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Epidemiology, risk factors, and outcomes of *Clostridium difficile* infection in kidney transplant recipients

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Abstract

Background—We sought to describe the epidemiology and risk factors for *Clostridium difficile* infection (CDI) among kidney transplant recipients (KTR) between 1 January 2008 and 31 December 2010.

Methods—A single-institution retrospective study was conducted among all adult KTR with CDI, defined as a positive test for *C. difficile*, by a cell cytotoxic assay for *C. difficile* toxin A or B or polymerase chain reaction test for toxigenic *C. difficile*.

Results—Among 603 kidney transplants performed between 1 January 2008 and 31 December 2010, 37 (6.1%) patients developed CDI: 12 (of 128; 9.4%) high-risk (blood group incompatible and/or anti-human leukocyte antigen donor-specific antibodies) vs. 25 (of 475; 5.3%, $P=0.08$) standard-risk patients. The overall rate of CDI increased from 3.7% in 2008 to 9.4% in 2010 ($P=0.05$). The median time to CDI diagnosis was 9 days, with 27 (73.0%) patients developing CDI within the first 30 days after their transplant, and 14 (51.8%) developing CDI within 7 days. A case-control analysis of 37 CDI cases and 74 matched controls demonstrated the following predictors for CDI among KTR: vancomycin-resistant *Enterococcus* colonization before transplant (odds ratio [OR]: 3.6, $P=0.03$), receipt of an organ from a Centers for Disease Control high-risk donor (OR: 5.9, $P=0.006$), and administration of high-risk antibiotics within 30 days post transplant (OR: 6.6, $P=0.001$).

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Conclusions—CDI remains a common early complication in KTR, with rates steadily increasing during the study period. Host and transplant-related factors and exposure to antibiotics appeared to significantly impact the risk for CDI among KTR.

Keywords

Clostridium difficile; kidney transplant

Nosocomial *Clostridium difficile* infection (CDI) is a significant problem that has worsened with the emergence of the NAP1/BI/027 (binary toxin) strain (1–7). Advanced age, antibiotic use, and immunosuppression (both acquired and inherited) are established risk factors that make hospitalized patients susceptible to CDI (1–7). Solid organ transplant (SOT) patients are a high-risk patient population for CDI because of their immunosuppressive regimens and increased frequency and duration of hospitalizations. The incidence of CDI among SOT recipients has ranged between 1.74% and 7.9% (8–10). Recent data on the incidence, timing, and risk factors for CDI among kidney transplant recipients (KTR) are lacking. This information is pertinent to the management and outcome optimization of these high-risk patients. We sought to review the epidemiology, timing, and outcomes of CDI and assess risk factors of CDI among KTR between 1 January 2008 and 31 December 2010.

Methods

Study design and patient population

The study was approved by the Institutional Review Board of the Johns Hopkins Hospital and was performed as part of a Quality Assessment and Performance Improvement project. In this retrospective study, all adult (age ≥ 18 years) patients that received a kidney transplant between 1 January 2008 and 31 December 2010 were identified using the database system of the Comprehensive Transplant Center (of the Johns Hopkins Hospital). Transplant recipients with a diagnosis of CDI, who were admitted to the same ward exclusively caring for kidney (and liver) transplant recipients during the study period, were identified by review of the databases of the Hospital Epidemiology Infection Control and the Comprehensive Transplant Center. Patients with CDI from day –7 of transplant to 6 months after transplantation were included. To specifically study risk factors for CDI among KTR, patients with CDI during the study period were identified as cases and were matched 1:2 to controls (no evidence of CDI) by day of transplant (± 3 days).

Immunosuppression and prophylactic regimen

All KTR at our institution receive induction immunosuppression, as per type-dependent protocol. Maintenance immunosuppression includes prednisone, tacrolimus, and mycophenolate mofetil (MMF). On occasion, based upon clinical indications, sirolimus rather than tacrolimus is used. Human leukocyte antibody (HLA) incompatible (positive crossmatch) KTR receive alternate-day plasmapheresis and 100 mg/kg of intravenous hyperimmune globulin (Cytogam, Medimmune, Inc., Gaithersburg, Maryland USA) before transplantation to remove donor-specific anti-HLA antibody, and quadruple-drug immunosuppression (daclizumab, tacrolimus or sirolimus, MMF, and steroids) as previously described (11, 12). Patients with persistent donor-specific antibody may additionally receive anti-CD20 antibody therapy or/and splenectomy. Blood group incompatible live donor KTR receive an anti-interleukin-2r antibody therapy.

