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Special Article

Clostridium difficile Infections in Solid Organ Transplantation

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Abbreviations: ABHR, alcohol based hand rubs; CDI, *Clostridium difficile* infection; ELISA, Enzyme-linked immunosorbent assay; GDH, glutamate dehydrogenase; IVIG, intravenous immunoglobulin; NAAT, nucleic acid amplification test; NAP1, North American pulsed field gel electrophoresis type 1; PPI, proton-pump inhibitors; SOT, solid-organ transplant.

Clostridium difficile infection (CDI) is a commonproblem encounteredin solid-organ transplant (SOT) recipients and the incidence is increasing. SOT recipients have an incidence of CDI that is higher than other postoperative patients, and this group has several unique risk factors that may contribute to more severe disease. Recent publications in nontransplant patients have indicated that treatment choices should be based on the severity of the illness (1). Although there continues to be a lack of well-designed, randomized, controlled trials to support the management decisions that must be made for SOT recipients with CDI, the available evidence is reviewed and summarized for these treatment guidelines.

Epidemiology and Risk Factors

Clostridium difficile is a spore-forming, anaerobic, Gram-positive bacillus. It causes 6–25% of cases of antibiotic-associated diarrhea, up to 75% of antibiotic-associated colitis, and over 90% of cases of antibiotic-associated pseudomembranous colitis (1). *C. difficile* causes inflammatory diarrhea and colonic mucosal injury through production of two exotoxins, toxin A and toxin B, which trigger a cytotoxic response, neutrophilic infiltrate and cytokine release (1). The resulting inflammatory response results in the visible yellow plaques that form the characteristic pseudomembrane. This finding is less commonly seen in patients on immunosuppressive medications (2). Although most strains of *C. difficile* produce both toxins A and B (toxigenic *C. difficile*), some produce only toxin B, and some do not produce any toxin. Strains that produce only toxin B can produce the same spectrum of illness as those that produce both toxins and are considered toxigenic. Strains that do not produce toxins A or B (nontoxigenic) are not capable of causing *C. difficile* infection (CDI). Some *C. difficile* strains also produce a binary toxin; however, what role this toxin plays in humans disease is not known (1). It is also important to note that 50% or more of patients in healthcare settings colonized with toxigenic *C. difficile* never develop CDI (1,3,4). Whether this proportion differs in SOT recipients is not known.

The incidence and severity of CDI have increased dramatically since the year 2000 (5). These changes in CDI epidemiology have been associated with the emergence of the North American pulsed field gel electrophoresis type 1 (NAP1)/restriction enzyme analysis type BI/PCR-ribotype 027 (NAP1/BI/027) strain of *C. difficile* (5). CDI is a more frequently encountered problem in SOT recipients than other hospitalized populations. The incidence of CDI is estimated to be 3–19% in liver recipients, 3.5–16% in kidney recipients, 1.5–7.8% in pancreas–kidney recipients, 9% in intestinal recipients, 8–15% in heart recipients and 7–31% in lung recipients (6,7). This is higher than that seen in other hospitalized patient populations, where the incidence is typically <1% (8,9). Fulminant colitis develops in up to 8% of immunocompetent patients and 13% of SOT recipients with CDI (10). The incidence of CDI in SOT recipients is highest within the first 3 months after the procedure, probably because of more frequent antimicrobial exposure, intense immunosuppression and increased exposure to the healthcare setting (6,10). Late-onset CDI occurs months to years after the transplant and is usually associated with either antimicrobial exposure or intensified immunosuppression to treat graft rejection (10). It is not known how the NAP1/BI/027 strain has impacted the

incidence and severity of CDI in SOT recipients relative to the general hospital population.

Antimicrobial exposure is the most important risk factor for development of CDI (7). Any antimicrobial agent may predispose to CDI, but clindamycin, ampicillin, cephalosporins and fluoroquinolones are most frequently implicated (1). The use of multiple antimicrobial agents and extended treatment courses have also been identified as risk factors (1). Antimicrobial agent administration has been associated with CDI in nearly all immunocompetent inpatients with CDI. However, some studies have found only 80% of transplant recipients who develop CDI have recent antimicrobial exposures (11). The reduced relationship with antimicrobial exposure in SOT recipients may be secondary to alterations in the normal flora and impaired immunity due to immunosuppressive medications, severe pretransplant illness and surgical intervention.

