Published in final edited form as:

JAMA Intern Med. 2016 December 01; 176(12): 1801–1808. doi:10.1001/jamainternmed.2016.6193.

Receipt of antibiotics in hospitalized patients and risk for *Clostridium difficile* infection in subsequent patients who occupy the same bed

Daniel E. Freedberg, MD, MS, Hojjat Salmasian, MD, PhD, Bevin Cohen, MPH, Julian A. Abrams, MD, MS, and Elaine L. Larson, RN, PhD

Division of Digestive and Liver Diseases, Columbia University Medical Center (Freedberg, Abrams), Department of Biomedical Informatics, NewYork-Presbyterian Hospital (Salmasian), Department of Epidemiology, Mailman School of Public Health (Cohen, Larson), School of Nursing, Columbia University (Cohen, Larson)

Abstract

Importance—Antibiotics are the crucial risk factor for *Clostridium difficile* infection (CDI) but it is unknown how one patient's receipt of antibiotics may affect risk for CDI for a different patient within the same environment.

Objective—To assess whether receipt of antibiotics by prior 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 one of four 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 <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 stool PCR for the *C. difficile* toxin B gene followed by treatment for CDI. Demographics, comorbidities, laboratory data, and medication exposures are reported.

Corresponding Author: Daniel Freedberg, MD, MS, Division of Digestive and Liver Diseases, Columbia University Medical Center, 630 West 168th Street, New York, NY 10032, USA. Phone: (212) 305-1021, Fax: (212) 305-5576, def2004@cumc.columbia.edu.

Conflict of Interest Disclosures: None.

Disclaimer: The views expressed in this article represent those of the authors and do not necessarily represent the views of the AGA or the NIH.

Author Contributions: Dr. Daniel Freedberg had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Freedberg. *Acquisition, analysis, or interpretation of data:* Freedberg, Salmasian, Abrams, Larson. *Drafting of the manuscript:* Freedberg. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Freedberg. *Administrative, technical, or material support:* Freedberg, Salmasian. *Study supervision:* Freedberg, Larson.

Role of the Funder/Sponsor: The funding sources played no role in the design and conduct of the study; collection, managements, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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 $P<0.01$). This relationship remained unchanged after adjusting for factors known to influence risk for CDI including receipt of antibiotics by the subsequent patient (aHR 1.22, 95% CI 1.02–1.45) and also after excluding 1,497 patient pairs where 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.

INTRODUCTION

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 CDI 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 micro-organisms 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 associated with increased risk for CDI in subsequent patients in the same bed.

METHODS

Population

This was a retrospective cohort study in four affiliated but geographically distinct hospitals in the New York City metropolitan area. Adults 18 years old admitted from 2010 to 2015 were considered for the study if they spent ≥48 hours in their first bed following hospital admission. For patients with multiple admissions, the first admission was analyzed. Electronic timestamps 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 24 hours in the bed and left the bed less than one 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. The study protocol was approved by the Institutional Review Boards of Columbia University Medical Center and Weill-Cornell Medical Center.

Clostridium difficile infection

C. difficile infection was defined as a positive PCR 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 utilized 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 (SHEA) and the Infectious Diseases Society of America (IDSA).¹³ These policies are summarized in eTable 1.

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 provider 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 (i.e., metronidazole or oral vancomycin). The antibiotic classes included in the study are listed in eTable 2. Antibiotic exposure was classified categorically as present versus 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, anti-metabolites, anti-TNF α 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 chi-squared test or Fisher's exact test when five 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 cut-off because this represents the period of maximum CDI risk following antibiotics,¹⁹ because the majority of patients who develop new CDI colonization do so within the first 14 days following hospitalization,⁹ and because 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 non-zero 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 10%. All analyses were performed on STATA 12 at the alpha 0.05 level of significance.

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 through February), spring (March through May), summer (June through August), and fall (September through November). To further explore the effect of ward type within our final model, stratified analyses and testing for interactions were performed.