Routine preoperative antibiotics, including cefazolin or vancomycin (for penicillin-allergic patients), are administered to all patients. *Pneumocystis* prophylaxis is initiated immediately

post transplant with trimethoprim-sulfamethoxazole (TMP/SMX) and continued for 6 months; atovaquone or dapsone may be used in patients with a history of allergic reaction to sulfa drugs or other reasons, as deemed suitable by the treating physicians. Prophylaxis against cytomegalovirus (CMV) with ganciclovir or valganciclovir is initiated post transplant and continued for 3 and 6 months for CMV-positive recipients and CMV-positive donor/CMV-negative recipients, respectively. Antifungal prophylaxis consists of clotrimazole troches for 30 days post transplant. All patients receive gastric prophylaxis with either a proton pump inhibitor or a histamine-2 blocker.

Clinical variables

The following host variables were collected for all patients: demographics, comorbidities (diabetes mellitus, coronary artery disease, liver disease), type and number of prior organ transplants, underlying disease leading to transplant, surveillance cultures for vancomycin-resistant *Enterococcus* (VRE) upon admission, and hospital and intensive care unit (ICU) days within the first 30 days post transplant. History and years of renal replacement therapy (hemodialysis or/and peritoneal dialysis) before kidney transplant were recorded. The following laboratory variables were collected: serum creatinine on days 1 and 7 post transplant, peak WBC count, and nadir absolute lymphocyte count within the first 30 days post transplant. Administration of high-risk antibiotics during the first 30 days post transplant and the number of days of antibiotic administration were recorded (13, 14). Transplant-related variables included the following: day of transplant, induction and maintenance immunosuppression regimens, transplant risk (standard vs. high-risk, defined as blood type or/and HLA incompatible donor-recipients), and donor status (deceased vs. live donor, related vs. unrelated live donor, Center of Disease Control [CDC] high-risk vs. not), and donor and recipient CMV serology status (15).

CDI-related variables included the diagnostic test used, presence of fever (temperature $>38.3^{\circ}\text{C}$), toxic megacolon, transfer to the ICU, treatments administered, and recurrent disease. Radiologic reports were evaluated for the presence of colonic distention, colonic wall thickening, pericolic fat stranding, and ascites. Physician notes and the electronic medical record were evaluated for the results of colonoscopies or flexible sigmoidoscopies.

Definitions

CDI was defined as a positive stool sample for *C. difficile*. Testing for *C. difficile* included a cell cytotoxic assay for *C. difficile* toxin A or B (until 1 October 2009) or a polymerase chain reaction (PCR) targeting the toxigenic *C. difficile* toxin B gene, thereafter. Recurrent CDI was defined as a new CDI episode at least 14 days after the completion of treatment for the primary CDI event (16). Severe CDI was defined by the presence of toxic megacolon, colitis requiring colectomy, or admission/transfer to the ICU because of CDI. High-risk antibiotics were defined as anti-pseudomonal penicillins, third- and fourth-generation cephalosporins, carbapenems, fluoroquinolones, and clindamycin (13, 14). Blood group incompatible and/or positive crossmatch KTR were defined as high-risk transplants.

Statistical analysis

Among the overall population of KTR between 2008 and 2010, rates of infection were calculated by dividing the number of patients who developed CDI over the total number of transplants performed in the cohort year. A test for linear trend was used to compare differences in rates of infection by year of transplant. Two-sided *P*-values of ≤ 0.05 were considered significant. Time to CDI after transplant was calculated using the first post-transplant episode of CDI. Using the case-control study population sample, we sought to identify risk factors for CDI among KTR. Variables that had a *p* value <0.10 in the univariate analyses were introduced into a stepwise multivariate logistic regression model to

assess risk factors. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented for all logistic regression analysis results. Statistical analyses were performed using Stata software v 11.1 2010 (StataCorp, College Station, Texas USA).