Immune system dysfunction may also be an important factor in the development of CDI in SOT recipients. The importance of the humoral immune response is demonstrated by a fourfold greater incidence of symptomatic disease in patients who are newly infected and lack preexisting immunity (12). A brisk humoral response to *C. difficile* toxins after infection reduces the likelihood of symptomatic disease (13). The hypogammaglobulinemia commonly associated with lung, heart and liver transplants may result in a poor immune response and increase the incidence of CDI by fivefold in some patient subsets (14).

The use of medications that suppress gastric acid, such as proton pump inhibitors and H2 receptor antagonists, is common in SOT recipients and may also serve as a significant risk factor for the development of CDI. The acidic environment of the stomach is usually fatal to vegetative forms of *C. difficile* and may prevent germination of the spore form of the organism. Proton-pump inhibitors (PPIs) may also cause disturbances in the gastrointestinal flora that can allow *C. difficile* to more easily colonize the bowel. However, whether gastric acid suppression plays a causative role in CDI pathogenesis or is a marker for patients at risk for CDI remains unresolved (1). Other risk factors commonly cited in the literature include age greater than 65 years old, severe underlying disease, uremia, gastrointestinal surgery, presence of a nasogastric or endotracheal tube and prolonged hospitalization (15). SOT recipients frequently have a combination of these risk factors.

Of note, infants under the age of 1 are generally not thought to be at risk for CDI; however, asymptomatic carriage of *C. difficile* in this population is common (12). In this population, detection of *C. difficile* or its toxins should not be assumed to be the cause of diarrhea until alternate causes of diarrhea are ruled out.

- Antimicrobial exposure, advanced age, immune system dysfunction or immunosuppression and gastric acid suppression are important risk factors for CDI (II-2).

Diagnosis

CDI is diagnosed by confirming the presence of toxigenic *C. difficile* in the stool of a symptomatic patient. Recent evidence suggests that clinical information is critical when it comes to interpreting *C. difficile* test results, especially if more sensitive assays such as nucleic acid amplification tests (NAAT) are used (16). While SOT patients may have an atypical presentation, their transplant status should not affect diagnostic assays. The laboratory gold standard for *C. difficile* toxin detection in stool is the cytotoxicity cell assay, and the gold standard for detecting toxin producing *C. difficile* is toxigenic culture. Cytotoxicity cell assays detect biologically active toxin in stool. However cytotoxicity cell assays have fallen out of favor because it is relatively labor intensive and the delay of at least 24 h before interpretation (1). Toxigenic culture involves anaerobic culture of *C. difficile* followed by testing isolates for toxin production. It is rarely used for clinical diagnosis due to slow turnaround time and costs. However it is an important tool for epidemiological studies.

According to a 2008 College of American Pathologists survey, 45% of institutions in the United States currently use commercially available ELISAs for *C. difficile* toxin detection (17). These assays provide a rapid turnaround of results and are relatively inexpensive. ELISAs are generally only 60–90% sensitive compared with cytotoxicity assays, though newer assays continue to improve detection rates (18) and may provide better specificity (16). Even with the relatively low sensitivity, the negative predictive value of a negative toxin ELISA is greater than 95%, and repeat testing increases the likelihood of a false positive result. Therefore additional diagnostic and treatment decisions after an initial negative toxin assay should be based on the clinical suspicion of CDI rather than automatically repeating the test (1). It is important to note some ELISAs only detect toxin A. These assays will miss strains that produce only toxin B.

While ELISA may still be a common diagnostic modality for CDI, more hospitals are converting to a two-step algorithm that utilizes new molecular methods (17). Screening stool for the presence of glutamate dehydrogenase (GDH), a common cell wall protein produced by both toxigenic and nontoxigenic *C. difficile*, is the foundation for many of the new protocols. Testing for the presence of GDH allows for rapid and cost-effective screening; however, as GDH does not differentiate toxigenic strains from nontoxigenic strains, subsequent toxin testing is required for those stool specimens that are GDH positive (1). The presence of toxigenic *C. difficile* in GDH positive specimens has been evaluated by several different assays. In addition to the previously mentioned ELISA and cytotoxicity cell assays, NAAT have been evaluated both as a stand-alone test as

well as to confirm the presence of toxigenic *C. difficile* in GDH positive specimens (19). While the sensitivity of using NAAT testing alone for detecting *C. difficile* in stool approaches 93–100% (20,21), the positive predictive value can be as low as 63% for the diagnosis of CDI, and it is the most costly method of diagnosis (16). The low positive predictive value is due to detection of *C. difficile* in asymptomatic carriers. Regardless of what assay or algorithm an individual hospital uses, caution should be employed for only testing patients for whom there is a clinical concern for CDI.