RESULTS

Patient Characteristics

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 2–14 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). The median duration of bed occupancy for the prior bed occupant was 3.0 days (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 appears in Table 1 and the characteristics of prior bed occupants appears 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. Subsequent patients with incident CDI were more likely to have contemporaneous patients on their wards with CDI. They 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 to 0.43% when prior bed occupants did not receive antibiotics (Log-Rank $P<0.01$, 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 receipt of antibiotics by the subsequent patient, the presence of a contemporaneous patient with CDI on the ward, receipt of acid suppression medications, and hospitalization in the ICU.

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 1,497 patient pairs in which the prior patient had recent CDI (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 to 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 ICU location was a significant independent risk factor for CDI. Stratifying by ICU versus 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 to 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 occupants' 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 impacts 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 on 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 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 co-housed, a roommate with CDI is a risk factor for incident CDI.^{9,11,25} Physical proximity to a patient with known CDI also appears to be a risk factor.^{26,27} Shaughnessy *et al.* studied ICU admissions and found a 3-fold increase in risk for CDI when the prior room occupant had CDI.¹² 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 *C. difficile* infection.^{3,31} Our study results extend the findings of these previous studies by demonstrating that the CDI risk profile of the prior bed occupant (i.e., 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} *C. difficile* spores are hardy, 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 ultraviolet 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 (such as 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—i.e., 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 (such as serum creatinine or albumin) in the prior patient and the subsequent patient's risk for CDI. However, aside from antibiotics, no other factors related to the prior patient 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 healthcare system and may not be generalizable to other institutions. The study was also conducted in a non-outbreak setting, and the relationship between antibiotics and CDI may fundamentally differ during an outbreak. Because we analyzed data that was 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 non-outbreak setting and in the face of a multi-faceted effort seeking to prevent healthcare-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding/Support: Dr. Freedberg was supported by a Research Scholar Award from the American Gastroenterological Association (AGA) and by the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), (KL2 TR000081, formerly KL2 RR024157).

We thank Jianhua Li, MD, MS and Barbara G. Ross, RN for programming assistance and data collection (affiliations: Department of Medicine, Columbia University Medical Center and Department of Epidemiology, NewYork-Presbyterian Hospital). Neither JianhuaLi nor Barbara Ross received any specific compensation for contributions to this article.

