20].

While previous studies support an important role for the hospital environment in the acquisition of nosocomial CDI, there have been no studies to date assessing the association between hospital room size and risk of CDI. The objective of our study was to evaluate the association between *C. difficile* infection and hospital room square footage, with the hypothesis that a greater square footage would be associated with an increased risk of acquiring *C. difficile*.

METHODS

Study design

A case-control study was performed at the Hospital of the University of Pennsylvania (HUP), a 775-bed tertiary care academic medical center. Case patients were defined as those with a first episode of nosocomial *C. difficile* (i.e., positive test result for *C. difficile* >72 hours after admission) from January 1, 2011 to December 31, 2011. A CDI case was confirmed as an initial episode according to standard surveillance definitions in a patient with no prior episode in the preceding 8 weeks [21] and was determined to represent an infection as opposed to colonization by case review by an infection preventionist. Testing

for *C. difficile* was performed at the HUP Clinical Microbiology Laboratory, and involved glutamate dehydrogenase antigen EIA screening followed by toxin A/B EIA testing to confirm positive results.

Study population

The source population for control patients was comprised of patients who were hospitalized at HUP in the same calendar year who did not have any positive CDI test results. Control patients were randomly selected and matched to case patients in a 2:1 ratio based on "time at risk" in 3-day strata. The "time at risk" for case patients was defined as the date of admission to the date of the first positive *C. difficile* test. For control patients, "time at risk" was defined as the date of admission to the date of hospital discharge. The primary exposure of interest was the square footage of the room (length × width) that the patient had occupied at the time of CDI diagnosis.

Patients known to be *C. difficile* positive from prior admissions (e.g., relapsing or recurrent disease) and those who were in the intensive care unit were excluded. Patients were also excluded if they had transferred room locations prior to the positive test for cases, or prior to discharge for controls. If a patient had more than one positive test for *C. difficile* during the study period, only the first episode was included. The study was approved by the institutional review board (IRB) of the University of Pennsylvania.

Data Collection

All cases of *C. difficile* during calendar year 2011 were ascertained from the University of Pennsylvania Health System (UPHS) Department of Healthcare Epidemiology and Infection Control. Data on case and control patients were abstracted from Penn Data Store, a comprehensive electronic database which includes demographic, laboratory, billing, and pharmacy information. Information was collected on demographics (e.g., age, weight), room locations within the hospital from admission to discharge, comorbidities (e.g., diabetes, malignancy), service of admission (e.g., general medicine, oncology), prior admission to UPHS in the previous 90 days, and hospital length of stay. Data was also collected on the square footage of the hospital rooms for case and control patients.

Data on medications received in the 30 days prior to the positive test date or discharge for case and control patients, respectively, were collected. Medication data included the use of antibiotics, proton-pump inhibitors, corticosteroids, and immunosuppressants (i.e. azathioprine, cyclosporine, mycophenolate, sirolimus, tacrolimus). Antibiotics were classified for the purposes of analysis, as follows: aminoglycosides; macrolides; fluoroquinolones; extended-spectrum cephalosporins (i.e. ceftriaxone, ceftazidime, cefpodoxime); first-generation cephalosporins (i.e. cefadroxil, cefazolin, cephalexin); penicillins (i.e. ampicillin, amoxicillin, amoxicillin-clavulanate, nafcillin); carbapenems; piperacillin-tazobactam; cefepime; metronidazole; intravenous vancomycin; clindamycin; trimethoprim-sulfamethoxazole; and anti-anaerobic agents.

Statistical Analysis

Case and control patients were characterized by potential risk factors, including demographics, square footage of the patient's hospital room, comorbidities, and prior medication use. Descriptive statistics were conducted to characterize the overall study population. Since data were matched, conditional bivariate logistic regression was used examine the relationship between each potential risk factor and infection with *C. difficile*. To examine the relationship between square footage while adjusting for other possible risk factors, multivariate conditional logistic regression was performed. To limit the number of variables tested in a single model, on initial pass, variables from bivariate analyses with *P* values <0.10 were evaluated and considered for inclusion in the final multivariate model. Backward stepwise selection was performed for selection of variables in the final explanatory model, with results confirmed using likelihood ratio testing. Data are presented as odds ratios (OR) with 95% confidence intervals (CI). All analyses were were performed using STATA v.12 (StataCorp, College Station, Texas).

RESULTS

Study population

A total of 468 cases of *C. difficile* occurred during the study period. Of these cases, 103 (22%) were confirmed to be hospital-acquired infections. After application of inclusion and exclusion criteria, there were a total of 75 case patients included in this study, each of which were randomly matched to controls in 2:1 ratio (n=150) based on "time at risk." Among case patients, the median length of stay prior to positive *C difficile* testing was 9 days (interquartile range [IQR], 7-15 days).

