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Receipt of Antibiotics in Hospitalized Patients and Risk for *Clostridium difficile* Infection in Subsequent Patients Who Occupy the Same Bed

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OBJECTIVE To assess whether receipt of antibiotics by prior hospital bed occupants is associated with increased risk for CDI in subsequent patients who occupy the same bed.

DESIGN, SETTING, AND PARTICIPANTS This is a retrospective cohort study of adult patients hospitalized in any 1 of 4 facilities between 2010 and 2015. Patients were excluded if they had recent CDI, developed CDI within 48 hours of admission, had inadequate follow-up time, or if their prior bed occupant was in the bed for less than 24 hours.

MAIN OUTCOMES AND MEASURES The primary exposure was receipt of non-CDI antibiotics by the prior bed occupant and the primary outcome was incident CDI in the subsequent patient to occupy the same bed. Incident CDI was defined as a positive result from a stool polymerase chain reaction for the *C difficile* toxin B gene followed by treatment for CDI. Demographics, comorbidities, laboratory data, and medication exposures are reported.

RESULTS Among 100 615 pairs of patients who sequentially occupied a given hospital bed, there were 576 pairs (0.57%) in which subsequent patients developed CDI. Receipt of antibiotics in prior patients was significantly associated with incident CDI in subsequent patients (log-rank $P < .01$). This relationship remained unchanged after adjusting for factors known to influence risk for CDI including receipt of antibiotics by the subsequent patient (adjusted hazard ratio [aHR], 1.22; 95% CI, 1.02-1.45) and also after excluding 1497 patient pairs among whom the prior patients developed CDI (aHR, 1.20; 95% CI, 1.01-1.43). Aside from antibiotics, no other factors related to the prior bed occupants were associated with increased risk for CDI in subsequent patients.

CONCLUSIONS AND RELEVANCE Receipt of antibiotics by prior bed occupants was associated with increased risk for CDI in subsequent patients. Antibiotics can directly affect risk for CDI in patients who do not themselves receive antibiotics.

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Supplemental content

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Clostridium difficile infection (CDI) is the most common cause of diarrhea in the hospital and is responsible for an estimated 27 000 deaths annually in the United States.[1] *Clostridium difficile* infection occurs when there is a susceptible host and sufficient exposure to the organism. Many factors may increase host susceptibility to CDI, but the most crucial host-related risk factor is exposure to antibiotics.[2] Antibiotics are a risk factor for CDI not only when they are assessed at the level of the individual patient but also when they are assessed at the level of the hospital ward,[3,4] the level of the institution,[5] and the regional level.[6]

Exposure to *C difficile* is common in the hospital because *C difficile* spores are capable of persisting in the environment for months.[7] High counts of *C difficile* spores can be detected in the stool of infected or colonized individuals, and *C difficile* can be readily cultured from the beds, bed rails, floors, and walls of hospital rooms where prior occupants have had CDI.[8,9] When individuals enter a new environment, they rapidly acquire *C difficile* as well as the other microorganisms that are present.[10] When one hospital roommate has CDI, patients who share that room are at increased risk for CDI.[11] Furthermore, when the previous occupant of a given hospital room has CDI, the subsequent patient in that room is at increased risk for CDI.[12]

It is uncertain how antibiotics or other CDI risk factors might act on one patient to increase risk for CDI in a subsequent patient who shares the same hospital environment. We examined whether receipt of antibiotics by prior occupants of

a given hospital bed was associated with increased risk for CDI in subsequent patients in the same bed.

Key Points

Question Is the receipt of antibiotics by prior hospital bed occupants associated with risk for *Clostridium difficile* infection (CDI) in subsequent patients who occupy the same bed?

Findings In this cohort study, receipt of antibiotics by prior patients was associated with a 22% relative increase in risk for CDI in subsequent patients who occupied the same bed. Aside from antibiotics, no other factors related to the prior bed occupants were associated with increased risk for CDI in subsequent patients.

Meaning Antibiotics given to one patient may alter the local microenvironment to influence a different patient's risk for CDI.

Importance Antibiotics are the crucial risk factor for CDI, but it is unknown how one hospitalized patient's receipt of antibiotics may affect risk for CDI for a different patient within the same environment.