Results

Rates and timing of CDI

A total of 603 kidney transplants (475 standard and 128 high-risk) were performed at our institution between 1 January 2008 and 31 December 2010. The overall rate of CDI among all KTR was 6.1% (37 of 603). A trend was seen for more high-risk KTR to develop CDI (12 of 128; 9.4%) compared with standard KTR (25 of 475; 5.3%, $P=0.08$). The rate of CDI increased from 3.7% (6 of 161) in 2008 to 9.4% (19 of 201, $P=0.05$) in 2010 among all KTR. This increase was mainly driven by higher yearly rates of CDI among standard-risk KTR, from 2.4% (3 of 125) in 2008 to 10.6% (16 of 151) in 2010 ($P=0.002$; Fig. 1). The rates of CDI among high-risk KTR remained high, but relatively stable, during the study period.

The median time to CDI diagnosis was 9 days post transplant (range: -6, 338) for all KTR. Notably, 27 (73.0%) patients developed CDI within the first 30 days after their transplant, and 14 (51.8%) of them within the first 7 days post transplant (Fig. 2). Recipients who received a transplant from a related donor appeared to develop CDI later (median: 170.9 days, range: 3, 338) compared with unrelated-donor KTR (median: 9 days, range: -6, 123, $P<0.001$). No significant differences were seen in timing to CDI diagnosis based on the kidney transplant risk status or other transplant related variables (alive vs. deceased, CDC high-risk donor vs. not; data not shown).

Case-control study

Of the 603 KTR, 37 CDI cases and 74 matched controls were included in the case-control analysis. Demographics and clinical characteristics of the patients are described in Table 1. More cases were colonized with VRE (43.2% vs. 17.6%, $P=0.004$) and had longer hospital (mean: 20.6 vs. 13.8 days, $P<0.001$) and ICU stay (mean: 3.1 vs. 1.5 days, $P=0.005$). Transplant variables differed between cases and controls, with more cases having received a transplant from a deceased (73.0% vs. 52.7%, $P=0.04$) or CDC high-risk donor (40.5% vs. 14.9%, $P=0.003$) and anti-thymocyte globulin for induction (97.3% vs. 83.8%, $P=0.02$). A greater proportion of case patients had received intravenously administered vancomycin (75.7% vs. 18.9%, $P<0.001$) and 1 high-risk antibiotic agents (83.8% vs. 44.6%, $P=0.007$) compared with controls. One case and 2 controls had a diagnosis of CDI 2 years and 3 and 5 months, respectively, before their transplant.

Independent variables studied to identify risk factors for CDI in univariate analyses are presented in Table 2. When variables with $P \leq 0.10$ were introduced in a stepwise multivariate logistic regression model, the major predictors for CDI among KTR were the following: prior VRE colonization (OR: 3.6, 95% CI: 1.1, 11.3, $P=0.03$), CDC high-risk donor (OR: 5.9, 95% CI: 1.7, 20.8, $P=0.006$), and administration of high-risk antibiotics (OR: 6.6, 95% CI: 2.1, 21.0, $P=0.001$).

Clinical presentation of CDI and treatment

Three (of 37, 8.1%) patients had a fever and 2 required admission to the ICU attributed to CDI. One of these 2 patients had evidence of toxic megacolon. None of the patients with CDI in this series had a colonoscopy. Owing to the retrospective nature of the study, we were not able to collect data on the presence and severity of diarrhea on these patients. A white blood cell (WBC) count $> 20,000$ cells/mm³ was observed in 9 (24.3%) patients. Most

patients with CDI were lymphopenic with a mean absolute lymphocyte count of 96.6 cells/mm³. The majority of patients (32, 86.5%) were treated with a single agent: 27 (of 32, 84.4%) with oral vancomycin and 5 (16.6%) with metronidazole (either intravenously or orally). Among 32 patients treated with oral vancomycin, 20 and 12 patients were administered 250 mg and 125 mg 4 times daily, respectively. Five (13.5%) patients were treated with combination therapy including orally administered vancomycin and metronidazole (either orally or intravenously). The median duration of treatment was 15 days (range: 10–42). Only one patient received treatment with intravenous hyperimmune globulin.

Among 37 patients with CDI, 4 (10.8%) were diagnosed with another CDI episode at a median time of 235.5 days (range: 27–307). All KTR with CDI were alive by 6 months after their CDI diagnosis.

