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Identification of Risk Factors for the Development of *Clostridium difficile*-Associated Diarrhea Following Treatment of Polymicrobial Surgical Infections

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Abstract

Objective—To identify risk factors for *Clostridium difficile*-associated diarrhea (CDAD) in surgical patients following treatment of polymicrobial infections.

Summary Background Data—Infections among surgical patients are frequently anaerobic or mixed aerobic-anaerobic infections and are therefore subject to polymicrobial antibiotic coverage, including metronidazole. While multiple antibiotics are known to contribute to the development of CDAD, the role of preventive antibiotics is unproven.

Methods—An 11-year dataset of consecutive infections treated in surgical patients at a single hospital was reviewed. All intra-abdominal, surgical site, or skin/skin structure infections were identified. Each infection was evaluated for antibiotic coverage and subsequent CDAD. Antibiotic usage was assessed using χ^2 analysis. A multiple logistic regression was used to identify independent predictors of CDAD.

Results—A total of 4178 intra-abdominal, surgical site, or skin/skin structure infections were identified. Of these infections, 98 were followed by CDAD. Only carbapenem use affected the incidence of CDAD: 3.5% of infections treated with a carbapenem were followed by CDAD, whereas only 2.1% of infections treated without carbapenems were followed by CDAD ($P = 0.04$). Metronidazole had no association with future CDAD. Only age and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were independently associated with CDAD by multiple logistic regression analysis.

Conclusions—Older patients with a high severity of illness are at greatest risk for developing CDAD following treatment of polymicrobial infections. No specific antibiotic class, including fluoroquinolones, is associated with an increased incidence of CDAD in this population. Although use of metronidazole in the treatment of polymicrobial infections is appropriate for anaerobic coverage, it does not reduce the risk of future CDAD.

The United States has experienced a recent rise in the incidence of *Clostridium difficile*-associated diarrhea (CDAD).^{1–6} Much of this rise is thought to be attributable to a new, more virulent strain of *C. difficile*.³ This strain, restriction-endonuclease analysis group BI

and North American Pulse Field Gel Electrophoresis type 1 (BI/NAP1), has been associated with an increasing morbidity and mortality among hospitalized patients who have developed CDAD since 2001, and has also been implicated in CDAD among otherwise healthy persons in the community.^{3,7-10} Both surgery and advanced age are risk factors for hospital-associated CDAD, making the problem especially pertinent to surgeons.^{4,11-13} Of equal importance, the Centers for Medicare and Medicaid Services has threatened to add CDAD to the list of healthcare-associated conditions for which Medicare will no longer pay at a higher weighted Medicare severity diagnosis-related group.¹⁴

Prevention of CDAD is of paramount importance and predicated on understanding and mitigating the risk factors associated with its development. Exposure to penicillins, clindamycin, and cephalosporins has classically conferred the greatest risk of CDAD development,^{11,15,16} while advanced age, increased exposure to *C. difficile* spores, and decreased immunity are commonly described host-derived risk factors.^{4,11-13,17} Other risk factors have more recently emerged including exposure to fluoroquinolones^{8,18-21} and proton-pump inhibitors.^{20,22} The role of certain antibiotics in lessening CDAD risk is less well defined.^{2,23} Specifically, the use of a CDAD therapeutic agent (metronidazole or vancomycin) during treatment of other infections to prevent the development of symptomatic CDAD has been employed despite the absence of guidelines or documented evidence supporting this approach²³; it can be reasonably inferred that the use of metronidazole to treat infections with a potential anaerobic component may have preventive effects against subsequent CDAD.

Infections among surgical patients, including intra-abdominal, surgical site, and skin/skin structure infections, are frequently anaerobic or mixed aerobic-anaerobic infections and are therefore subject to polymicrobial antibiotic coverage, including metronidazole. Accordingly, we sought to identify risk factors for CDAD development in surgical patients following treatment of polymicrobial infections. Specifically, we hypothesized that those patients treated with metronidazole would be at lower risk for subsequent *C. difficile* infection.