In cases where the presentation of CDI is atypical or the presence of ileus results in a lack of diarrhea, clinicians will need to rely on physical examination and laboratory findings. Fever, abdominal pain and abdominal distension are typically present in severe colitis, even in the absence of diarrhea (1). Striking bandemia and a leukemoid reaction can be seen in SOT recipients with CDI. CT scan findings suggestive of severe colitis include significant bowel wall edema and ascites. These exam and laboratory findings usually precede organ dysfunction. A high index of suspicion for CDI is necessary in SOT patients with these otherwise unexplained exam and laboratory findings.

- Providers should be familiar with the *C. difficile* diagnostic modalities available at their institution and customize their clinical evaluations accordingly (III).
- Testing of stool for *C. difficile* and/or its toxins should only be performed in symptomatic patients who have stool that is not formed (II-2). If the initial ELISA test is negative, testing should be repeated only if there is a high index of suspicion for CDI and if test results will alter clinical management (II-2). Immediate repeat toxin testing is not indicated for cytotoxic tissue assays, GDH based algorithms and NAAT (II-2).
- Test of cure assays (i.e. testing stool for the presence of C diff toxin at the completion of therapy) should be avoided (III).
- Otherwise unexplained fever, abdominal pain and leukocytosis in a patient with ileus should prompt the clinician to consider CDI despite a lack of diarrhea (II-2). The presence of formed bowel movements indicates CDI is unlikely the cause of these symptoms (II-2).

Treatment

Severity of CDI can be divided into three categories: mild-to-moderate, severe and severe with complications (1). Of note, there are no validated methods to objectively categorize patients as such. Mild-to-moderate CDI is typically patients with diarrhea and possibly also with mild abdominal pain and minimal systemic symptoms. Severe CDI includes abdominal pain, leukocytosis and fever or other systemic symptoms along with profuse diarrhea. Advanced age and patients with hypoalbuminemia are at increased risk for severe disease (1). Severe disease with complications includes the symptoms of severe disease accompanied by life-threatening conditions such as paralytic ileus, toxic megacolon, refractory hypotension and/or multi-organ failure secondary to CDI. The disease severity may rapidly progress so clinicians should frequently reassess and adjust therapy accordingly.

The first intervention that should occur in any patient with CDI is cessation of the inciting antimicrobial agent whenever possible. Removing antimicrobial pressure on the normal flora was curative in roughly 15–25% of immunocompetent patients prior to the NAP1/BI/027 epidemic (1). If antimicrobial agents must be continued in order to treat another ongoing bacterial infection, clinicians may consider changing to a more narrow-spectrum regimen or an alternate antimicrobial agent with less association with CDI.

Previously published guidelines support basing the initial antibiotic choice on the severity of CDI (1) (Figure 1). Oral metronidazole is recommended for mild-to-moderate disease in both the general population and SOT recipients. Metronidazole undergoes biliary excretion and crosses the inflamed colonic mucosa so it also reaches adequate levels in the feces when given intravenously. This route of administration has not been rigorously studied, but is supported by several case series (22). There has also been a long-held concern that the use of oral vancomycin will increase the incidence of vancomycin-resistant enterococci, but recent studies have not substantiated this effect (23). A major disadvantage of metronidazole use in SOT recipients is an interaction with medications such as tacrolimus or sirolimus, so that levels of tacrolimus should be monitored during treatment. Readers are referred to the corresponding guidelines on interactions between antiinfective agents and immunosuppressants published in this supplement for further comment.