Methods

Population

This was a retrospective cohort study in 4 affiliated but geographically distinct hospitals in the New York City metropolitan area. Adults at least 18 years old admitted from 2010 to 2015 were considered for the study if they spent at least 48 hours in their first bed following hospital admission. For patients with multiple admissions, the first admission was analyzed. Electronic time stamps were used to identify sequential patients who occupied a given hospital bed in either a single-occupancy or multiple-occupancy hospital room. We required that the prior patient spent at least 24 hours in the bed and left the bed less than 1 week before the next patient's admission. These requirements were based on the assumption that there would be minimal potential exposure to *C difficile* spores if beds were occupied very briefly or were vacant for long periods before the arrival of subsequent patients. Subsequent patients with a known diagnosis of CDI within the 90 days preceding room admission were excluded to focus on incident rather than recurrent CDI. Subsequent patients were also excluded if they tested positive for CDI within the first 48 hours after admission. Flow into the study is shown in eFigure 1 in the Supplement. The study protocol was approved by the institutional review boards of Columbia University Medical Center and Weill-Cornell Medical Center.

Clostridium difficile Infection

Clostridium difficile infection was defined as a positive result from a polymerase chain reaction (PCR) test for the *C difficile* toxin B gene from an unformed stool followed by receipt of appropriate anti-CDI antibiotics. We selected 2010 for the start of the study because it represents the earliest time when all participating institutions uniformly used the stool PCR test for the diagnosis of CDI. For the duration of the study, the environmental policies related to CDI at the participating institutions met or exceeded current guidelines from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America.[13] These policies are summarized in eTable 1 in the Supplement.

Primary Exposure

The primary exposure was receipt of antibiotics by the prior bed occupant during the relevant hospitalization, prior to discharge from the shared bed. Receipt of antibiotics was assessed using data from a computerized clinician order entry system. To ensure that antibiotics did not function as a surrogate for suspected but undiagnosed CDI, patients were not classified as having received antibiotics if the only antibiotics they received were those specifically used for treatment of CDI (ie, metronidazole or oral vancomycin). The antibiotic classes included in the study are listed in eTable 2 in the Supplement. Antibiotic exposure was classified categorically as present vs absent because the best evidence suggests that even a single dose of antibiotics affects risk for CDI for up to 90 days.[14-16]

Covariates

Automated queries were used to retrieve demographic information, laboratory values at the time of room admission, comorbidities using claims data (to compute the Charlson Comorbidity Index),[17,18] duration of hospital stay, the presence or absence of contemporaneous cases of hospital-onset CDI (to capture the concept *of C difficile* colonization pressure),[3] ward type (classified as cardiac, medical, surgical, neurological, or intensive care unit), and treatments received during hospitalization including receipt of antibiotics, hemodialysis, acid suppression medications (proton pump inhibitors or histamine-2 receptor antagonists), and immunosuppressive medications (including systemic steroids at a minimum dose of 5 mg of prednisone or equivalent, calcineurin inhibitors, antimetabolites, anti–tumor necrosis factor agents, and mycophenolate).

Statistical Approach

For continuous variables, means were computed if data were normally distributed, or medians and interquartile ranges if data were skewed. Differences in medians were compared using the Hodges-Lehmann estimate. Categorical variables were compared using the χ^2 test or Fisher exact test when 5 or fewer events were expected in any category. The multivariable analysis was constructed using a Cox proportional hazards model with patients followed from the time of room admission until discharge, death, CDI, or for a maximum of 14 days. We selected 14 days as a cutoff because (1) this represents the period of maximum CDI risk following antibiotics,[19] (2) most patients who develop new CDI colonization do so within the first 14 days following hospitalization,[9] and (3) the prior bed occupant's contribution to the microbial milieu of a given hospital room is likely to become diluted with the passage of time. The proportional hazards assumption was verified by visual inspection of time-to-event data and by testing for a nonzero slope in the Schoenfeld residuals.[20] To build the final model, variables were tested stepwise and included if they had a significant independent relationship with CDI or if they altered the β-coefficient representing the previous patient's receipt of antibiotics by at least 10%. All analyses were performed using Stata statistical software (version 12; StataCorp) at the $\alpha = .05$ level of significance.