METHODS

Study Design

A prospective cohort of all adult general surgery and trauma surgery patients admitted to the University of Virginia Hospital and treated for any infection between December 1996 and September 2007 was reviewed. Institutional Review Board approval was obtained prior to initiation of data review and the need for informed consent was waived due to the observational nature of the study.

During the 11-year study period, data were collected prospectively until patient death or hospital discharge. Additionally, data were collected if patients previously treated for any infection on the surgical services were subsequently readmitted to the hospital with any new infection, including CDAD. Data were obtained by every other day chart review, by patient examination, physician interview, and review of pharmacy, laboratory, and microbiologic data. Variables recorded at study entry included age, gender, patient-defined race, patient location at time of onset of infection (intensive care unit [ICU], home, hospital ward), preinfection medical comorbidities, and use of blood cell product transfusions (packed red blood cells or platelets). The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was determined at the time of initiation of treatment of infection as a measure of illness severity.²⁴ Infections were defined per the Centers for Disease Control and Prevention²⁵; *C. difficile* infection was confirmed by culture or toxin assay (Enzyme

Immunoassay for toxins A or B) collected for diarrhea. Hospital-acquired infections were those neither documented nor suspected at admission.

The dataset was reviewed to identify all cases ("index infections") likely to be polymicrobial, mixed aerobic-anaerobic infections, including intra-abdominal, surgical site, and skin/skin structure. Surgical site infections included incisional as well as organ/space infections, since deep incisional infections involving the fascia may have an anaerobic component. These index infections were further evaluated to assess their relationship, if any, to subsequent CDAD. *C. difficile* infections were counted if treatment for at least one index infection preceded treatment for *C. difficile* in the same patient. For cases where treatment for the index infection and CDAD were started on the same calendar day, CDAD was not felt to be related to the index infection. CDAD occurring more than 30 days after the end of treatment for an index infection was not included. Additional CDAD episodes in the same patient were included only when preceded by treatment for a new index infection; *C. difficile* relapses, multiple infections with *C. difficile* without the intervening receipt of other antibacterial agents, were not included.

All index infections treated at any time with metronidazole, penicillins, ureidopenicillins, cephalosporins, carbapenems, aminoglycosides, fluoroquinolones, and clindamycin were identified and categorized by occurrence of subsequent CDAD. Penicillins included: penicillin, ampicillin, amoxicillin, nafcillin/oxacillin, dicloxacillin, piperacillin, and mezlocillin. Ureidopenicillins included: amoxicillin/clavulanate, ampicillin/sulbactam, ticarcillin/clavulanate, and piperacillin/tazobactam. Cephalosporins included: cephalexin, cefazolin, cefaclor, cefuroxime, cefoxitin, cefotetan, cefotaxime, ceftriaxone, ceftazidime, cefepime, cefadroxil, and cefpodoxime. Carbapenems included: imipenem, meropenem, and ertapenem. Aminoglycosides included: gentamicin, tobramycin, amikacin, and streptomycin. Fluoroquinolones included: ciprofloxacin, ofloxacin, moxifloxacin, trovafloxacin, levofloxacin, and gatifloxacin. A subgroup analysis was performed for infections treated with fluoroquinolones occurring after January 1, 2001 to assess for changes associated with the changing epidemiology of *C. difficile* (possibly due to BI/NAP1).

Statistical Analysis

Data management and statistical analyses were performed with SAS 9.1.3 (SAS Institute). Demographics and preinfection risk factors were tabulated and reported. Binary categorical variables were compared with χ^2 analysis or Fisher exact test where appropriate; continuous variables were compared using Student's *t* test. Differences in proportions of antibiotic usage between groups were compared using χ^2 analysis. Significance was considered $P \leq 0.05$. To determine risk factors independently associated with CDAD, a multiple logistic regression analysis was performed controlling for significant univariate variables, antibiotic usage, and length of time in the hospital as a measure of potential exposure to pathogens via patient-to-patient transmission.^{12,26,27} Length of time in the hospital equaled patient length of stay for infections not associated with CDAD; for index infections, it was calculated as the time from admission date until initiation of treatment for CDAD.