Oral vancomycin is the preferred therapy for severe CDI. Several studies demonstrated improved response rates with vancomycin compared to metronidazole in severe disease. Two randomized studies found that 85–97% of patients with severe CDI were cured with vancomycin therapy, but only 65–76% of patients were cured with oral metronidazole (24,25). These same studies continue to show no significant difference between the two antimicrobial agents in mild-to-moderate disease (24,25). Vancomycin typically is administered at 125 mg four times daily in adults because higher doses have increased cost and side effects without improved efficacy (26). This regimen achieves stool vancomycin concentrations that are hundreds of times greater than the minimum inhibitory concentration (MIC) of *C. difficile* (27). The usual dose of oral vancomycin for children is 40 mg/kg daily given in three or four divided doses. Many pharmacies now constitute oral vancomycin solution from IV vancomycin with marked cost savings yet no obvious impact in clinical outcomes.

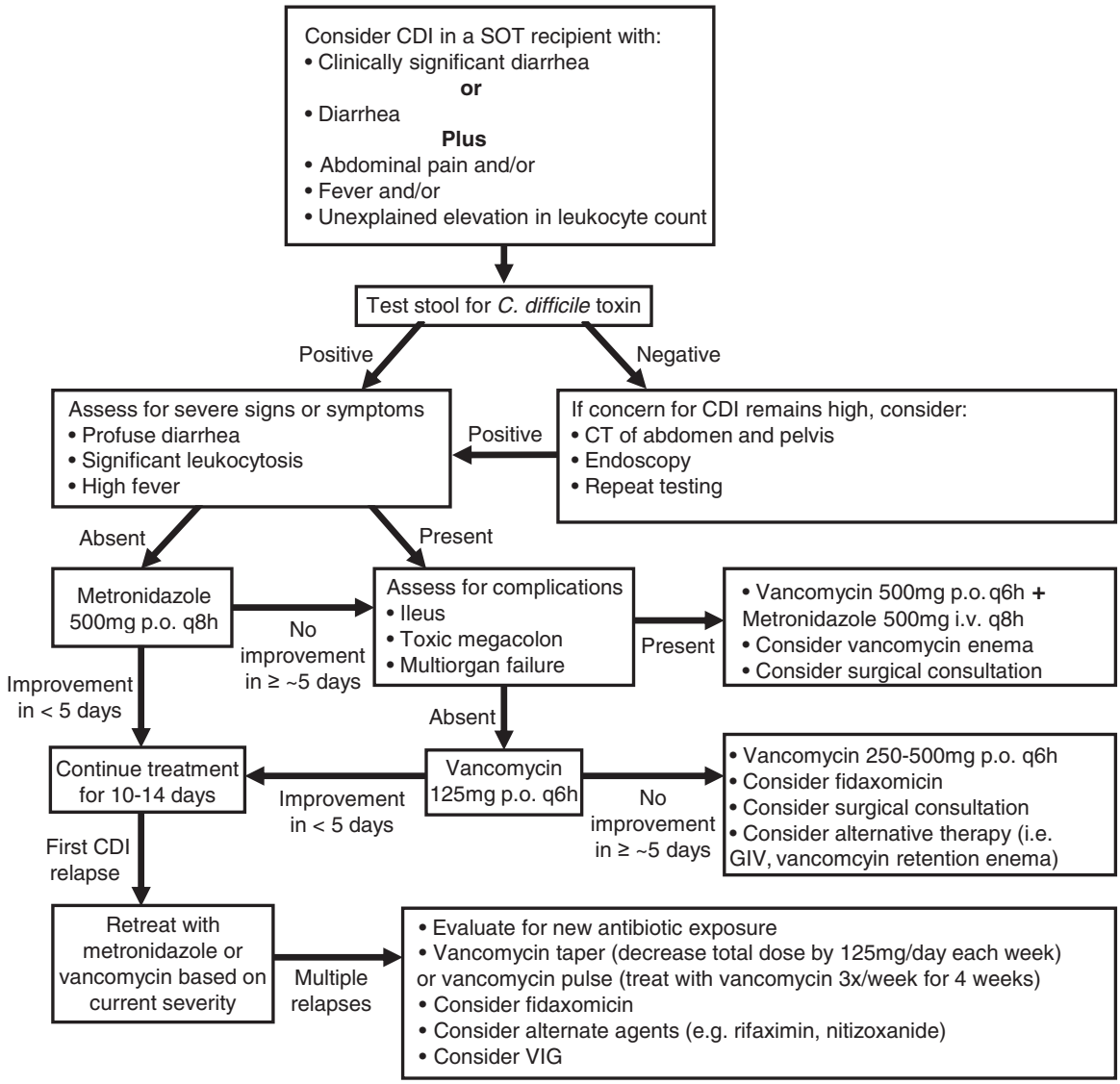

Figure 1: Recommended approach to the diagnosis and treatment of CDI presenting with diarrhea in adult SOT recipients.