Table 1. Characteristics of Subsequent Patients Who Did and Did Not Develop *Clostridium difficile* Infection (CDI)[a]

Characteristic	Patient		Estimates, OR (95% CI)[b]
	Developed CDI (n = 576)	Did Not Develop CDI (n = 100 039)	
Male sex	279 (48)	49 192 (49)	0.97 (0.82 to 1.14)
Age, y			
<55	142 (25)	34 183 (34)	1 [Reference]
55-70	175 (31)	29 116 (29)	1.45 (1.16 to 1.81)
>70	259 (45)	36 740 (37)	1.70 (1.38 to 2.08)
Race/ethnicity			
White	240 (42)	39 316 (39)	1 [Reference]
Black	47 (8.2)	10 208 (10)	0.75 (0.55 to 1.03)
Hispanic	119 (21)	22 790 (23)	0.86 (0.69 to 1.07)
Other/unknown	170 (30)	27 725 (28)	1.00 (0.82 to 1.22)
Ward type			
Medical	193 (34)	40 830 (41)	1 [Reference]
Cardiac	72 (13)	15 308 (15)	1.00 (0.76 to 1.31)
Intensive care unit	178 (31)	12 109 (12)	3.11 (2.53 to 3.82)
Surgical	100 (17)	21 788 (22)	0.97 (0.76 to 1.24)
Neurological	33 (5.7)	10 004 (10)	0.70 (0.48 to 1.01)
Charlson Comorbidity Index, median (IQR)	2 (0 to 3)	1 (0 to 2)	0 (0 to 1)
Laboratory values at the time of room admission, median (IQR)			
Serum creatinine level, mg/dL	1.0 (0.8 to 1.7)	0.9 (0.7 to 1.2)	0.1 (0.1 to 0.2)
Serum albumin level, g/dL	3.2 (2.7 to 3.7)	3.9 (3.3 to 4.5)	−0.6 (−0.7 to −0.1)
White blood cell count, cells $\times 10^9$/L	10.6 (7.3 to 14.5)	8.6 (6.3 to 11.7)	1.7 (1.3 to 2.1)
Length of stay, median (IQR), d	17 (11 to 26)	6 (4 to 10)	10 (9 to 11)
Treatments and medications received prior to the diagnosis of CDI			
Antibiotics	386 (67)	27 045 (27)	5.48 (4.61 to 6.53)
Hemodialysis	75 (13)	2434 (2.4)	6.00 (4.69 to 7.68)
Acid suppression medications	441 (77)	45 949 (46)	3.85 (3.17 to 4.66)
Immunosuppressants	178 (31)	13 750 (14)	2.81 (2.35 to 3.35)
Contemporaneous CDI[c]	159 (28)	8372 (8.4)	4.17 (3.47 to 5.02)

Abbreviations: IQR, interquartile range; OR, odds ratio.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; to convert albumin to grams per liter, multiply by 10.

[a] Data are given as No. (%) except where noted.

[b] Confidence estimates are for ORs for categorical variables and for the difference of medians for continuous variables (median for those with CDI vs median for those without CDI).

[c] Contemporaneous CDI approximates *C difficile* colonization pressure and represents the presence or absence of another case of hospital-onset CDI on the ward during each patient's at-risk period.

Sensitivity Analyses

To test whether the relationship between the prior patient's receipt of antibiotics and CDI in the subsequent patient was mediated by CDI in the prior patient, a restriction analysis was performed excluding patient pairs in which the prior patient in the bed had known CDI. Previous studies have suggested a seasonal pattern to CDI in the United States, with a rise in cases during the winter months presumably due to increased prescription of antibiotics.[19,21] To test the effect of season on the model, quarterly periods were generated corresponding to the seasons as follows: winter (December-February), spring (March-May), summer (June-August), and fall (September-November). To further explore the effect of ward type within our final model, stratified analyses and testing for interactions were performed.

Results

Patient Characteristics

Data for a total of 100 615 pairs of patients sequentially admitted to a given hospital bed were analyzed, including 576 subsequent patients who developed CDI within 2 to 14 days after arriving at their bed. There was no evidence of CDI outbreaks or of a change in the incidence rate of CDI during the course of the study (eFigure 2 in the Supplement). The median duration of bed occupancy for the prior bed occupant was 3.0 days (interquartile range [IQR], 1.9-5.4). There was a median duration of 10 hours (IQR, 4-29) during which the bed was vacant between patients. When the subsequent patient developed CDI, the median time from bed admission to CDI was 6.4 days (IQR, 4.0-9.5).