For analysis, each intra-abdominal, surgical site, and skin/skin structure infection was treated as a separate infection, even if occurring in the same patient. Some CDAD episodes were preceded by more than one infection of interest; in these cases, each preceding index infection was counted as being followed by a single episode of CDAD.

RESULTS

A total of 4178 separate intra-abdominal, surgical site, or skin/skin structure infections were identified between December 1996 and September 2007. Of these infections, 98 (2.3%) were followed by CDAD; as some episodes were preceded by more than one index infection, the total number of CDAD episodes arising in this setting was 79. The group not followed by CDAD consisted of 1967 intra-abdominal, 1406 surgical site, and 707 skin/skin structure infections. The group followed by CDAD was comprised of 65, 22, and 11 intra-abdominal, surgical site, and skin/skin structure infections, respectively.

The demographics, preinfection comorbidities, and APACHE II score recorded for all index infections are listed in Table 1 (unit of analysis equals an infection). Infections followed by CDAD were largely similar to those without subsequent CDAD with respect to demographics and comorbidities. However, those followed by CDAD were more commonly associated with advanced age, preexisting pulmonary disease, prior transfusion, and were more likely to be hospital-acquired (especially in the ICU) and associated with a higher severity of illness, as measured by APACHE II score. The crude, in-hospital mortality was not significantly different between patients with and without subsequent CDAD.

Selected preinfection comorbidities that could have changed since onset of the index infection (ventilator dependence, dialysis dependence, and cell product transfusion), patient location (ward vs. ICU), and APACHE II score were also recorded at the onset of CDAD. Since some episodes of CDAD were preceded by more than one index infection, the denominator for this group was 79. Eleven instances of CDAD (13.9%) occurred among ventilator dependent patients, 5 (6.3%) in dialysis dependent patients, and 36 (45.6%) were preceded by cellular blood product transfusion. Fifty-two cases of CDAD (65.8%) were acquired on the ward, 20 (25.3%) in the ICU, 4 (5.1%) at home, and 3 (3.8%) were acquired in the hospital but not on a surgical ward. At the time of diagnosis, white blood cell count was 13.7 ± 7.3 k/ μ L and APACHE II score was 12.2 ± 6.6 . A total of 10 cases were followed by death for a crude mortality of 12.7% ($P = 0.07$ compared with index infections not followed by CDAD, 7.3% crude mortality).

On average, treatment for CDAD following intra-abdominal, surgical site, or skin/skin structure infections started 13 days (inter-quartile range [IQR], 6–21) after diagnosis of the incident infection. The median length of antibiotic exposure prior to treatment initiation for CDAD was 8.5 days (IQR, 5–14). Forty-three index infections (43.9%) followed by CDAD were treated with more than one antibiotic; 2028 index infections (49.7%) not followed by CDAD were treated with more than one antibiotic ($P = 0.25$). Forty-nine infections (50%) followed by CDAD were still being treated for the original infection at the onset of treatment for *C. difficile*. For those not concurrently treated, the median number of antibiotic free days prior to initiation of treatment for CDAD was 8 (IQR, 4–13).

Among index infections treated with metronidazole ($n = 20$), the median duration of therapy was 9.5 days (IQR, 5–13.5). A median of 12.5 days (IQR, 4–18.5) elapsed between treatment with metronidazole and initiation of treatment for *C. difficile*. Only 3 of these infections were still being treated with metronidazole at the start of CDAD; most (85%), however, were still receiving other antibiotics.