In contrast to metronidazole, vancomycin does not reach adequate levels in the feces when given intravenously and should never be administered intravenously to treat CDI.

In 2011, fidaxomicin was FDA approved for the treatment of CDI (28,29). Fidaxomicin is a macrocycline (in the United States it is designated as a macrolid; in Europe as a macrocycle) antibiotic with minimal systemic absorption, high colonic concentrations and limited impact on normal gut flora. It has been evaluated in patients with no or 1 prior episode of CDI. Data reveal similar clinical response, but decreased rates of recurrent infection, as compared with vancomycin 125 mg orally every 6 h (28,29). Limitations to fidaxomicin include drug acquisition costs and lack of data in SOT recipients. One publication did suggest fidaxomicin has improved success rates in patients who are on concomitant antibiotics for other infections compared to vancomycin (30).

In cases of severe CDI with complications, decreased gastrointestinal motility may limit the efficacy of oral vancomycin by preventing the drug from reaching the site of infection. In these patients, 500 mg every 6 h of oral vancomycin may be warranted in an attempt to increase the probability that adequate levels of vancomycin will be achieved in the colon as quickly as possible. Several case reports also support the use of vancomycin administered by retention enema in cases of ileus (31). Novel surgical approaches such as diverting loop ileostomy are being studied though their exact role in the management of complicated CDI is still being determined (32). Bloodstream infections from colonic flora have been reported following

administration of vancomycin enemas so clinicians should exercise caution when considering this approach (31).

Intravenous metronidazole should also be administered with oral vancomycin in an attempt to ensure drug delivery to the site of infection in more severe cases. Antimicrobial therapy alone may be insufficient treatment in patients with severe CDI and surgical intervention may be a necessary addition. Less than 3% of immunocompetent patients with CDI develop fulminant pseudomembranous colitis that requires colectomy; however, colectomy is performed in up to 13% of SOT recipients with CDI (10). Surgical intervention within the first 48 h of a failure to respond to medical therapy, bowel perforation, or multiorgan failure may reduce mortality in patients with severe disease (10). Serum lactate levels and peripheral WBC count may be helpful in determining timing of surgical intervention. Lactate levels rising to 5 mmol/L and WBC count rising to 50 000 cells/μL are associated with perioperative mortality; thus intervention prior to reaching these cut offs should be considered. Patients at higher risk for postoperative mortality include those admitted for a diagnosis other than CDI, mental status changes, and vasopressor support prior to colectomy (33).

Intravenous immunoglobulin (IVIG) has been attempted with variable success in the treatment of CDI. IVIG is known to contain *C. difficile* antitoxin antibodies; but its use is supported only by case studies and series. A retrospective analysis of 18 pair-matched patients with severe CDI did not show any benefit to combining IVIG with standard antimicrobial therapy; however, this study did not control for the time from onset of symptoms to IVIG administration (34). In a retrospective review of heart transplant recipients with hypogammaglobulinemia, a lower incidence of CDI was noted in the patients treated with IVIG (14); however, these results were not statistically significant. At this time, IVIG remains a treatment option that is worth further study, but cannot be broadly recommended.