Baseline Risk Factors

The characteristics of subsequent patients appear in **Table 1**, and the characteristics of prior bed occupants appear in **Table 2**. Subsequent patients with incident CDI were more likely to have traditional CDI risk factors including older age, increased creatinine, decreased albumin, and receipt of antibiotics. Compared with subsequent patients without incident CDI, subsequent patients with incident CDI were more likely to have traditional CDI risk factors including older age, increased creatinine level, decreased albumin level, receipt of antibiotics, and contemporaneous patients on their wards with CDI. They

Table 2. Characteristics of the Prior Bed Occupants, Organized According to Whether or Not the Subsequent Patient Developed *Clostridium difficile* Infection (CDI)[a]

Characteristic of the Prior Bed Occupant	Subsequent Patient		Estimates, OR (95% CI)[b]
	Developed CDI (n = 576)	Did Not Develop CDI (n = 100 039)	
Male sex	293 (51)	49 494 (49)	1.06 (0.90 to 1.25
Age, y			
<55	161 (28)	32 922 (33)	1 [Reference]
55-70	178 (31)	29 648 (30)	1.23 (0.99 to 1.50)
>70	237 (41)	37 469 (37)	1.29 (1.06 to 1.58)
Race/ethnicity			
White	247 (43)	38 605 (39)	1 [Reference]
Black	66 (11)	10 513 (11)	0.98 (0.75 to 1.29)
Hispanic	135 (23)	24 709 (25)	0.85 (0.69 to 1.05)
Other/unknown	128 (22)	26 212 (26)	0.76 (0.62 to 0.95)
Charlson Comorbidity Index, median (IQR)	1 (0-3)	1 (0-2)	0 (0 to 0)
Laboratory values at the time of room admission, median (IQR)			
Serum creatinine level, mg/dL	1.0 (0.8-1.3)	0.9 (0.7-1.3)	0.0 (0.0 to 0.1)
Serum albumin level, g/dL	3.5 (2.9-4.3)	3.8 (3.2-4.5)	−0.2 (−0.3 to −0.1)
White blood cell count, cells ×10^9/L	8.9 (6.5-12.4)	8.3 (6.3-11.5)	0.5 (0.2 to 0.9)
Treatments and medications received			
Antibiotics	353 (61)	48 720 (49)	1.67 (1.41 to 1.97)
Hemodialysis	41 (7.1)	3960 (4.0)	1.86 (1.35 to 2.56)
Acid suppression medications	368 (64)	54 959 (55)	1.45 (1.22 to 1.72)
Immunosuppressants	172 (29)	21 718 (22)	1.54 (1.28 to 1.84)
CDI			
Within 90 d before room admission	1 (0.17)	146 (0.15)	1.19 (0.17 to 8.52)
During room admission	11 (1.90)	1339 (1.30)	1.44 (0.79 to 2.61)

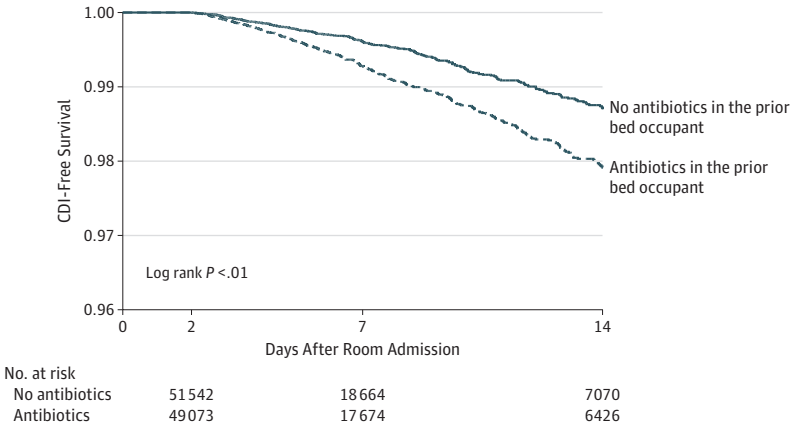
Abbreviation: IQR, interquartile range.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; to convert albumin to grams per liter, multiply by 10.