References

1. Lessa FC, Mu Y, Bamberg WM, et al. Burden of Clostridium difficile infection in the United States. *N Engl J Med*. 2015; 372(9):825–834. [PubMed: 25714160]
2. Dubberke ER, Reske KA, Yan Y, Olsen MA, McDonald LC, Fraser VJ. Clostridium difficile--associated disease in a setting of endemicity: identification of novel risk factors. *Clin Infect Dis*. 2007; 45(12):1543–1549. [PubMed: 18190314]
3. Dubberke ER, Reske KA, Olsen MA, et al. Evaluation of Clostridium difficile-associated disease pressure as a risk factor for C difficile-associated disease. *Arch Intern Med*. 2007; 167(10):1092–1097. [PubMed: 17533213]
4. Brown K, Valenta K, Fisman D, Simor A, Daneman N. Hospital ward antibiotic prescribing and the risks of Clostridium difficile infection. *JAMA Intern Med*. 2015; 175(4):626–633. [PubMed: 25705994]
5. Miller AC, Polgreen LA, Cavanaugh JE, Polgreen PM. Hospital Clostridium difficile infection (CDI) incidence as a risk factor for hospital-associated CDI. *Am J Infect Control*. 2016
6. Brown KA, Jones M, Daneman N, et al. Importation, Antibiotics, and Clostridium difficile Infection in Veteran Long-Term Care: A Multilevel Case-Control Study. *Ann Intern Med*. 2016
7. Fekety R, Kim KH, Brown D, Batts DH, Cudmore M, Silva J Jr. Epidemiology of antibiotic-associated colitis; isolation of Clostridium difficile from the hospital environment. *Am J Med*. 1981; 70(4):906–908. [PubMed: 7211925]
8. Gerding DN, Muto CA, Owens RC Jr. Measures to control and prevent Clostridium difficile infection. *Clin Infect Dis*. 2008; 46(Suppl 1):S43–49. [PubMed: 18177221]
9. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of Clostridium difficile infection. *N Engl J Med*. 1989; 320(4):204–210. [PubMed: 2911306]
10. Lax S, Smith DP, Hampton-Marcell J, et al. Longitudinal analysis of microbial interaction between humans and the indoor environment. *Science*. 2014; 345(6200):1048–1052. [PubMed: 25170151]
11. Echaiz JF, Veras L, Zervos M, Dubberke E, Johnson L. Hospital roommates and development of health care-onset Clostridium difficile infection. *Am J Infect Control*. 2014; 42(10):1109–1111. [PubMed: 25278404]
12. Shaughnessy MK, Micielli RL, DePestel DD, et al. Evaluation of hospital room assignment and acquisition of Clostridium difficile infection. *Infect Control Hosp Epidemiol*. 2011; 32(3):201–206. [PubMed: 21460503]
13. Dubberke ER, Carling P, Carrico R, et al. Strategies to prevent Clostridium difficile infections in acute care hospitals: 2014 update. *Infect Control Hosp Epidemiol*. 2014; 35(Suppl 2):S48–65.
14. Dial S, Kezouh A, Dascal A, Barkun A, Suissa S. Patterns of antibiotic use and risk of hospital admission because of Clostridium difficile infection. *CMAJ*. 2008; 179(8):767–772. [PubMed: 18838451]
15. Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for Clostridium difficile infection after exposure to antibiotics. *J Antimicrob Chemother*. 2012; 67(3):742–748. [PubMed: 22146873]
16. Rashid MU, Zaura E, Buijs MJ, et al. Determining the Long-term Effect of Antibiotic Administration on the Human Normal Intestinal Microbiota Using Culture and Pyrosequencing Methods. *Clin Infect Dis*. 2015; 60(Suppl 2):S77–84. [PubMed: 25922405]

17. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987; 40(5):373–383. [PubMed: 3558716]
18. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992; 45(6):613–619. [PubMed: 1607900]
19. Brown KA, Fisman DN, Moineddin R, Daneman N. The magnitude and duration of *Clostridium difficile* infection risk associated with antibiotic therapy: a hospital cohort study. *PLoS One.* 2014; 9(8):e105454. [PubMed: 25157757]
20. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994; 81:515–526.
21. Polgreen PM, Yang M, Bohnett LC, Cavanaugh JE. A time-series analysis of *clostridium difficile* and its seasonal association with influenza. *Infect Control Hosp Epidemiol.* 2010; 31(4):382–387. [PubMed: 20175682]
22. Simmering JE, Polgreen LA, Campbell DR, Cavanaugh JE, Polgreen PM. Hospital Transfer Network Structure as a Risk Factor for *Clostridium difficile* Infection. *Infect Control Hosp Epidemiol.* 2015; 36(9):1031–1037. [PubMed: 26072907]
23. Vincent C, Manges AR. Antimicrobial Use, Human Gut Microbiota and *Clostridium difficile* Colonization and Infection. *Antibiotics (Basel).* 2015; 4(3):230–253. [PubMed: 27025623]
24. Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. *Lancet Infect Dis.* 2001; 1(2):101–114. [PubMed: 11871461]
25. Hamel M, Zoutman D, O’Callaghan C. Exposure to hospital roommates as a risk factor for health care-associated infection. *Am J Infect Control.* 2010; 38(3):173–181. [PubMed: 20022405]
26. Chang VT, Nelson K. The role of physical proximity in nosocomial diarrhea. *Clin Infect Dis.* 2000; 31(3):717–722. [PubMed: 11017821]
27. King MF, Noakes CJ, Sleigh PA. Modeling environmental contamination in hospital single- and four-bed rooms. *Indoor Air.* 2015; 25(6):694–707. [PubMed: 25614923]
28. Huang SS, Datta R, Platt R. Risk of acquiring antibiotic-resistant bacteria from prior room occupants. *Arch Intern Med.* 2006; 166(18):1945–1951. [PubMed: 17030826]
29. Bracco D, Dubois MJ, Bouali R, Eggimann P. Single rooms may help to prevent nosocomial bloodstream infection and cross-transmission of methicillin-resistant *Staphylococcus aureus* in intensive care units. *Intensive Care Med.* 2007; 33(5):836–840. [PubMed: 17347828]
30. Tornieporth NG, Roberts RB, John J, Hafner A, Riley LW. Risk factors associated with vancomycin-resistant *Enterococcus faecium* infection or colonization in 145 matched case patients and control patients. *Clin Infect Dis.* 1996; 23(4):767–772. [PubMed: 8909842]
31. Lawrence SJ, Puzniak LA, Shadel BN, Gillespie KN, Kollef MH, Mundy LM. *Clostridium difficile* in the intensive care unit: epidemiology, costs, and colonization pressure. *Infect Control Hosp Epidemiol.* 2007; 28(2):123–130. [PubMed: 17265392]
32. Carling PC, Parry MM, Rupp ME, et al. Improving cleaning of the environment surrounding patients in 36 acute care hospitals. *Infect Control Hosp Epidemiol.* 2008; 29(11):1035–1041. [PubMed: 18851687]
33. Goodman ER, Platt R, Bass R, Onderdonk AB, Yokoe DS, Huang SS. Impact of an environmental cleaning intervention on the presence of methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci on surfaces in intensive care unit rooms. *Infect Control Hosp Epidemiol.* 2008; 29(7):593–599. [PubMed: 18624666]
34. Kim KH, Fekety R, Batts DH, et al. Isolation of *Clostridium difficile* from the environment and contacts of patients with antibiotic-associated colitis. *J Infect Dis.* 1981; 143(1):42–50. [PubMed: 7217711]
35. Samore MH, Venkataraman L, DeGirolami PC, Arbeit RD, Karchmer AW. Clinical and molecular epidemiology of sporadic and clustered cases of nosocomial *Clostridium difficile* diarrhea. *Am J Med.* 1996; 100(1):32–40. [PubMed: 8579084]
36. Sasahara T, Ae R, Watanabe M, et al. Contamination of healthcare workers’ hands with bacterial spores. *J Infect Chemother.* 2016
37. Guerrero DM, Nerandzic MM, Jury LA, Jinno S, Chang S, Donskey CJ. Acquisition of spores on gloved hands after contact with the skin of patients with *Clostridium difficile* infection and with

- environmental surfaces in their rooms. *Am J Infect Control*. 2012; 40(6):556–558. [PubMed: 21982209]
38. Landelle C, Verachten M, Legrand P, Girou E, Barbut F, Brun-Buisson C. Contamination of healthcare workers' hands with *Clostridium difficile* spores after caring for patients with *C. difficile* infection. *Infect Control Hosp Epidemiol*. 2014; 35(1):10–15. [PubMed: 24334792]
39. Nerandzic MM, Cadnum JL, Pultz MJ, Donskey CJ. Evaluation of an automated ultraviolet radiation device for decontamination of *Clostridium difficile* and other healthcare-associated pathogens in hospital rooms. *BMC Infect Dis*. 2010; 10:197. [PubMed: 20615229]
40. Longtin Y, Paquet-Bolduc B, Gilca R, et al. Effect of Detecting and Isolating *Clostridium difficile* Carriers at Hospital Admission on the Incidence of *C difficile* Infections: A Quasi-Experimental Controlled Study. *JAMA Intern Med*. 2016; 176(6):796–804. [PubMed: 27111806]
41. Clabots CR, Johnson S, Olson MM, Peterson LR, Gerding DN. Acquisition of *Clostridium difficile* by hospitalized patients: evidence for colonized new admissions as a source of infection. *J Infect Dis*. 1992; 166(3):561–567. [PubMed: 1323621]

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.

