Evaluating contemporary antibiotics as a risk factor for *Clostridium difficile* infection in surgical trauma patients

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BACKGROUND: With most *Clostridium difficile* infections (CDI) occurring after exposure to antimicrobial treatment, specific antibiotics and duration of exposure were evaluated independently for increased risk of CDI in surgical patients.

METHODS: A retrospective, case-control design was used to study surgical inpatients. The case group had a positive *Clostridium difficile* toxin assay, whereas the control group did not.

RESULTS: Four antibiotics had a risk that was statistically significant for causing CDI in surgical patients: cefepime (odds ratio [OR], 5.7; 95% confidence interval [CI], 1.7–19.1; $p = 0.0044$), imipenem/cilastatin (OR, 3.2; 95% CI, 1.2–8.9; $p = 0.0388$), piperacillin/tazobactam (OR, 2.4; 95% CI, 1.3–4.5; $p = 0.0067$), and vancomycin (OR, 1.9; 95% CI, 1.0–3.5; $p = 0.0439$). Exposure longer than 7 days to cefepime ($p = 0.0006$), piperacillin/tazobactam ($p = 0.0021$), and imipenem/cilastatin ($p = 0.0171$) also increased risk for development of CDI.

CONCLUSION: The use of cefepime, imipenem/cilastatin, piperacillin/tazobactam, and vancomycin and the use of multiple classes of antibiotics for at least 7 days significantly increased the risk of CDI in surgical inpatients. (*J Trauma.* 2012;72: 691–695. Copyright © 2012 by Lippincott Williams & Wilkins)

KEY WORDS: *Clostridium difficile* infection; antibiotics; surgical patients; nosocomial infection.

Clostridium difficile may be found in 1% to 3% of all healthy adults and 15% to 25% of individuals with recent healthcare exposure, often without clinical disease. There now is an epidemic in the incidence and severity of *C. difficile* infection (CDI), partly due to more invasive strains and increased antimicrobial resistance.[1–3] The incidence in North America and Europe of the surgical intervention for colectomy has increased over the past 10 years because of complications of pseudomembranous colitis, toxic megacolon, and colonic perforation.[2]

CDI is a unique institutional infection that occurs almost entirely in patients who have received previous antimicrobial treatment. The use of broad-spectrum antibiotics or the use of two or more antibiotics in combination has been suggested to increase the risk of CDI.[4] Data suggest that antibiotic exposure disrupts normal gastrointestinal flora, enabling spores of toxigenic *C. difficile* to colonize the colon and produce toxins able to cause disease.[5] Agents that are active against anaerobic bacteria (other than *C. difficile*) are thought to present the greatest risk because of their ability to alter intestinal flora.[5] Identifying specific antimicrobials that are most strongly associated with the development of CDI in vivo may help surgeons select appropriate agents and guide antimicrobial stewardship programs.

Evidence suggests that specific antibiotic classes including lincosamides (clindamycin), broad-spectrum penicillins, cephalosporins, and fluoroquinolones may increase the risk of developing CDI.[6] Clindamycin had a strong correlation for developing CDI in the 1970s, but its use has decreased in North America and Europe resulting in a reduction in attributable risk of antibiotic-associated diarrhea and CDI.[6] As time progressed into the late 1980s and 1990s, broad-spectrum penicillins (e.g., ampicillin/sulbactam) and second- and third-generation classes of cephalosporins (e.g., cefotetan) became the agents with the highest relative risk and highest attributable risk because of frequent use in hospitals.[7] In the early 2000s, the newest class of antibiotics to be associated with increased risk of CDI was the fluoroquinolones (e.g., levofloxacin).[8–10] The changing epidemiology and the development of the new NAP1/BI/027 strain resulted in *C. difficile* isolates with a high resistance to fluoroquinolones and an increasing risk of developing a CDI.[11]

Several potential risk factors have been studied for CDI. Antibiotic use has been studied; however, evidence is not clear regarding a specific antibiotic or antibiotic class as almost all antibiotics have been implicated as risk factors for CDI in hospitalized patients, including metronidazole. It is still not clearly understood which antibiotics are important in surgical patients based on other risk factors that may be present.[4] Duration of antibiotic exposure has also been studied, but findings were varied as CDI was reported after

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prolonged antibiotic exposure by a meta-analysis,[12] brief surgical antimicrobial prophylaxis,[13,14]and also not reported after extended prophylaxis.[15]Antisecretory medications such as histamine 2 receptor antagonists (H2RA) and proton pump inhibitors (PPI) decrease gastric acidity and theoretically increase the survival of *C. difficile* by inhibiting this host defense mechanism.[16]

The primary objective of this study was to determine whether a specific antibiotic is independently associated with increasing the risk of CDI in hospitalized surgical patients to better guide surgeons in selecting specific antibiotic therapy. Secondary objectives included to determine the effect of duration of antibiotic exposure, exposure to multiple antibiotics and multiple classes of antibiotics, serum albumin, and the use of antisecretory medications for development of CDI.

