Prevention and Treatment of *Clostridium difficile*-Associated Diarrhea in Solid Organ Transplant Recipients

Stephanie M. Pouch, MD, MS*, Rachel J. Friedman-Moraco, MD

KEYWORDS

• *Clostridium difficile* infection • Solid organ transplant • Prevention • Infection control • Antimicrobial stewardship • Treatment • Fecal microbiota transplant

KEY POINTS

- *Clostridium difficile* infection is a significant cause of morbidity and mortality in solid organ transplant recipients.
- Antimicrobial stewardship and infection control are the mainstays of *C difficile* infection prevention.
- Novel approaches to primary and secondary prevention of *C difficile* infection are on the horizon but require formal evaluation in the solid organ transplant population.
- Fecal microbiota transplantation is a promising treatment modality for *C difficile* infection in solid organ transplant recipients.

INTRODUCTION

Clostridium difficile is among the most frequently encountered nosocomial pathogens and is associated with significant morbidity, mortality, and excess health care expenditures.[1–4] Compared with other patient populations, solid organ transplant (SOT) recipients are disproportionately affected by this pathogen; reported rates of posttransplant *C difficile* infection (CDI), defined as diarrhea with evidence of *C difficile* toxin, toxigenic *C difficile*, or pseudomembranous colitis,[5] are as high as 30%.[6] The estimated incidence of CDI varies by organ transplanted, but ranges from 1.5% to 7.8% in kidney-pancreas recipients, 3% to 19% in liver recipients, 3.5% to 16.0%

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Division of Infectious Diseases, Emory University School of Medicine, 101 Woodruff Circle, WMB #2101, Atlanta, GA 30322, USA
* Corresponding author.
E-mail address: spouch@emory.edu

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in kidney recipients, 8% to 15% in heart recipients, 9% in intestinal recipients, and 7% to 31% in lung recipients.[6,7] SOT recipients may be at higher risk for adverse outcomes related to CDI, including fulminant colitis and death, than immunocompetent hosts[8,9] Further, CDI has also been associated with allograft loss in SOT recipients.[10]

The incidence of CDI after SOT is greatest within the first 3 months of transplantation, likely owing to frequent hospitalization, increased exposure to antimicrobials, and receipt of induction immunosuppression.[6,7,11] Although antimicrobial use is the most significant risk factor for CDI acquisition,[6] up to 25% of patients have no history of antibiotic exposure during the month preceding CDI.[12,13] This discordance may be explained by other characteristics that have been associated with disruption of the intestinal microbiome and are common in SOT recipients, such as advancing age, uremia, gastrointestinal surgery, severity of underlying disease, and the use of gastric acid-suppressing medications.[14] Additional potential risk factors for CDI unique to SOT recipients include hypogammaglobulinemia, retransplantation, use of antithymocyte globulin and prophylactic ganciclovir, and receipt of corticosteroids before transplantation.[6,7,11,13,15,16]

The incidence and potential for significant adverse outcomes among SOT recipients with CDI highlight the evolving need for strategic CDI risk factor modification and novel approaches to disease management in this patient population. This review focuses on current concepts related to the prevention and treatment of CDI in SOT recipients.

PREVENTION OF *CLOSTRIDIUM DIFFICILE* INFECTION IN SOLID ORGAN TRANSPLANT RECIPIENTS

The prevention of CDI among SOT recipients requires interdisciplinary engagement between transplant physicians, nurses, pharmacists, infection control, the microbiology laboratory, environmental services, information technology, and hospital administration.[14,17] To date, strategies for CDI prevention have largely focused on antimicrobial stewardship and reduction of horizontal *C difficile* transmission within the inpatient setting; however, immunization and therapeutics targeted toward the maintenance of a diverse intestinal microbiome are being studied as potential prophylactic approaches. As with other patient populations, the mitigation of other risk factors, including the use of gastric acid suppressants, is also essential.

Antimicrobial Stewardship

Because antibiotic exposure remains the most significant modifiable risk factor for CDI, antimicrobial stewardship programs (ASPs) are pivotal to CDI prevention and recommended in the most recent Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) CDI guidelines.[5] ASPs aim to coordinate "interventions designed to improve and measure the appropriate use of [antibiotic] agents by promoting the selection of the optimal [antibiotic] drug regimen including dosing, duration of therapy, and route of administration."[18] Interventions, including formulary restriction, prospective audit and feedback, use of antibiotic time-outs, and provider education, aim to improve patient outcomes and antibiotic susceptibility rates and optimize the use of resources.[18] Several recent studies have shown that implementation of ASPs, particularly those that limit the use of broad-spectrum or high-risk antibiotics such as fluoroquinolones, cephalosporins, and clindamycin, decrease the incidence of CDI by as much as 48%.[19–21]

Most academic medical centers performing SOT procedures within the United States have active institutional ASPs.[22] However, although SOT recipients likely benefit from facility-wide stewardship efforts, the efficacy of transplant-specific antimicrobial