Among the entire study cohort, the median age of patients was 60 years (IQR, 50-70 years), and 117 (52%) were men. Of these 225 patients, 139 (62%) were categorized as "white" in regard to racial classification. Notably, there was a high prevalence of overweight/obesity (body mass index [BMI] ≥25) (65%) and malignancy (47%) present in the study cohort. None of the patients in the study cohort were located in a room where the immediately preceding occupant had CDI.

Risk factors for nosocomial CDI

On bivariate analyses (Table 1), there was a significant association between risk of *C. difficile* and non-white race (OR, 0.37; 95% CI, 0.20-0.72; *P*=0.003), as well as overweight or obesity (OR, 2.74; 95% CI, 1.39-5.40; *P*=0.004). Bivariate analysis also demonstrated a significant association between CDI and location in a single room (OR, 3.74; 95% CI, 1.76-7.96; *P*=0.001), hospital room square footage (OR, 2.03; 95% CI, 1.40-2.94; *P*<0.001), prior admission to the hospital within the past 90 days (OR, 2.59; 95% CI, 1.04-6.50; *P*=0.04), and malignancy (OR, 2.92; 95% CI, 1.56-5.47; *P*=0.001).

Regarding medication use, there was a significantly increased risk of CDI with prior receipt of clindamycin (OR, 3.50; 95% CI, 1.02-12.0; *P*=0.046), cefepime (OR, 1.94; 95% CI, 1.05-3.59; *P*=0.03), corticosteroids (OR, 2.14; 95% CI, 1.20-3.80; *P*=0.009), and immunosuppressants (OR, 5.70; 95% CI, 2.07-15.7; *P*=0.001).

On subsequent multivariate analyses (Table 2), hospital room square footage was an independent risk factor for acquisition of nosocomial *C. difficile* (OR for every 50 ft^2, 3.00; 95% CI, 1.75-5.16; *P*<0.001). Single room assignment (OR, 3.43; 95% CI, 1.31-9.05; *P*=0.01), malignancy (OR, 4.56; CI, 1.82-11.4; *P*=0.001), and previous receipt of cefepime (OR, 2.48; 95% CI, 1.06-5.82; *P*=0.04) and immunosuppressants (OR, 6.90; 95% CI, 2.07-23.0; *P*=0.002) were also significantly associated with an increased risk for acquiring nosocomial *C. difficile*.

DISCUSSION

In this case-control study, we found that that greater hospital room square footage was a significant risk factor for acquisition of nosocomial *C. difficile* after adjustment for other known risk factors. CDI was also significantly associated with single room assignment, presence of malignancy, and recent receipt of cefepime.

Previous epidemiologic studies have demonstrated that the hospital environment, including room assignment, is critical in the acquisition of nosocomial CDI.[11, 19, 20] However, to our knowledge, this is the first study to demonstrate an association between hospital room square footage and CDI. Environmental contamination plays an important role in the transmission of *C. difficile* in the hospital setting, with greater intensity of contamination increasing transmission risk [22, 23]. It is likely that a larger hospital room allows for more contamination of surfaces with *C. difficile* spores and subsequent increased risk of acquisition. In addition, a hospital room with greater square footage is more likely to contain a greater number of objects (e.g., medical equipment) that may become contaminated and thereby increase risk of transmission to subsequent room occupants. Finally, it is likely that a larger room increases the potential for inadequate room cleaning, particularly given the high demand for bed turnover in many hospitals.

Given that up to 50% of hospital surfaces are not cleaned appropriately by hospital environmental services staff during terminal cleaning [24, 25], this finding has important implications for the hospital setting. It is clear that interventions to improve room cleaning, including all surfaces in addition to high-risk objects, are needed. Newer modalities (e.g., hydrogen peroxide vapor or mist, UV-C light) [26, 27] show significant promise in reducing surface contamination with *C. difficile* in hospital rooms. In addition, organizational factors, including education of environmental services staff, bed management, and allocation of time and resources for cleaning dependent on different factors (e.g., prior occupant colonized or infected with a multidrug-resistant organism, room size), should be the focus of future studies.

The results of our study also demonstrated a significant association between malignancy and CDI. Patients with malignancies are at an increased risk for acquiring CDI for a number of reasons, including prolonged hospitalization, use of broad-spectrum antibiotics, bone marrow and peripheral blood stem cell transplantation, and neutropenia [28]. The incidence of CDI in cancer patients receiving chemotherapy has been reported to be as high as 7%, compared to 1–2% in the general hospitalized population [28]. Patients with malignancy, as in our study, frequently receive chemotherapeutic agents, which likely increases the risk of

CDI given alterations in bowel flora and depression of the immune system [29]. Along these lines, patients who received immunosuppressants in the past 30 days in our study were also found to have a significantly increased risk for acquiring *C. difficile*, including those who were recent recipients of solid organ transplants [30].

