Implications for vancomycin-resistant *Enterococcus* colonization associated with *Clostridium difficile* infections

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Background: Vancomycin-resistant *Enterococcus* (VRE) colonization of the gastrointestinal tract shares similar risk factors with *Clostridium difficile* infection. We sought to elucidate the prevalence and risk factors of VRE colonization associated with *C difficile* infection.
Methods: All adult inpatients with *C difficile* infection from July 2006 to October 2006 were prospectively evaluated. All *C difficile* toxin-positive stool samples were screened for detection of VRE. Risk factors for VRE colonization were compared in patients with *C difficile* infection with and without VRE colonization.
Results: Of the 158 cases of *C difficile* infection evaluated, 88 (55.7%) involved VRE colonization. Independent risk factors for VRE colonization were admission from long-term care facilities ($P = .013$), dementia ($P = .017$), and hospitalization in the previous 2 months ($P = .014$). No statistically significant difference between *C difficile* infection cases with and without VRE colonization in terms of previous receipt (within 1 month) of antibiotics, including metronidazole and vancomycin, was found on multivariate analysis. *C difficile* infection cases with VRE colonization had a higher prevalence of coinfection with methicillin-resistant *Staphylococcus aureus* ($P = .002$) and *Acinetobacter* spp ($P = .006$).
Conclusion: VRE colonization was associated with >50% of *C difficile* infection cases and with a higher rate of coinfection with multidrug-resistant pathogens. Given the high rate of *C difficile* infection associated with VRE colonization, active surveillance of VRE in patients with *C difficile* infection is reasonable in high-risk settings.
Key Words: *Clostridium difficile*; vancomycin-resistant *Enterococcus*; multidrug-resistant pathogens.

Clostridium diffcile is the most common pathogen associated with nosocomial diarrhea. Numerous studies have identified risk factors for nosocomial colonization or infection by individual multidrug-resistant (MDR) pathogens. Colonization or infection with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), extended-spectrum beta-lactamase-producing gram-negative bacilli, and *Candida* share similar risk factors with *C difficile* infection.[1] Increased frequencies of VRE infection and colonization also has been observed, coinciding with the increased incidence of *C difficile* infection.[2] The reported rate of VRE colonization associated with *C difficile* infection is as high as 41%.[2-4] Little is known about the risk factors for *C difficile* infection and VRE colonization occurring together in the hospital setting, however. The present study was undertaken to determine the prevalence of VRE colonization associated with *C difficile* infection in a single tertiary hospital, and to identify the risk factors associated with VRE colonization in patients with *C difficile* infection.

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MATERIALS AND METHODS

All adult inpatients at a university-affiliated tertiary hospital (Cedars-Sinai Medical Center) with *C difficile* infection between July and October 2006 were prospectively evaluated. All patients had diarrhea (≥3 watery stools in 24 hours and/or abdominal pain) and a positive *C difficile* toxin result (Meridian Premier Toxins A&B, Meridian Bioscience, Cincinnati, OH). All

stool samples with a positive *C difficile* toxin were screened for VRE colonization using vancomycin screening agar (BD Diagnostic Systems, Sparks, MD). VRE detection was routinely performed for *C difficile* toxin–positive samples in accordance with the institutional infection control policy. We excluded patients with recurrent *C difficile* infection. A patient was considered to have had a recurrence if within 1 month before the initial diagnosis, (1) there was recurrence of diarrhea, (2) an additional specimen was positive for *C difficile* toxin, or (3) the attending physician ordered a second course of treatment for *C difficile*. Other exclusion criteria were no diarrhea (or <3 episodes of diarrhea/day), other causes of colitis including inflammatory bowel disease (IBD), discharge without receiving treatment for *C difficile* infection, recurrent *C difficile* infection, age <18 years, outpatient, and ileostomy. This study was approved by the Cedars-Sinai Medical Center's Institutional Review Board.

Data collection

Patients' demographic characteristics and laboratory data (eg, complete blood count, electrolytes, blood urea nitrogen, creatinine, glucose, total protein, albumin, total bilirubin, aspartate aminotransferase, alanine aminotransferase, arterial blood gases, lactate, amylase, lipase, imaging studies) were collected on the day of detection of a positive *C difficile* toxin. Laboratory data, clinical symptoms, and antibiotic treatment (including treatment for *C difficile* infection) were recorded by one of the authors (S.F.) on days 1, 3, 7, 10, and 14 or until the patient was discharged before day 14.

The following risk factors for VRE colonization/infection were collected: exposure to any antibiotics within the previous 1 month, receipt of a proton pump inhibitor or H2 blocker on the day of collection of a positive *C difficile* toxin, gastrointestinal or other surgery within the previous 2 months, admission source, serious underlying illness, conditions that compromise immunity (eg, human immunodeficiency virus infection, neutropenia, chemotherapy, therapy with prednisone 10 mg/day for more than 1 month), altered mental status, history of hospitalization within the previous 2 months, tube feeding, and use of narcotics or antiperistaltic agents.

Any treatments for *C difficile* infection (eg, metronidazole oral or intravenously [IV], vancomycin oral only, a combination of metronidazole oral or IV and vancomycin oral, IV immunoglobulin, cholestyramine) were recorded. The following outcome indicators were recorded: disposition (ie, death, discharge, or transfer to another facility), need for surgery, other interventions (eg, gastrointestinal procedures, paracentesis), hospital length of stay (LOS), intensive care unit LOS, laboratory findings (peak white blood cell count, peak percentage of bands, and peak creatinine level during the 7 days after the initial diagnosis). Fisher's exact test and the χ^2 test were used for categorical variables. The Mann-Whitney test was used for continuous variables, using the StatFlex 6.0 statistical software program (Artec, Osaka, Japan). Variables with a P value of <.20 on univariate analysis were candidates for multivariate analysis, using binary logistic regression.

Definitions

Nosocomial *C difficile* infection was defined as the onset of diarrhea ≥48 hours after admission. Recurrent cases were considered unique episodes of *C difficile* infection at least 1 month after the first positive *C difficile* toxin. The Centers for Disease Control and Prevention (CDC) definition, which has been published but not validated,[5-7] was used to describe severe *C difficile* infection. Severe *C difficile* infection was defined as the presence of any of the following within 30 days after the diagnosis of *C difficile* infection: (1) admission to an intensive care unit due to complications associated with *C difficile* infection; (2) surgery for toxic megacolon, large bowel perforation, or refractory colitis; and (3) death attributed to *C difficile* infection within 30 days after symptom onset.[5-7] Day 0 was defined as the day on which *C difficile* infection was initially diagnosed.

Multidrug resistance was defined as resistance to 3 or more classes of antibiotics (beta-lactam antibiotics, including carbapenems, quinolones, and aminoglycosides). Infection with an MDR pathogen within 2 weeks of the diagnosis of *C difficile* infection was considered to represent coinfection with *C difficile*. Cases of MDR infection were determined based on CDC criteria and excluded cases deemed to be colonization or contamination and cases documented by infectious disease specialists.

The patients were classified into two groups, VRE-colonized [VRE(+)] and not VRE-colonized [VRE(−)].

RESULTS

A total of 158 cases of *C difficile* infection were analyzed. Ten patients had 2 episodes of *C difficile* infection during the study period, which were counted as unique cases. VRE colonization was detected in 88 cases (55.7%) (Table 1); the rate remained almost the same when the 10 patients with 2 *C difficile* infections were excluded (56.1%; 83/148). Univariate analysis identified the following significant risk factors for *C difficile* infection associated with VRE colonization: a history of *C difficile* infection (P = .019), direct admission from a long-term care facility (LTCF) or a skilled nursing