Table 2 presents the proportion of infections treated at any point with different antibiotic classes among each group of index infections (those followed or not followed by CDAD). Only carbapenem use affected the incidence of CDAD; 3.5% of infections treated with a carbapenem went on to develop CDAD, whereas only 2.1% of infections treated without carbapenems went on to develop CDAD ($P = 0.04$). Metronidazole had no association with future CDAD; 2.1% of infections treated with metronidazole went on to develop CDAD,

whereas 2.4% of infections not treated with metronidazole went on to develop CDAD ($P = 0.51$). A separate analysis performed in the subgroup of infections occurring after January 1, 2001 (2654 intra-abdominal, surgical site, or skin/skin structure infections) did not identify a statistical difference in the use of fluoroquinolones between index case groups; 2.0% of infections treated with fluoroquinolones went on to develop CDAD, whereas 2.5% of infections not treated with fluoroquinolones developed CDAD ($P = 0.33$).

Finally, only age (odds ratio [OR], 1.02 [per year]; 95% confidence interval [CI], 1.00–1.03) and APACHE II score (OR, 1.03 [per point]; 95% CI, 1.00–1.06) were independently associated with CDAD development by multiple logistic regression (Table 3). Significant factors associated with the development of CDAD by univariate analysis (Tables 1, 2; $P \leq 0.05$) were included in the final model, including age, APACHE II score, history of pulmonary disease, prior transfusion, location of patient at time of onset of the index infection, and carbapenem exposure. Other antibiotic usage including metronidazole, penicillins, ureidopenicillins, cephalosporins, aminoglycosides, fluoroquinolones, and clindamycin as well as length of time in the hospital were also included based on previously published literature.^{8,11,12,16,18–21,26,28,29} Previous antibiotic exposure, regardless of class, was not predictive of future *C. difficile* infection.

DISCUSSION

Our results are consistent with prior research demonstrating CDAD acquisition to be related to increasing age as well as underlying illness severity. However, unlike previous literature, we did not find any one class of antibiotics to be independently associated with a higher risk of subsequent CDAD when used to treat surgical patients with polymicrobial infections. Additionally, contrary to our hypothesis, the use of metronidazole in these patients did not reduce the incidence of subsequent CDAD and cannot be used as a risk-reduction strategy.

An analysis of the National Hospital Discharge Survey from 1996 to 2003 demonstrated marked variation in CDAD rates among different age groups, with rates in patients ≥ 65 years of age several fold higher than rates in the next youngest age group (45–64 years).⁴ Baxter et al²⁷ demonstrated age to be independently predictive of CDAD (OR, 1.01; 95% CI, 1.02–1.02) among 1142 matched cases of CDAD. Increased exposure to the healthcare system (including both short and long-term facilities), and therefore to *C. difficile* spores, explains at least part of this association. Additionally, recent evidence highlighting the importance of a humoral immune response in the outcome of those colonized with *C. difficile*,^{17,30} suggests that the decreased immune responsiveness commonly observed in older patients is important in the development of CDAD.

Similar to both Kyne et al,¹⁷ and McFarland et al,³¹ who used a modified Horn's index to measure severity of disease, we demonstrated increased odds of developing CDAD as the severity of the index infection, as measured by APACHE II score, increased (per point). Those with severe or extremely severe presenting illness were over 7 times as likely to develop CDAD than those with mild or moderate initial illnesses in Kyne's study¹⁷; extreme severity of the index disease was associated with 5 times the rate of CDAD in McFarland's group.³¹

Despite these similarities, our study does not support previously published studies through which nearly all antibiotic classes, including penicillins, cephalosporins, clindamycin, and recently fluoroquinolones have been associated with CDAD.^{8,11,15,16,18–21} Other studies including Loo et al⁸ have also failed to demonstrate an independent association between clindamycin, aminoglycosides, penicillins, carbapenems, and CDAD. Likewise, a recent case-control study among 16 hospitals in Northern California found no independent

association with CDAD and penicillins (ampicillin, amoxicillin), ureidopenicillins (amoxicillin/clavulanate, ampicillin/sulbactam, piperacillin/tazobactam), aminoglycosides (gentamicin), cephalosporins (cefotetan, cefazolin, cephalexin), and some fluoroquinolones including levofloxacin and ciprofloxacin.²⁷ Among carbapenems, however, this group did find a predictive, independent relationship between CDAD and imipenem-cilastatin only; a subgroup analysis of CDAD occurring between 2003 and 2005 was associated with all carbapenems.²⁷ We found carbapenem usage to be associated with CDAD on univariate analysis, but it did not retain significance as an independent predictor on multivariate analysis. Subgroup analysis may have yielded results similar to Baxter et al,²⁷ suggestive of a change in the susceptibility profile of *C. difficile* over time possibly as a result of changes in the patterns of use of other CDAD-associated antibiotics.