Twenty- to 30 percent of patients with CDI will suffer at least one recurrence (1). Patients treated with fidaxomicin have demonstrated less episodes of recurrent CDI, though studies to date have not included transplant recipients (29). Treatment of the first recurrence should again be guided by the disease severity as recurrence is not related to the development of antimicrobial resistance to the first course of treatment (1). Management of patients with multiple recurrences has not been thoroughly studied, but there are reports of success with either a prolonged tapering or pulse-dosing schedule of oral vancomycin. Metronidazole should not be tapered or pulsed (1). One suggested regimen for vancomycin tapering is included in Figure 1 and would include the following: after the usual dosage of 125 mg 4 times per day for 10–14 days, vancomycin is administered at 125 mg 2 times per day for a week, 125 mg once per day for a week, and then 125 mg every 2 or 3 days for 2–8 weeks (1). Pulse dosing recommendations include 125 mg every 2 or 3 days for 4 weeks. Studies have demonstrated similar outcomes between tapered dosing and pulse therapy. The hope of both the taper and the pulse therapy is that *C. difficile* vegetative forms will be kept in check while allowing restoration of the normal flora (1).

There has been great interest in the use of adjunctive therapies with conventional antibiotics in order to reduce the frequency of CDI recurrences. Several retrospective studies and case series in patients suffering from recurrent disease have revealed a modest benefit after treatment with IVIG or probiotics (1). Clear benefits have not been reported in placebo-controlled trials probiotics, and IVIG has not been studied with placebo-controlled trials. Probiotic use also carries the risk of superinfection (including bloodstream infections) from the organisms in probiotic formulas, but this complication appears rare (1,35). Fecal flora restoration therapy (e.g. fecal enemas) appears beneficial at preventing relapses in immunocompetent hosts (1). However, similar to recommendations supporting avoidance of probiotics in immunocompromised hosts because of risk of infection, it also appears prudent to avoid fecal flora restoration therapy in SOT recipients given the absence of supportive data in SOT recipients and theoretical potential for infection. Cholestyramine and colestipol have also been investigated as adjunctive therapy in case studies and series since they bind the *C. difficile* toxins *in vitro*, but have demonstrated inconsistent clinical results. Caution should be used when the binding resins are administered in conjunction with vancomycin since cholestyramine has been shown to complex with it *in vitro* and may result in subtherapeutic fecal concentrations in addition to having numerous other drug interactions. A small case series indicates rifaximin may be of benefit to prevent relapses; however there are concerns for the rapid development and dissemination of resistance (36,37).

Patients with confirmed CDI and continued diarrhea despite appropriate therapy should be evaluated for other causes of diarrhea, including coinfection with other pathogens. Parasites such as giardia or cryptosporidium, viral infection with CMV or HSV, bacterial coinfection with Salmonella, Shigella or Campylobacter and noninfectious causes such as laxative use, other concomitant antibiotics, or ischemic colitis may occur concomitantly. Appropriate diagnostic testing should be pursued.

- The first intervention that should occur in any patient with CDI is cessation of the inciting antimicrobial agent whenever possible (II-2).
- For mild-to-moderate CDI, oral metronidazole remains the drug of choice (I). The accepted dose of metronidazole is 500 mg TID for adults and 30–50 mg/kg/day divided TID for pediatric patients (not to exceed adult dosing).
- For severe CDI, oral vancomycin is the treatment of choice (I). The accepted dose of vancomycin is 125 mg

QID for adults and 40–50 mg/kg/day divided QID for pediatric patients (not to exceed adult dosing).
- In cases of severe CDI with complications, the dose of oral vancomycin may be increased up to 500 mg orally QID (III), vancomycin may be administered by retention enema (II-2), and intravenous metronidazole may be added (II-3).
- Surgical intervention should be considered in cases of complicated CDI (II-3).
- Patients suffering from multiple recurrences of CDI may respond to prolonged courses of oral vancomycin, either in a tapering or pulse dose schedule (II-2).
- Role of fidaxomicin in solid-organ transplant recipients is not yet clear.
- There is insufficient evidence to recommend routine use of IVIG (II-2), probiotics (I), or toxin-binding resins (I) in the treatment of initial or recurrent CDI. Probiotics and toxin-binding resins may be potentially harmful due to the risk of bacteremia or reducing the effectiveness of antimicrobial therapy, respectively.