PATIENTS AND METHODS

This study used a retrospective case-control design. Patients who were 18 years or older and admitted to the inpatient surgical teams were included at the University of Louisville Hospital from January 1, 2008, to July 31, 2009. Case patients developed a positive *C. difficile* toxin A or B assay more than 48 hours after admission on diarrheal stool, whereas control patients did not have a positive stool for *C. difficile* toxin assay documented. Patients with diarrhea are routinely checked for *C. difficile* toxin because of a recent outbreak in the hospital, whereas those without diarrhea are not.[17] Control patients were excluded if they did not receive a course of antibiotics (defined as uninterrupted treatment duration of at least 48 hours). The control group was matched for age and length of stay in a fixed 2:1 ratio. Length of stay in case patients was defined as the duration of time from day of admission to day toxin positive. Patients were excluded if they were younger than 18 years, admitted to nonsurgical teams, or developed a positive *C. difficile* toxin assay within 48 hours of admission. The following parameters were collected and analyzed: antibiotics administered during hospitalization, duration of therapy for each antibiotic, presence or absence of an antisecretory medication (histamine receptor blocker or PPI), and serum albumin. Parameters were collected before positive *C. difficile* toxin for case patients and throughout hospitalization for control patients.

Antibiotics were chosen for comparison if greater than 5% of the study population was exposed to the antibiotic. For the primary analysis, the association between exposure to the antibiotic (dichotomized as yes/no) and case and control status was evaluated. Antibiotic exposure was further stratified into less than 3 days, 3 days to 7 days, and greater than 7 days to determine whether a relationship existed between length of exposure and risk of CDI. Prolonged exposure was defined as antibiotic exposure greater than 7 days. Statistical significance was determined using the χ^2 test for nominal data and the trend test for ordinal data. In addition, estimated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were reported using the control group as a baseline comparison group. All calculations were completed using SAS 9.2 software (SAS, Cary, NC). A p value less than 0.05 was considered statistically significant.

RESULTS

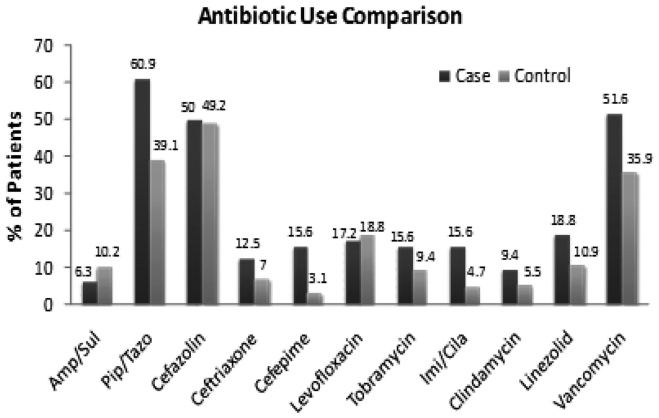
A total of 67 patients with a positive assay for *C. difficile* toxin were analyzed. Three patients were excluded because of a short onset of infection (n = 2) and young age (n = 1). A total of 3,480 surgical patients were identified as possible controls and 124 patients were chosen randomly. The case and control patients were closely matched by sex (66.5% vs. 66.2% males), age (50 years vs. 50 years), and length of stay (13.8 days vs. 14.0 days), respectively. Trauma had the highest proportion of patients in both the case and control groups comprising greater than 50% of the patients, followed by neurosurgeons and general surgeons. Table 1 demonstrates the proportion of case and control patients prescribed three or more antibiotics or antibiotic classes among surgical specialties. Overall, among the case patients, 18 patients tested positive for the toxin assay at 48 hours to 8 days, 22 patients at 8 days to 14 days, 20 patients at 15 days to 30 days, and 4 patients greater than 30 days.

The antibiotics chosen for analysis included the following: ampicillin/sulbactam, piperacillin/tazobactam, cefazolin, ceftriaxone, cefepime, levofloxacin, tobramycin, imipenem/cilastatin, clindamycin, linezolid, and vancomycin. The proportion of use of each antibiotic for case and control patients is shown in Figure 1. This study found that exposure to cefepime, imipenem/cilstatin, piperacillin/tazobactam, or vancomycin, not clindamycin, was associated with statistical significance in surgical patients with CDI as demonstrated in Figure 2. However, only patients with prolonged exposure to cefepime ($p = 0.0006$), imipenem/cilastatin ($p = 0.0021$), and piperacillin/tazobactam ($p = 0.0171$) were more likely to develop CDI in surgical patients.