One potential explanation for our data is the fact that all of the index infections studied required some mechanical intervention for cure, be it drainage, resection, or debridement. It is possible that these infections may have a fundamentally different pathogen-host relationship than infections where antibiotics (often fluoroquinolones) are the sole form of treatment, such as pneumonia, bloodstream infections, or urinary tract infections. Since alterations in host immunity may play an important role in the pathogenesis of CDAD,^{17,30} it may be that certain characteristics of the management of intra-abdominal or skin structures infection render the nature of antimicrobial exposure less relevant to the acquisition or growth of *C. difficile*.

Lastly, our evaluation of risk factors in the development of CDAD following treatment of polymicrobial infections failed to identify a protective role of metronidazole. Previously described as “early preventative therapy,” the use of metronidazole during treatment of other infections to prevent the development of symptomatic CDAD has been employed.²³ Similarly, it can be reasonably inferred that the use of metronidazole to treat infections with a potential anaerobic component may have preventive effects against subsequent CDAD. A similar hypothesis was investigated nearly 2 decades ago.³² Gerding et al compared treatment of intra-abdominal infections with amikacin/clindamycin to amikacin/metronidazole and found significantly lower rates of both *C. difficile* disease and colonization among patients in the metronidazole group. However, these results are not surprising given the comparison group and the known risk of CDAD associated with clindamycin use.²⁹

Several possibilities exist to explain why metronidazole given for therapy is not protective against subsequent CDAD. One, *C. difficile* spores are not eradicated by metronidazole treatment; thus, although bactericidal for vegetative *C. difficile*, spores remain following treatment.³³ Although concurrent metronidazole use could be effective against vegetative *C. difficile*, spores could remain after treatment cessation. Prior to recolonization of the normal intestinal flora, these spores could germinate and facilitate CDAD. Two, preventive use of metronidazole in patients without CDAD is unlikely to either completely eradicate *C. difficile* (or toxin) or lead to bactericidal levels of metronidazole within the intestinal tract. McFarland et al have reported the presence of vegetative *C. difficile* cells, as well as toxin, in stool specimens collected after metronidazole treatment.^{33,34} Johnson et al studied asymptomatic, hospitalized *C. difficile* carriers and found a 10-day course of metronidazole was ineffective in eliminating *C. difficile* excretion. In fact, fecal levels of metronidazole were low or absent.³⁴ Other studies have also demonstrated undetectable levels of fecal metronidazole in healthy volunteers while bactericidal levels have been shown in those with acute CDAD.^{35,36} Lastly, the most plausible explanation is that the disruption of intestinal microflora incited by concurrent antibiotic therapy outweighs any potential benefit of metronidazole administration. Metronidazole does not help to replenish nor prevent disruption of colonic microflora and is ineffective at completely clearing *C. difficile*. Those

who go on to develop CDAD do so regardless of metronidazole use, a mechanism potentially mediated via the host immune response, as suggested by others.^{17,30}

Our study does have limitations. Accurately measuring the effects of individual antibiotics is difficult and many index infections were coincident with other infections not evaluated in this study. Specifically, some CDAD was preceded by not only intra-abdominal, surgical site, or skin/skin structure infections, but also by other infections, including pneumonia, urinary tract infections, or blood stream infections. Antibiotic treatment for infections coincident with our index infections may have contributed to CDAD, but would not have been reviewed. Similarly, the number of antibiotic combinations used among the index cases was too great to assess possible interaction effects among different antibiotics.