Prevention and Prophylaxis

Prevention of CDI is a multidisciplinary effort, involving infection prevention and control, physicians, hospital administration, nursing, housekeeping, pharmacy and the microbiology laboratory (38). Transplant physicians should play an active role on the hospital CDI prevention team if CDI is problematic in their patients. In addition to infection control measures (discussed below), prevention of CDI must focus on reducing the risk factors for developing the disease in patients that acquire *C. difficile*. The most significant modifiable risk factor for CDI remains antimicrobial exposure, especially to broad-spectrum antimicrobial agents. Many institutions have succeeded in limiting the use of broad-spectrum antimicrobial agents through use of formulary restrictions and antimicrobial stewardship programs. This strategy was effective in reducing the incidence of CDI by 60% when a stewardship program was implemented during the nosocomial outbreak in Quebec (39). Programs that reduced broad spectrum antimicrobial agent use without altering overall antimicrobial use also resulted in significant reductions in the incidence of CDI (39). Other interventions that specifically limit only high-risk antimicrobial agents such as cephalosprins and clindamycin also meet with statistically significant reductions in CDI at many other centers (40).

There is no known effective prophylaxis against *C. difficile*. CDI can be caused by any antimicrobial therapy, including metronidazole and vancomycin, so it is recommended that no antimicrobial agent be given with the intention of preventing the disease. Preexisting colonization with *C. difficile* also appears to be protective against development of CDI after a patient is hospitalized, so the presence of the organism or its toxin in an asymptomatic patient would not be cause for preemptive therapy (41). The use of probiotics as a preventative measure has also had inconsistent success in several small studies, and there are currently no adequate studies that specifically support the use of probiotics as effective prophylaxis against CDI. Vaccines may be beneficial in the future; however vaccine development has not progressed beyond animal and phase II studies at this time.

- Limiting antimicrobial use through formulary restrictions and/or antimicrobial stewardship programs reduces the incidence of CDI (II-3).
- Other modifiable risk factors for the development of CDI, such as gastric acid suppression or prolonged hospitalization, should be reduced if possible (III).

Infection Control Issues

Both strict hand hygiene and appropriate contact precautions are essential in order to limit the spread of *C. difficile* within institutions. Patients with CDI should be placed into contact precautions as soon as possible to limit the spread of *C. difficile*. Contact precautions should be at least until diarrhea resolves, or a few days after diarrhea cessation, and possibly until discharge during outbreaks (38). An area of confusion and controversy when preventing CDI is the preferred method of hand hygiene after caring for a patient with CDI. Alcohol-based hand rubs (ABHR) do not kill *C. difficile* spores and are less effective than soap and water at removing *C. difficile* spores (42). However several studies have failed to demonstrate either an increase in CDI with ABHR or a decrease in CDI with soap and water (38). Conversely, several of these studies did demonstrate a reduction in infections due to other antimicrobial resistant organisms. Currently it is felt ABHR are an adequate form of hand hygiene when gloves are worn when caring for a patient with CDI. However, soap and water should be considered during outbreaks where other measures are not successful at reducing CDI incidence (38). *C. difficile* spores are known to contaminate the environment, are resistant to standard disinfectants, and are capable of surviving for months on dry surfaces within a hospital room. It is not yet clear if routine environmental decontamination with sporicidal agents is necessary, although it is reasonable to consider during disease outbreaks. Whether to use diluted bleach, or a new technology such as UVA or hydrogen peroxide vapor, to kill *C. difficile* spores should be individualized to the institution (38).

- The combination of strict hand hygiene and contact precautions significantly reduces the incidence of CDI through limiting patient acquisition of *C. difficile* (II-3).
- 1:10 dilution of household bleach solutions are sporicidal with $\geq$ 6 log reduction in viable *C. difficile* spores after 10 min contact time and may be used for environmental decontamination during outbreaks (II-3).

Future Research

There are many unknowns with regard to CDI, including the optimal method to diagnose CDI, optimal treatment strategies especially for recurrent and severe CDI with complications, and optimal methods to prevent CDI. This is true for both immunocompetent and immunocompromized patient populations. Studies on CDI diagnosis should include clinical information on the patient, as the detection of *C. difficile* from stool alone does not equate to CDI. Ideally, data on treatments the patient received and outcomes should be included as well. Studies are needed to better stratify severe from nonsevere CDI, with validation that treatment based on this stratification results in improved outcomes. Methods to predict patients at highest risk for CDI recurrence and methods to manage multiply recurrent CDI are needed. Higher quality data are needed to validate our current methods to prevent CDI and to determine if novel prevention approaches are needed.

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Disclosure

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