Discussion

Our observations suggest that CDI remains a common early complication in a contemporary cohort of KTR, with rates steadily increasing during the study period. The higher rates of CDI observed among KTR and the overall hospital patient population (personal communication with Hospital Epidemiology and Infection Control) during the study period may, in part, be related to the more sensitive test (PCR) used for the diagnosis of CDI that was implemented after October 2009. PCR testing may lead to more false-positive diagnoses of CDI, as a positive stool test for *C. difficile* by PCR may imply CDI or simply colonization with *C. difficile*, depending on the setting. In fact, the majority of CDI cases in KTR were diagnosed within 30 days (half of them within a week) after their transplant. It is likely that some of them (i) might have acquired *C. difficile* in the past, from multiple exposures to the healthcare setting for renal replacement therapies or other complications of their underlying disease before their admission, or (ii) they did not have CDI, but their diarrhea was rather a result of other causes, including medications (e.g., MMF, antibiotic-related diarrhea) or other infections. Colonization with *C. difficile* has been described in healthy outpatients, hospitalized patients, and patients in long-term care facilities at rates up to 1–2%, 10–30%, and 10–30%, respectively (17–23). Hence, we hypothesize that a subset of patients may already be colonized with *C. difficile* coming in for their transplant. The impact of *C. difficile* asymptomatic colonization on the risk for active disease should be further studied in prospective studies.

High-risk KTR, defined as ABO or/and HLA incompatible, appeared to have the highest rates of CDI, averaging 11.5% during the study period. This finding may, in part, be related to the higher degree of immunosuppression required for these patients. Recent data suggest that B-cell immunity, particularly immunoglobulin-G response to toxin A, is crucial to contain CDI (24, 25). In addition to their profound T-cell suppression, some of these high-risk kidney recipients received B-cell suppressing agents, including rituximab, daclizumab, or/and plasmapheresis. Moreover, these patients may require more frequent and longer hospitalizations for post-transplant complications, such as rejection, increasing their exposure to the healthcare environment and risks for acquiring *C. difficile*. Notably, the incidence of CDI among high-risk KTR did not change during the study period, perhaps, in part, as a result of healthcare personnel being more careful when caring for sicker, more immunosuppressed patients, and applying infection control practices in a stricter way.

As previously reported, administration of high-risk antibacterial agents was the most significant predictor of CDI in KTR (26–28). Colonization with VRE before a kidney transplant was another significant predictor for CDI in this cohort, as previously described in hematopoietic stem cell transplant recipients (28). Notably, in a review of 18 case-control

studies, similar risk factors, including antimicrobial exposure, number of antimicrobials, days of antimicrobial use, and specific agents (third-generation cephalosporins, clindamycin, and imipenem) were identified for both VRE infection/colonization and CDI (27). It is likely that VRE colonization may, in part, represent a surrogate marker of underlying disease severity and exposure to healthcare system, both leading to higher risks for CDI. Receipt of an organ from a CDC high-risk donor was a strong predictor for CDI. This may, in part, be attributed to the status of patients who are more willing to accept an organ from a high-risk CDC donor, including patients at high risk of death or with poor quality of life on dialysis (28, 29).

KTR are administered medicines with potential bone marrow toxicity (e.g., MMF, TMP/SMX, or ganciclovir) that may prevent them from mounting a high WBC count. In fact, only a minority of patients (9; 24.3%) had a WBC $< 20,000$ cells/mm³. Another potential explanation of the lower WBC counts observed in this series may be the fact that a number of patients were colonized with *C. difficile*, rather than having disease. In fact, only 1 patient had severe CDI, presenting with toxic megacolon and requiring colectomy and transfer to the ICU in this series. In total, 10.8% of KTR with CDI had a CDI relapse, consistent with relapse rates in general hospitalized population and data from hematopoietic stem cell transplant recipients (30).

This was a retrospective 3-year observational study with inherent limitations, including the small sample of patients and limited data availability. The definition of CDI was based on a positive stool test rather than established guidelines (31). Owing to the retrospective nature of this study, we were not able to collect more specific information about the consistency and frequency of stools to accurately define diarrhea. Finally, disparities in patient follow-up (e.g., closer monitoring of high-risk kidney transplants) and thus more frequent CDI testing may explain some of the differences in CDI rates among kidney transplant types.