[a] Data are given as No. (%) except where noted.

[b] Confidence estimates are for odds ratios for categorical variables and for the difference of medians for continuous variables (median for those with CDI vs median for those without CDI).

Figure 1. Kaplan-Meier Plot Showing Survival Free From *Clostridium difficile* Infection (CDI) Through 14 Days, Stratified According to the Antibiotics Received by the Prior Bed Occupant



were also more likely to have prior bed occupants with similar traditional CDI risk factors.

Multivariable Analysis

The cumulative incidence of CDI in subsequent patients was 0.72% when prior bed occupants received antibiotics compared with 0.43% when prior bed occupants did not receive antibiotics (log-rank $P < .01$) (**Figure 1**). In the final Cox proportional hazards model, receipt of antibiotics was the only characteristic related to prior patients that was associated with increased risk for CDI in subsequent patients (**Table 3**). The most important risk factors for CDI were all related to the subsequent patient: receipt of antibiotics, the presence of a contemporaneous patient with CDI on the ward, receipt of acid suppression medications, and hospitalization in the ICU.

Table 3. Final Cox Proportional Hazards Model of Risk Factors for *Clostridium difficile* Infection (CDI)

Risk Factors	Patients With CDI/ Total Exposed (%)	Hazard Ratio (95% CI)	
		Full Model	Final Model
Prior Bed Occupant Risk Factors			
Age, y			
<55	161 of 33 083 (0.5)	1 [Reference]	NA
55-70	178 of 29 826 (0.6)	1.11 (0.89-1.37)	NA
>70	237 of 37 706 (0.6)	1.17 (0.95-1.43)	NA
Antibiotics	353 of 49 073 (0.7)	1.21 (1.01-1.46)	1.22 (1.02-1.45)
Acid suppression medications	368 of 55 327 (0.7)	0.95 (0.79-1.14)	NA
Immunosuppressants	172 of 21 890 (0.8)	0.95 (0.79-1.15)	NA
Serum			
Creatinine level[a]	NA	0.96 (0.91-1.01)	NA
Albumin level[b]	NA	1.05 (0.94-1.18)	NA
Patient Risk Factors			
Age, y			
<55	142 of 34 325 (0.4)	1 [Reference]	1 [Reference]
55-70	175 of 29 291 (0.6)	1.12 (0.89-1.39)	1.12 (0.90-1.40)
>70	259 of 36 999 (0.7)	1.38 (1.12-1.71)	1.40 (1.14-1.73)
Antibiotics	386 of 27 431 (1.4)	4.21 (3.53-5.03)	4.20 (3.52-5.02)
Acid suppression medications	441 of 46 390 (1.0)	2.15 (1.76-2.62)	2.14 (1.75-2.61)
Immunosuppressants	178 of 13 928 (1.3)	1.52 (1.26-1.84)	1.50 (1.25-1.81)
Serum			
Creatinine level[a]	NA	1.07 (1.04-1.11)	1.07 (1.03-1.11)
Albumin level[b]	NA	1.29 (1.16-1.44)	1.29 (1.16-1.44)
Contemporaneous CDI[c]	159 of 8531 (1.9)	4.00 (3.32-4.83)	3.99 (3.31-4.81)
Common risk factors			
Ward type			
Medical	193 of 41 023 (0.5)	1 [Reference]	1 [Reference]
Cardiac	72 of 15 380 (0.5)	1.06 (0.80-1.41)	1.08 (0.82-1.43)
Intensive care unit	178 of 12 287 (1.4)	1.96 (1.58-2.44)	1.94 (1.57-2.40)
Surgical	100 of 21 888 (0.5)	1.25 (0.98-1.61)	1.23 (0.95-1.56)
Neurological	33 of 10 037 (0.3)	1.14 (0.78-1.65)	1.13 (0.78-1.64)

Abbreviation: NA, not applicable.

[a] Per mg/dL increase in serum creatinine level.

[b] Per mg/dL decrease in serum albumin level.

[c] Contemporaneous CDI approximates *C difficile* colonization pressure and represents the presence or absence of another case of hospital-onset CDI on the ward during each patient's at-risk period.