Figure 2. Schematic depicting risk factors significantly associated with increased risk for *Clostridium difficile* infection

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 associated with increased risk for CDI in subsequent patients.

Table 1Characteristics of subsequent patients who did and did not develop *Clostridium difficile* infection.

Characteristics of subjects	Patient Developed CDI (n=576)	Patient Did Not Develop CDI (n=100,039)	95% Confidence Estimates [*]
Male sex	279 (48%)	49,192 (49%)	0.97 (0.82–1.14)
Age			
Under 55	142 (25%)	34,183 (34%)	Ref
55 to 70	175 (31%)	29,116 (29%)	1.45 (1.16–1.81)
Over 70	259 (45%)	36,740 (37%)	1.70 (1.38–2.08)
Race/ethnicity			
White	240 (42%)	39,316 (39%)	Ref
Black	47 (8.2%)	10,208 (10%)	0.75 (0.55–1.03)
Hispanic	119 (21%)	22,790 (23%)	0.86 (0.69–1.07)
Other/Unknown	170 (30%)	27,725 (28%)	1.00 (0.82–1.22)
Ward type			
Medical	193 (34%)	40,830 (41%)	Ref
Cardiac	72 (13%)	15,308 (15%)	1.00 (0.76–1.31)
Intensive care unit	178 (31%)	12,109 (12%)	3.11 (2.53–3.82)
Surgical	100 (17%)	21,788 (22%)	0.97 (0.76–1.24)
Neurological	33 (5.7%)	10,004 (10%)	0.70 (0.48–1.01)
Charlson Comorbidity Index (median/IQR)	2 (0–3)	1 (0–2)	0 (0 to 1)
Laboratory values at the time of room admission (median/IQR)			
Serum creatinine (mg/dl)	1.0 (0.8–1.7)	0.9 (0.7–1.2)	0.1 (0.1 to 0.2)
Serum albumin (g/dl)	3.2 (2.7–3.7)	3.9 (3.3–4.5)	–0.6 (–0.7 to –.05)
White blood cell count (cellsx10 ⁹ /L)	10.6 (7.3–14.5)	8.6 (6.3–11.7)	1.7 (1.3 to 2.1)
Length of stay in days (median, IQR)	17 (11–26)	6 (4–10)	10 (9 to 11)
Treatments and medications received prior to the diagnosis of CDI			
Antibiotics	386 (67%)	27,045 (27%)	5.48 (4.61–6.53)
Hemodialysis	75 (13%)	2,434 (2.4%)	6.00 (4.69–7.68)
Acid suppression medications	441 (77%)	45,949 (46%)	3.85 (3.17–4.66)
Immunosuppressants	178 (31%)	13,750 (14%)	2.81 (2.35–3.35)
Contemporaneous CDI [†]	159 (28%)	8,372 (8.4%)	4.17 (3.47–5.02)

^{*} 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).

[†] 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 subject's at-risk period. CDI, *Clostridium difficile* infection; IQR, interquartile range.

Table 2

Characteristics of the prior bed occupants, organized according to whether or not the subsequent patient developed *Clostridium difficile* infection.