Overall, we report a 6.1% incidence of CDI among KTR, with ABO or/and HLA incompatible kidney transplants demonstrating the highest rates of CDI. The early diagnosis of CDI in the majority of KTR raises concerns about *C. difficile* colonization on admission. The impact of the latter on the development of active disease after exposure to conditioning agents and preoperative antibacterial therapy early post transplant remains to be defined. Prospective studies to identify colonized patients pre-transplant and associated risks for active disease may improve our understanding of the natural history of this infection and enable the development of preventive strategies in the future.

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Fig. 1.

Rates of *Clostridium difficile* infection (CDI) -calculated by number of CDI cases/number of kidney transplant per year, among all (standard and high-risk) kidney transplant recipients between 1 January 2008 and 31 December 2010. *P*-values were calculated with the chi - square test for 1) all kidney ($P=0.05$), 2) standard risk kidney ($P=0.002$), and 3) high-risk kidney transplant recipients ($P=0.4$) with CDI between 2008 and 2010.

Fig. 2.
Time to diagnosis of *Clostridium difficile* infection (CDI) for all kidney transplant recipients between 1 January 2008 and 31 December 2010.

Table 1

Characteristics of kidney transplant recipients with (cases) and without (controls) *Clostridium difficile* infection(CDI)

Variables	Cases N=37 (%)	Controls N=74 (%)	P value
Host variables			
Demographics			
Gender, Female	12 (32.4)	36 (48.6)	0.8
Ethnicity, Caucasian	14 (37.8)	40 (54.0)	0.1
Age (mean; range)	50.9 (18–75)	49.1 (18–77)	0.1
Comorbidities			
Diabetes mellitus	28 (75.7)	58 (78.4)	0.7
Cardiovascular disease	6 (16.2)	19 (25.8)	0.2
Liver disease	7 (18.9)	12 (16.2)	0.7
VRE colonization on admission	16 (43.2)	13 (17.6)	0.005
Prior transplant, Kidney	11 (29.7)	11 (14.9)	0.07
Renal replacement therapy prior to transplant ¹	31 (88.6)	49 (73.1)	0.08
Years of renal replacement therapy (mean, range)	4.8 (0–32)	2.9 (0–12)	0.07
Transplant-related variables			
High-risk ²	12 (32.4)	17 (23.0)	0.3
Donor, Deceased	27 (73.0)	39 (52.7)	0.04
Donor, Related	9 (24.3)	5 (6.8)	0.1
Donor, CDC high-risk ²	15 (40.5)	11 (14.9)	0.004
Immunosuppression, Induction			
Thymoglobulin	36 (97.3)	62 (83.8)	0.02
Monoclonal antibodies ³	10 (27.0)	20 (27.0)	1.0
Immunosuppression, Maintenance			
Corticosteroids	37 (100)	72 (97.3)	0.3
Tacrolimus	35 (94.6)	73 (98.6)	0.2
Mycophenolate mofetil	37 (100)	72 (97.3)	0.3
CMV status			0.5
Recipient +	25 (67.6)	48 (64.9)	
Donor +/Recipient –	6 (16.2)	8 (10.8)	
Other variables			
Number of inpatient days ^{*,4} , (mean; range)	20.6 (7–30)	13.8 (2–30)	<0.001
Number of ICU days ^{*,4} , (mean; range)	3.1 (0–15)	1.5 (0–7)	0.0009
Laboratory findings			
Diagnostic test for CDI, PCR	31 (83.8)	NA	
Creatinine (mg/dL), day 1, (mean; range) ⁵	8.7 (2.3–23.5)	7.4 (1–16.8)	0.15
Creatinine (mg/dL), day 7, (mean; range) ⁶	3.9 (0.2–15.1)	2.8 (0.2–12.8)	0.08

Variables	Cases N=37 (%)	Controls N=74 (%)	P value
Peak WBC (cells/mm ³), (mean; range)	18696 (7530–77500)	15520 (6970–34030)	0.06
Nadir ALC (cells/mm ³), (mean; range) ⁷	96.6 (0–480)	285.6 (0–2220)	0.02
High risk antibiotics ^{4,8}			
Antipseudomonal penicillins	13 (35.1)	19 (25.7)	0.3
Cephalosporins 3rd-4th generation	6 (16.2)	8 (10.8)	0.4
Carbapenems	6 (16.2)	5 (6.7)	0.11
Vancomycin (intravenous)	28 (75.7)	14 (18.9)	<0.001
Fluoroquinolones	15 (40.5)	16 (21.6)	0.04
Clindamycin	3 (8.1)	5 (6.7)	0.8
Number of high-risk antibiotics ⁴ , 1 agents	31 (83.8)	33 (44.6)	0.007
Days to CDI diagnosis post transplant (median; IQR)	9 (25.2)	NA	
Mortality at 6 months post CDI	0	6 (8.1)	0.03

* Based on the early occurrence of CDI, number of inpatient and ICU days were not included in the multivariate logistic regression analysis.