Sensitivity Analyses

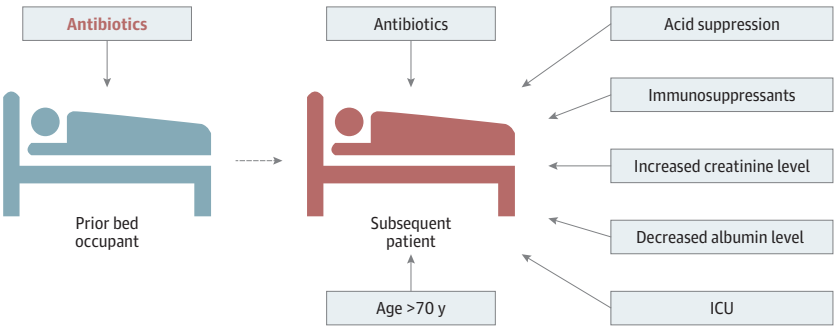
The relationship between receipt of antibiotics by prior patients and risk for CDI in subsequent patients remained unchanged when the analysis was restricted by excluding 1497 patient pairs in which the prior patient had recent CDI (adjusted hazard ratio [aHR], 1.20; 95% CI, 1.01-1.43). When season was tested in the final model, there was a significant increase in risk for CDI during the summer compared with the winter months (aHR, 1.38; 95% CI, 1.09-1.74), although this did not alter the relationship between prior patients' receipt of antibiotics and risk for CDI in subsequent patients (aHR, 1.20; 95% CI, 1.01-1.43). We observed that an intensive care unit (ICU) location was a significant independent risk factor for CDI. Stratifying by ICU vs non-ICU locations, the association between prior patients' receipt of antibiotics and risk for CDI in subsequent patients was stronger in the ICU (aHR, 1.58; 95% CI, 1.05-2.36) compared with non-ICU locations (aHR, 1.17; 95% CI, 0.96-1.43), although this interaction was not statistically significant (P = .19).

Discussion

In pairs of patients sequentially admitted to a given hospital bed, receipt of antibiotics by prior bed occupants was associated with increased risk for CDI in subsequent patients. This association was modest in strength but remained statistically significant after adjusting for potential confounders such as patient comorbidities, CDI colonization pressure, ward type, and the subsequent patient's exposure to antibiotics. This association was independent of the prior bed occupant's CDI status, and persisted through multiple sensitivity analyses. We examined several traditional risk factors for CDI in the prior patient, including antibiotics, hemodialysis, acid suppression medications, and immunosuppressants. Of these risk factors, only receipt of antibiotics by prior bed occupants was associated with increased risk for CDI in subsequent patients. These findings are summarized graphically in **Figure 2**.

Antibiotics have long been established as the crucial risk factor for CDI. Previous studies have shown that use of antibiotics has an impact on individual risk for CDI when use of antibiotics is evaluated at the ward level, or even at the broader level of the hospital or the regional network.[3-6,22] Our study may be the most direct example to date of the potential effect of antibiotics in patients who do not themselves receive the antibiotics. In patients colonized by *C difficile*, antibiotics may promote *C difficile* proliferation and the number of *C difficile* spores that are shed into the local environment.[23] In turn, this may result in a higher environmental burden of *C difficile* and greater risk for acquisition and infection in future patients who

Figure 2. Schematic Depicting Risk Factors Significantly Associated With Increased Risk for *Clostridium difficile* Infection (CDI)



Multiple risk factors were identified related to the subsequent patient but, of all the potential risk factors examined that were related to the prior bed occupant, only antibiotics were associated with increased risk for CDI in subsequent patients. ICU indicates intensive care unit.

share the same environment. Alternatively, antibiotics may affect the gastrointestinal microbiome more globally to decrease bacterial species that are protective against *C difficile* or to increase bacterial species that facilitate *C difficile*.[24] Subsequent patient-to-patient transmission of these bacterial species may then drive risk for CDI in future patients. The specific mechanisms underlying the herd effects of antibiotics may be a fruitful area for future research.