Characteristics of the prior bed occupant	Subsequent Patient Developed CDI (n=576)	Subsequent Patient Did Not Develop CDI (n=100,039)	95% Confidence Estimates *
Male sex	293 (51%)	49,494 (49%)	1.06 (0.90–1.25)
Age			
Under 55	161 (28%)	32,922 (33%)	Ref
55 to 70	178 (31%)	29,648 (30%)	1.23 (0.99–1.50)
Over 70	237 (41%)	37,469 (37%)	1.29 (1.06–1.58)
Race/ethnicity			
White	247 (43%)	38,605 (39%)	Ref
Black	66 (11%)	10,513 (11%)	0.98 (0.75–1.29)
Hispanic	135 (23%)	24,709 (25%)	0.85 (0.69–1.05)
Other/Unknown	128 (22%)	26,212 (26%)	0.76 (0.62–0.95)
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 (mg/dl)	1.0 (0.8–1.3)	0.9 (0.7–1.3)	0.0 (0.0 to 0.1)
Serum albumin (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 (1.41–1.97)
Hemodialysis	41 (7.1%)	3,960 (4.0%)	1.86 (1.35–2.56)
Acid suppression medications	368 (64%)	54,959 (55%)	1.45 (1.22–1.72)
Immunosuppressants	172 (29%)	21,718 (22%)	1.54 (1.28–1.84)
<i>C. difficile</i> infection			
Within 90 days before room admission	1 (0.17%)	146 (0.15%)	1.19 (0.17–8.52)
During room admission	11 (1.9%)	1,339 (1.3%)	1.44 (0.79–2.61)

* 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). CDI, *Clostridium difficile* infection; IQR, interquartile range.

Table 3Final Cox proportional hazards model of risk factors for *Clostridium difficile* infection.

Risk Factors	Subjects with CDI/Total Exposed (%)	Full Model Hazard Ratio (95% CI)	Final Model Hazard Ratio (95% CI)
Prior bed occupant risk factors			
Age (years)			
Under 55	161/33,083 (0.5%)	Ref	---
55 to 70	178/29,826 (0.6%)	1.11 (0.89–1.37)	---
Over 70	237/37,706 (0.6%)	1.17 (0.95–1.43)	---
Antibiotics	353/49,073 (0.7%)	1.21 (1.01–1.46)	1.22 (1.02–1.45)
Acid suppression medications	368/55,327 (0.7%)	0.95 (0.79–1.14)	---
Immunosuppressants	172/21,890 (0.8%)	0.95 (0.79–1.15)	---
Serum creatinine *	---	0.96 (0.91–1.01)	---
Serum albumin **	---	1.05 (0.94–1.18)	---
Subject risk factors			
Age (years)			
Under 55	142/34,325 (0.4%)	Ref	Ref
55 to 70	175/29,291 (0.6%)	1.12 (0.89–1.39)	1.12 (0.90–1.40)
Over 70	259/36,999 (0.7%)	1.38 (1.12–1.71)	1.40 (1.14–1.73)
Antibiotics	386/27,431 (1.4%)	4.21 (3.53–5.03)	4.20 (3.52–5.02)
Acid suppression medications	441/46,390 (1.0%)	2.15 (1.76–2.62)	2.14 (1.75–2.61)
Immunosuppressants	178/13,928 (1.3%)	1.52 (1.26–1.84)	1.50 (1.25–1.81)
Serum creatinine *	---	1.07 (1.04–1.11)	1.07 (1.03–1.11)
Serum albumin **	---	1.29 (1.16–1.44)	1.29 (1.16–1.44)
Contemporaneous CDI †	159/8,531 (1.9%)	4.00 (3.32–4.83)	3.99 (3.31–4.81)
Common risk factors			
Ward type			
Medical	193/41,023 (0.5%)	Ref	Ref
Cardiac	72/15,380 (0.5%)	1.06 (0.80–1.41)	1.08 (0.82–1.43)
Intensive care unit	178/12,287 (1.4%)	1.96 (1.58–2.44)	1.94 (1.57–2.40)
Surgical	100/21,888 (0.5%)	1.25 (0.98–1.61)	1.23 (0.95–1.56)
Neurological	33/10,037 (0.3%)	1.14 (0.78–1.65)	1.13 (0.78–1.64)

CI, confidence interval; CDI, *Clostridium difficile* infection; IQR, interquartile range; WBC, white blood cell.

* Per mg/dl increase in serum creatinine.

** Per g/dl decrease in serum albumin.

† 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 subject's at-risk period.