While our study population limits the generalizability of our results, the patients included are very relevant to practicing surgeons. We can conclude that older patients with a high severity of illness are at greatest risk for developing CDAD following treatment of polymicrobial infections. Contrary to previously published reports, no specific antibiotic class, including fluoroquinolones, appears to be associated an increased incidence of *C. difficile* infection in this population. Additionally, while use of metronidazole in surgical patients with intra-abdominal, surgical site, or skin/skin structure infections is appropriate for anaerobic coverage, it is not effective for CDAD risk reduction. Prevention measures incorporating sound infection control practices must remain at the forefront of our defense against CDAD. Although our study does not support antibiotic class restriction, antimicrobial stewardship (particularly the elimination of unnecessary antimicrobial use and shortening the duration of antimicrobial therapy) will also continue to be instrumental in limiting the evolution of epidemic CDAD.

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TABLE 1

Demographics, Preinfection Comorbidities, and Illness Severity Measures

	Index Infections			P
	Total (N = 4178)	Not Followed by CDAD (N = 4080)	Followed by CDAD (N = 98)	
Gender, n (%)				
Male	2289 (54.8)	2237 (54.8)	52 (53.1)	0.73
Female	1889 (45.2)	1843 (45.2)	46 (46.9)	0.73
Mean age $\pm$ SD	52.9 $\pm$ 15.9	52.8 $\pm$ 15.9	58.6 $\pm$ 15.8	0.0004
Race, n (%)				
White	3407 (81.6)	3325 (81.5)	82 (83.7)	0.58
African American	657 (15.7)	644 (15.8)	13 (13.3)	0.50
Hispanic	56 (1.3)	53 (1.3)	3 (3.1)	0.13
Other	58 (1.4)	58 (1.4)	0 (0.0)	0.23
Preinfection comorbidities, n (%)				
Diabetes	920 (22.0)	899 (22.0)	21 (21.4)	0.89
Cardiac disease	758 (18.1)	739 (18.1)	19 (19.4)	0.75
Hypertension	1471 (35.2)	1428 (35.0)	43 (43.9)	0.07
Peripheral vascular disease	186 (4.5)	183 (4.5)	3 (3.1)	0.80
Cerebral vascular disease	138 (3.3)	134 (3.3)	4 (4.1)	0.57
Renal insufficiency*	236 (5.7)	230 (5.6)	6 (6.1)	0.84
Dialysis dependence	274 (6.6)	270 (6.6)	4 (4.1)	0.32
Pulmonary diagnosis	455 (10.9)	438 (10.7)	17 (17.4)	0.04
Ventilator dependence [†]	335 (8.0)	327 (8.0)	8 (8.2)	0.96
Active malignancy	534 (12.8)	519 (12.7)	15 (15.3)	0.45
Hepatic insufficiency	258 (6.2)	254 (6.2)	4 (4.1)	0.38
Chronic steroid use	828 (19.8)	803 (19.7)	25 (25.5)	0.15
Psychiatric diagnosis	337 (8.1)	330 (8.1)	7 (7.1)	0.73
IBD	255 (6.1)	252 (6.2)	3 (3.1)	0.20
Previous transplant	634 (15.2)	616 (15.1)	18 (18.4)	0.37
Cell product transfusion [‡]	880 (21.1)	844 (20.7)	36 (36.7)	0.0001
Location at time of index infection, n (%)				
Home	2303 (55.1)	2275 (55.8)	28 (28.6)	<0.0001
Hospital ward	1281 (30.7)	1233 (30.2)	48 (49.0)	<0.0001
ICU	432 (10.3)	416 (10.2)	16 (16.3)	0.05
Other	162 (3.9)	156 (3.8)	6 (6.1)	0.28
Mean WBC count, k/ μ L	14.3 $\pm$ 8.1	14.2 $\pm$ 8.0	15.3 $\pm$ 10.0	0.31
Mean APACHE II score	11.2 $\pm$ 7.2	11.2 $\pm$ 7.2	14.1 $\pm$ 7.3	<0.0001
Died, n (mortality)	308 (7.4)	297 (7.3)	11 (11.2)	0.14

Binary categorical variables compared with χ^2 analysis or Fisher exact test where appropriate; continuous variables compared using Student's *t* test.