We also found a significant association between CDI and location in a single room. Single rooms are often reserved for patients on contact precautions due to colonization or infection with multidrug-resistant organisms. Therefore, location in a single room may be a proxy for patients who are at greater risk for hospital-acquired infections such as CDI. In addition, while there was no significant difference in median square footage of single versus double rooms in our study (P=0.75), patients with malignancy were more likely to be located in single rooms (P<0.001). Finally, single rooms are often in the highest demand for new hospital admissions, and the requirement to turn over these rooms on a timely basis may increase the potential for inadequate cleaning.

In the final multivariable model, cefepime use in the prior 30 days was also shown to increase the risk for acquiring nosocomial *C. difficile*. While a wide variety of antibiotic agents and classes have been associated with CDI [9, 10], given its broad-spectrum activity, cefepime may be particularly likely to disrupt the endogenous gastrointestinal flora, thereby increasing the risk of colonization and infection with *C. difficile*.

There are potential limitations of our study. Misclassification bias is a concern in case-control studies. However, the outcome of nosocomial CDI was validated through chart review by infection preventionists rather than relying on diagnostic or billing codes. While there were no health system changes in regard to room cleaning or isolation precaution protocols during the study period, we did not have data on adequacy of room cleaning or adherence to contact precautions that may have affected surface contamination with *C. difficile*. Given the retrospective nature of the study, we also did not have data on the number of objects (e.g., medical equipment) present in the hospital room. Finally the present study was conducted in a single healthcare system, and these results may not be generalizable to other institutions.

In conclusion, the results of our study demonstrate that greater hospital room square footage is a significant risk factor for nosocomial CDI. This finding highlights the importance of the hospital environment in the transmission of CDI, and the need for interventions to improve environmental disinfection processes in the hospital setting. Future studies should also focus on the role of organizational factors and CDI transmission risk, including bed management and allocation of disinfection and environmental services resources based on patient location and characteristics.

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Summary: We evaluated risk factors for nosocomial *C. difficile* infection (CDI), with a specific focus on the hospital environment. We found that increased square footage of the hospital room was a significant risk factor for CDI.

Table 1

Bivariate conditional logistic regression of risk factors for nosocomial *C. difficile* infection among hospitalized patients

Variable	Cases (n=75)	Controls (n=150)	OR (95% CI)	*P* value
Age, median years (IQR)	60 (51-70)	59 (49-70)	----	0.66
Female sex	35 (47)	73 (49)	0.93 (0.54-1.56)	0.78
Non-white race	18 (24)	68 (45)	0.37 (0.20-0.72)	0.003
Overweight/Obesity[b]	59 (79)	88 (59)	2.74 (1.39-5.40)	0.004
Surgical service	20 (27)	49 (33)	0.74 (0.39-1.38)	0.34
Single room	66 (88)	97 (65)	3.74 (1.76-7.96)	0.001
Hospital room square footage, median (IQR)	191 (191-244)	180 (168-198)	2.03 (1.40-2.94)	<0.001
Hospital admission in the previous 90 days	11 (15)	9 (6)	2.59 (1.04-6.50)	0.04
Comorbidities				
Chronic kidney disease	5 (7)	28 (19)	0.31 (0.11-0.84)	0.02
Malignancy	47 (63)	59 (39)	2.92 (1.56-5.47)	.001
Pulmonary disease	5 (67)	17 (11)	0.56 (0.20-1.58)	0.27
Cardiac disease	12 (16)	29 (19)	0.79 (0.37-1.67)	0.53
Solid organ or hematopoietic stem cell transplant in prior 6 months	3 (4)	9 (6)	0.64 (0.17-2.50)	0.52
Cirrhosis	2 (3)	8 (5)	0.50 (0.10-2.35)	0.38
Cerebrovascular disease	1 (1)	8 (5)	0.22 (0.27-1.87)	0.17
Medications[c]				
Cefepime	39 (52)	57 (38)	1.94 (1.05-3.59)	0.03
Clindamycin	7 (9)	4 (3)	3.50 (1.02-12.0)	0.046
First-generation cephalosporin	9 (12)	36 (24)	0.39 (0.16-0.92)	0.03
Corticosteroids	45 (60)	62 (41)	2.14 (1.20-3.80)	0.009
Immunosuppressants	17 (23)	9 (6)	5.70 (2.07-15.7)	0.001

Abbreviations: OR, odds ratio; CI, confidence interval; IQR, interquartile range.

[a] Data are presented as numbers (percentages) except where noted.

[b] BMI ≥25.

[c] Only variables with $P<0.05$ are shown.

Table 2

Multivariate conditional logistic regression of risk ractors for nosocomial *C. difficile* infection among hospitalized patients

Variable	OR (95% CI)	*P* value
Square footage (every 50 ft^2)	3.00 (1.75-5.16)	<0.001
Single room	3.43 (1.31-9.05)	0.01
Malignancy	4.56 (1.82-11.4)	0.001
Cefepime[a]	2.48 (1.06-5.82)	0.04
Immunosuppressants[a]	6.90 (2.07-23.0)	0.002

Abbreviations: OR, odds ratio; CI, confidence interval.

[a]Receipt within prior 30 days.