The analysis was repeated for case patients who fulfilled the national guideline criteria for severe CDI versus the control patients and for those who had mild to moderate CDI versus the control patients.[18] The guidelines define severe CDI as a patient with leukocytosis with a white blood cell count greater than 15,000 cells/mL^3 or a serum creatinine greater than or equal to 1.5 times the premorbid level. An increased risk was associated with exposure to imipenem/cilastatin (OR, 5.9; 95% CI, 1.1–32.5; $p = 0.0383$) in patients

TABLE 1. Case and Control Patients Prescribed Three or More Antibiotics and Antibiotic Classes Among the Surgical Specialties

	Three or More Antibiotics Used, n (%)		Three or More Antibiotic Classes Used, n (%)	
	Case Group	Control Group	Case Group	Control Group
Trauma Surgery	30 (67)	32 (49)	30 (67)	28 (43)
Neurosurgery	6 (60)	14 (52)	6 (60)	14 (52)
General Surgery	2 (50)	9 (29)	1 (25)	9 (29)
Plastic surgery	2 (100)	1 (50)	2 (100)	1 (50)
Otolaryngology	0 (0)	1 (33)	0 (0)	1 (33)



Amp/Sul= ampicillin/sulbactam; Pip/Tazo= piperacillin/tazobactam; Imi/Cila= imipenem/cilastatin

Figure 1. Antibiotic use comparison between case and control patients with *C. difficile* infection.

with severe CDI and cefepime (OR, 8.4; 95% CI, 1.7–43.1; $p = 0.0060$) in patients with mild to moderate CDI.

The total number of antibiotics and antibiotic classes patients were exposed to before the development of CDI are shown in Tables 2 and 3, respectively. Case patients received more regimens with three or more antibiotics ($p = 0.0489$) and three or more antibiotic classes ($p = 0.0299$) compared with control patients. Specifically, within this surgical patient population, as antimicrobial therapy was broadened with the addition of a different antimicrobial class, the risk of developing CDI was increased by approximately 1.5 (CI, 1.03- 2.06). Case patients had an average serum albumin of 2.63 versus 3.14 in the controls (OR, 2.62; $p < 0.0001$). Regarding the use of antisecretory medications, the use of a PPI increased the risk for the development of CDI ($p = 0.0071$; OR, 10.8; CI, 1.4–86.4). No significant difference was associated with use of H2RA or the combination of H2RA and PPI.

DISCUSSION

This study provides information about specific antibiotics other than clindamycin that may increase the risk of CDI, whereas previous studies have focused on classes of antibiotics. By evaluating specific antibiotics, this study can be used to guide surgeons to select appropriate antibiotic therapy. A focus on surgical patients provides better generalizability for surgeons as opposed to extrapolating other studies with mixed populations or medical patients alone.

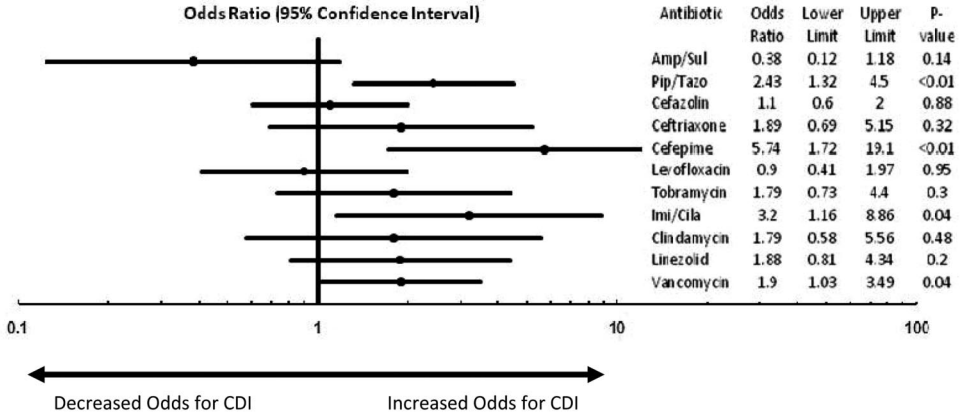
This study found that surgical patients with CDI were more frequently exposed to cefepime, imipenem/cilastatin, piperacillin/tazobactam, and vancomycin. The first three antibiotics are broad-spectrum antibiotics. Vancomycin (intravenous) is for gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA) and is now reported to be associated with CDI for the first time. Finding that the prolonged use of those antibiotics in surgical patients increases risk for CDI supports de-escalating and discontinuing antibiotics when appropriate.