* Baseline serum creatinine >2.0 mg/dL.

[†] Before infection.

[‡] Packed red blood cells or platelets transfused before initiation of treatment for infection.

TABLE 2

Univariate Analysis of Index Infections and CDAD by Antibiotic Exposure

Antibiotic, n (%)	Index Infections		P
	Not Followed by CDAD (N = 4080)	Followed by CDAD (N = 98)	
Metronidazole	949 (23.3)	20 (20.4)	0.51
Penicillins*	304 (7.5)	6 (6.1)	0.62
Ureidopenicillins [†]	1845 (45.2)	40 (40.8)	0.39
Cephalosporins [‡]	1025 (25.1)	22 (22.5)	0.55
Carbapenems [§]	607 (14.9)	22 (22.5)	0.04
Aminoglycosides [¶]	199 (4.9)	7 (7.1)	0.34
Fluoroquinolones ^{//}	1506 (36.9)	33 (33.7)	0.51
Clindamycin	308 (7.6)	4 (4.1)	0.20

Comparison of proportions performed using χ^2 analysis.

* Penicillin, ampicillin, amoxicillin, nafcillin/oxacillin, dicloxacillin, piperacillin, mezlocillin.

[†] Amoxicillin/clavulanate, ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam.

[‡] Cephalexin, cefazolin, cefaclor, cefuroxime, cefoxitin, cefotetan, cefotaxime, ceftriaxone, ceftazidime, cefepime, cefadroxil, cefpodoxime.

[§] Imipenem, meropenem, ertapenem.

[¶] Gentamicin, tobramycin, amikacin, streptomycin.

^{//} Ciprofloxacin, ofloxacin, moxifloxacin, trovafloxacin, levofloxacin, and gatifloxacin.

TABLE 3

Logistic Regression Analysis of Risk Factors Associated With CDAD Acquisition in Surgical Patients Following Treatment of Polymicrobial Infections

Risk Factor	Odds Ratio	95% CI	P
Age (per yr)	1.02	1.00–1.03	0.02
APACHE II (per point)	1.03	1.00–1.06	0.05
Pulmonary diagnosis	1.52	0.87–2.63	0.14
Cell product transfusion	1.38	0.81–2.36	0.24
Location at time of index infection			
Home	0.46	0.18–1.18	0.11
Ward	1.30	0.53–3.23	0.57
ICU	0.94	0.34–2.62	0.99
Metronidazole	0.86	0.50–1.50	0.60
Penicillins*	0.82	0.35–1.94	0.66
Ureidopenicillins [†]	0.91	0.59–1.40	0.65
Cephalosporins [‡]	0.88	0.53–1.46	0.61
Carbapenems [§]	1.33	0.80–2.24	0.29
Aminoglycosides [¶]	1.51	0.66–3.46	0.33
Fluoroquinolones ^{//}	0.99	0.62–1.56	0.96
Clindamycin	0.54	0.19–1.50	0.23
Length of time in hospital (per d)	0.99	0.98–1.00	0.21

c statistic = 0.71.

* Penicillin, ampicillin, amoxicillin, nafcillin/oxacillin, dicloxacillin, piperacillin, mezlocillin.

[†] Amoxicillin/clavulanate, ampicillin/sulbactam, ticarcillin/clavulanate, piperacillin/tazobactam.

[‡] Cephalexin, cefazolin, cefaclor, cefuroxime, cefoxitin, cefotetan, cefotaxime, ceftriaxone, ceftazidime, cefepime, cefadroxil, cefpodoxime.

[§] Imipenem, meropenem, ertapenem.

[¶] Gentamicin, tobramycin, amikacin, streptomycin.

^{//} Ciprofloxacin, ofloxacin, moxifloxacin, trovafloxacin, levofloxacin, and gatifloxacin.