Several studies have examined how individual patient-to-patient networks affect risk for CDI. In patients who are cohoused, a roommate with CDI is a risk factor for incident CDI.[9,11,25] Physical proximity to a patient with known CDI also seems to be a risk factor.[26,27] Shaughnessy et al[12] studied ICU admissions and found a 3-fold increase in risk for CDI when the prior room occupant had CDI. Studies focused on the acquisition of multidrug-resistant organisms have reached similar conclusions.[28-30] More generally, the CDI status of prior room occupants can be considered as a component of the colonization pressure related to *C difficile*. The concept of colonization pressure—essentially the number of patients nearby who already have the infection—is well established for carriage of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* and also for CDI.[3,31] Our study results extend the findings of these previous studies by demonstrating that the CDI risk profile of the prior bed occupant (ie, whether or not that patient received antibiotics) is likely to be a part of *C difficile* colonization pressure.

During the period of our study, all participating institutions had policies that met or exceeded current environmental cleaning protocols for CDI. However, the presence of a policy does not necessarily mean that the policy is being effectively implemented.[32,33] *Clostridium difficile* spores are hardy, are not killed by gastric acid, and are ubiquitous in the hospital environment and easily cultured from patient beds and other locations.[9,34] As the burden of *C difficile* spores increases, it is likely to be increasingly difficult to prevent the spread of spores to patients by hospital personnel or by other vectors.[35-38] Many institutions, including the institutions that participated in this study, currently target the rooms of patients with CDI for additional cleaning measures, such as UV radiation.[39] Our study provides further, albeit indirect, evidence of the importance of colonized patients in the nosocomial transmission of *C difficile*.[40,41] Overall rates of CDI may be improved by focusing cleaning protocols on the rooms of patients who have risk factors for CDI (eg, receipt of antibiotics) rather than focusing exclusively on patients with known CDI. In this study, CDI in prior bed occupants was not a risk factor for CDI in subsequent patients. This may indicate that the beds and rooms of patients with known CDI are cleaned more effectively than other beds and rooms.

This study was observational and, as with all observational studies, the potential for confounding should be carefully assessed. Selective housing of patients—that is, the housing of the sickest patients in certain rooms—must be considered as a source for residual confounding. Because baseline severity of illness is an important risk factor for CDI, selective housing of patients could cause bias away from the null. Several pieces of evidence argue against this as an explanation for our results. First, adjusting for patient comorbidities did not significantly alter the relationship between the antibiotics received by prior bed occupants and subsequent patients' risk for CDI. Second, if the sickest patients were housed in certain rooms one would expect to see an association between traditional risk factors for CDI (eg, serum creatinine or albumin levels) in the prior patient and the subsequent patient's risk for CDI. However, aside from antibiotics, no other factors related to the prior patient were associated with CDI in the subsequent patient in our final model. Finally, the strength of association increased when we examined only patients housed in the ICU, where patients are likely to be more homogeneous and preferential admission of sicker patients to certain rooms is unlikely.

There are additional limitations to this study. It was conducted in a single health care system and may not be generalizable to other institutions. The study was also conducted in a nonoutbreak setting, and the relationship between antibiotics and CDI may fundamentally differ during an outbreak. Because we analyzed data that were previously collected, we were not able to directly assess the mechanism by which *C difficile* may be transmitted from prior bed occupants to subsequent patients. We were not able to demonstrate a dose-response effect. Last, the observed effect size was small. Although this translates into a modest absolute risk associated with antibiotics in the prior bed occupant, it remains

important because use of antibiotics in the hospital is so common. Our results show that antibiotics can potentially cause harm to patients who do not themselves receive the antibiotics and thus emphasize the value of antibiotic stewardship.

Conclusions

In this large cohort study, receipt of antibiotics by prior occupants of a given hospital bed was associated with increased risk for CDI in subsequent patients hospitalized in the same bed. This finding remained true after excluding patient pairs in which the prior bed occupant had known CDI. The increase in risk was small but is of potential importance given the frequency of use of antibiotics in the hospital. These data imply that patient-to-patient transmission of *C difficile* or other bacteria that mediate susceptibility to CDI takes place in the nonoutbreak setting and in the face of a multifaceted effort seeking to prevent health care–associated CDI. More generally, these data support the hypothesis that antibiotics given to one patient may alter the local microenvironment to influence a different patient's risk for CDI.

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Study concept and design: Freedberg, Cohen, Abrams, Larson.
Acquisition, analysis, or interpretation of data: Freedberg, Salmasian, Abrams, Larson.
Drafting of the manuscript: Freedberg, Salmasian.
Critical revision of the manuscript for important intellectual content: All authors.
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