TABLE 2. Number of Antibiotics Used by Case Patients With *C. difficile* Infection Compared With Control Patients

Number of Antibiotics Used	Case Patients, n (%)	Control Patients, n (%)
None	4 (6)	0 (0)
One	8 (12)	44 (34)
Two	12 (19)	27 (21)
Three or more	40 (63)	57 (45)
Total	64 (100)	128 (100)

TABLE 3. Number of Antibiotic Classes Used by Case Patients With *C. difficile* Infection Compared With Control Patients

Number of Classes of Antibiotics Used	Case Patients, n (%)	Control Patients, n (%)
None	4 (6)	0 (0)
One	9 (14)	48 (38)
Two	12 (19)	27 (21)
Three or More	39 (61)	53 (41)
Total	64 (100)	128 (100)



Amp/Sul= ampicillin/sulbactam; Pip/Tazo= piperacillin/tazobactam; Imi/Cila= imipenem/cilastatin

Figure 2. Forest plot with ORs of antibiotic use among case and control patients with *C. difficile* infection.

Contrary to published literature, clindamycin was not associated with increasing the risk of CDI in this surgical patient population. Overall, more of the case patients were exposed to clindamycin compared with the control patients, but the difference was not statistically significant. However, the use of clindamycin has declined in North America, thus CDI rates associated with clindamycin have declined respectively.[6] The association between vancomycin and CDI may has been enhanced for the opposite reason; its use has increased over the past 2 decades for empiric therapy in nosocomial infections.

Although not addressing specific antibiotics used by surgeons, previous studies have found exposure to multiple antibiotics and antibiotic classes to be associated with an increased risk for development of CDI.[4,18] This study was consistent with these other findings. As clinicians, it is important to select antibiotics based on the type of infection suspected and streamline an antibiotic choice to provide coverage for the most common pathogens while taking into account institution-specific resistance patterns. This process of decreasing exposure to multiple antibiotic and antibiotic classes could help to decrease incidence of developing CDI.

The 2010 Society for Healthcare Epidemiology and Infectious Diseases Society of America CDI Treatment Guidelines reported that a prolonged length of exposure of antibiotics increases the risk of development of CDI based on moderate evidence from clinical trials without randomization.[18] The results of this study are consistent with the guidelines as the prolonged length of exposure was found to increase risk of CDI. Surgical patients with extended hospitalizations are at risk for nosocomial infections requiring the use of broad spectrum of antibiotics for a prolonged length of exposure.

Previous studies also identified low serum albumin and use of antisecretory medications as potential independent risk factors for CDI.[4,12,16,18] Consistent with existing literature, case patients with CDI had a lower albumin than control patients. However, the question remains whether the low albumin is a marker of patients who are more likely to be susceptible to infection or is a result of the actual disease state of CDI. Previous studies have also found a stronger association with PPI versus H2RA with CDI.[16,18] Complementing existing literature, surgical patients exposed to PPI were more likely to develop CDI, whereas the use of H2RA between cases and controls was not significant.

This study had several limitations as patients were matched by age and length of stay, and there could have been differences in patients' underlying conditions or disease states and immune status affecting their risk of developing CDI. It is possible that a control patient could have had CDI without diarrhea and thus been a false negative. On the other hand, there was a possibility for a false-positive patient in the case group who might have had a relatively recent case of CDI and was no longer diseased, but merely shedding toxin. It is also conceivable that some study patients could have received additional antibiotics at a transferring facility or outpatient clinic before admission. Any of these factors may have potentially affected the risk of developing CDI in a patient.

The importance of consistent infection control practices must be included among any efforts to minimize patient risk of developing a nosocomial infection, including CDI as 6% of the case patients were not exposed to any antibiotics within the previous 30 days. This allowed for the possibility of transfer of *C. difficile* from an infected to a noninfected patient.

Surgical patients with CDI more frequently had a history of the use of cefepime, imipenem/cilastatin, piperacillin/tazobactam, and vancomycin and also had a history of prolonged exposure and length of exposure to multiple classes of antibiotics. Based on these findings, surgeons should be prompted to assess appropriateness based on specific antibiotic choice, the use of multiple antibiotics, and length of therapy. As sources of infection are identified, this study suggests to de-escalate antimicrobial therapy to an appropriate antibiotic selection, dose, and duration as clinically indicated to reduce the risk of developing CDI.

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DISCLOSURE

The authors declare no conflicts of interest.

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