¹ Data on renal replacement therapy prior to transplant were available for 35 and 67 cases and controls, respectively.

² High-risk kidney transplants: blood type or/and HLA incompatible donor-recipient transplants. High-risk CDC were defined based on (28, 29).

³ Monoclonal antibodies included daclizumab, basiliximab, rituximab, and eculizumab. Patients could have received more than of these agents.

⁴ From day of transplant (day=1) to 30 days post transplant.

⁵ Data on creatinine on day 1 were available for 36 and 74 cases and controls, respectively.

⁶ Data on creatinine on day 7 were available for 35 and 71 cases and controls, respectively.

⁷ Data on ALC nadir were available for 36 and 73 cases and controls, respectively.

⁸ High-risk antibiotics included anti-pseudomonal penicillins, third- and fourth-generation cephalosporins, carbapenems, fluoroquinolones, and clindamycin (13, 14).

VRE, vancomycin-resistant *Enterococcus*; ICU, intensive care unit; CDI, *Clostridium difficile* infection; CMV, cytomegalovirus; NA, not applicable; WBC, white blood cell count; ALC, absolute lymphocyte count; HLA, human leukocyte antigen; CDC, Centers for Disease Control and Prevention.

Table 2
Results of univariate and multivariate analyses for risk factors for *C. difficile* colitis

Variables	Univariate analysis			Multivariate analysis		
	OR	P-value	95%CI	OR	P-value	95% CI
Demographics						
Age, vs. <50 years (ref: <50 years)	1.1	0.79	0.5, 2.5			
Gender, Male vs. female (ref: female)	1.9	0.11	0.9, 4.5			
Race, Caucasian vs. other (ref: other)	1.9	0.11	0.8, 4.3			
Host-related variables (ref: No)						
Diabetes mellitus (Yes vs. No)	1.2	0.75	0.4, 2.9			
Coronary artery disease (Yes vs. No)	1.9	0.21	0.7, 5.3			
HCV+ (Yes vs. No)	1.2	0.72	0.4, 3.4			
VRE colonization ¹ (Yes vs. No)	3.6	0.005	1.5, 8.7	3.6	0.03	1.1, 11.3
Prior transplant (Yes vs. No)	2.4	0.07	0.9, 6.3			
History of hemodialysis (Yes vs. No)	2.8	0.08	0.9, 9.2			
Transplant-related variables						
Donor, Alive vs. deceased (ref: deceased)	0.4	0.04	0.2, 0.9			
Donor, Unrelated vs. related (ref: related)	3.4	0.12	0.7, 16			
Donor, High-risk CDC vs. no (ref: no) ²	3.9	0.004	1.5, 9.8	5.9	0.006	1.7, 20.8
Standard vs. high-risk transplant (ref: standard) ²	1.6	0.29	0.7, 3.9			
Other						
Administration of high-risk antibiotics ³ , (Yes vs. No; ref: No)	6.4	<0.001	2.4, 17	6.6	0.001	2.1, 21.0
CMV donor/recipient status, D+/R- vs. D-/R- vs. R+ (ref: D+R-)	1.4	0.54	0.4, 4.6			

¹ Pre-transplant.

² High-risk CDC were defined based on (28, 29). High-risk kidney transplants: blood type or/and HLA incompatible donor-recipient transplants.

³ High-risk antibiotics included anti-pseudomonal penicillins, third and fourth generation cephalosporins, carbapenems, fluoroquinolones, and clindamycin (13, 14). One patient might have received >high-risk antibiotics.

OR, odds ratio; CI, confidence interval; HCV+, hepatitis C virus positive; Ref, reference variable; VRE, vancomycin-resistant *Enterococcus* species; CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; D, donor; R, recipient; HLA, human leukocyte antigen.