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Clostridium difficile Infection: New Insights Into Management

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Abstract

Clostridium difficile was first described as a cause of diarrhea in 1978 and is now among the leading 3 hospital-acquired infections in the United States, along with methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. In the past 2 decades, there has been an increase in the incidence, severity, and recurrence rates of *C difficile* infection, all of which are associated with poor outcomes. In addition, several novel risk factors and newer treatment methods are emerging, including fidaxomicin therapy, treatment using monoclonal antibodies, and fecal microbiota transplantation, that have shown promise for the treatment of *C difficile* infection. This review focuses on the changing epidemiology, risk factors, and newer methods for treatment of *C difficile* infection.

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For more than 30 years, *Clostridium difficile* has been recognized as a toxin-producing anaerobic bacterium responsible for antibiotic-associated colitis, and it is now the most common infectious cause of nosocomial diarrhea.[1,2] Despite advances in infection control and newer options for treatment of *C difficile* infection (CDI), there has been a steady and considerable increase in the incidence and severity of CDI, associated with increased morbidity and mortality.[3-6] These changes in CDI epidemiology, attributed in part to an emerging hypervirulent strain of *C difficile*, have been documented in several studies worldwide, which have emphasized the need for improving diagnostic methods and management strategies. Traditionally recognized risk factors for CDI include hospitalization, advanced age, gastrointestinal surgery or procedures, and antibiotic exposure,[7] and novel risk factors have been identified more recently. Outcomes in patients with marked leukocytosis or acute kidney injury (defined as severe CDI) are worse than in those who do not have these laboratory abnormalities, and thus treatment recommendations are stratified according to disease severity. The review discusses the epidemiology, traditional and novel risk factors, and recent advancements in the management of CDI.

EPIDEMIOLOGY OF CDI

The incidence of CDI was stable until the late 1990s but has increased substantially in both hospital and community settings since the early 2000s. Most epidemiologic data for CDI are derived from hospital-based reports and administrative databases such as the US Nationwide Inpatient Sample data and the national mortality data for CDI surveillance.[8-10] In several large epidemiologic studies in the United States, the incidence of hospital-acquired CDI increased by 2- to 2.5-fold from the late 1990s to the early 2000s, and this increase was more pronounced in the elderly.[5,11] A large outbreak of CDI reported from Quebec noted a 4-fold increase in CDI over 13 years, with overall mortality of 6.9%.[6] Germane to the increasing epidemiology is the classification of CID by mode of acquisition. *C difficile* infection is defined as (1) community-acquired if symptom onset occurs in the community or within 48 hours of admission to a hospital, after no hospitalization in the past 12 weeks; (2) hospital-acquired if onset of symptoms occurs more than 48 hours after admission to or less than 4 weeks after discharge from a health care facility[12,13]; or (3) indeterminate if symptom onset occurs in the community between 4 and 12 weeks after discharge from a hospital.[12,13]

Theories that have been advanced to explain the increase in incidence of CDI include changes in the hospitalized patient population (older and sicker patients), changes in antibiotic prescribing patterns (in particular, increased use of newer-generation fluoroquinolones), a new more virulent strain of *C difficile*, potentially novel risk factors (eg, treatment using proton pump inhibitors [PPIs]), and changes in infection control practices (eg, use of alcohol gel hand washes). *C difficile* infection is more common in the elderly, who also are at higher risk of severe or severe-complicated infection. Some of the increase in incidence and severity found in recent reports likely reflects that our population is aging, a statistic that is particularly evident on inpatient wards.

Emergence of Newer "At-Risk" Populations

C difficile infection is now being described in populations who have traditionally been considered at low risk such as children and community dwellers, who lack the usual risk factors.[14] Few population-based studies have described the epidemiology of CDI. In one such study from Olmsted County, Min-

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nesota, a large proportion of cases (41%) were community acquired.[4] In that study, from 1991 to 2005, the overall incidence of community-acquired and hospital-acquired CDI increased by 5.3-fold and 19.3-fold, respectively. Patients with community-acquired CDI were younger, often had no history of recent hospitalization, and had fewer comorbid conditions.[4] Similarly, studies have suggested that CDI is emerging as an increasingly common cause of diarrhea in children, both in the community and in hospitals.[15-20] The largest study of CDI in children was in hospitalized patients and reported that the incidence of CDI increased substantially from 2001 to 2006, from 4.4 to 6.5 cases per 10,000 patient-days.[15] The median patient age was 4 years, and about one-fourth of the patients were younger than 1 year.[15]

The increased incidence of CDI in the community may be due to an increased prevalence of asymptomatic colonizers.[21] *C difficile* can colonize the stool in 1% to 3% of healthy adults and as many as 30% of infants.[22] Additional factors that contribute to an increase in the incidence of community-acquired CDI include more prescriptions for antibiotics, greater use of acid-suppression medications, contamination of processed meat products, more person-to-person transmission, and increased environmental exposure to spores on fomites.[21] Higher clinician awareness of CDI as a possible explanation of diarrhea in the community probably also contributes to the increased incidence through an increase in the number of stool assays ordered in patients with diarrhea.

Emergence of a Hypervirulent Strain

An important consideration in the increasing incidence of CDI is the emergence of a hypervirulent strain of the bacterium, known as ribotype 027, NAP1 (North American pulsed-field gel electrophoresis type 1), or restriction endonuclease analysis group BI. This strain has been isolated from most states in the United States and in several countries in Europe. The hypervirulent strain has a sequence variation in the *tcdC* repressor gene, which results in loss of function of the gene product, a protein that normally suppresses the transcription of toxin A and B genes.[23] Therefore, this *tcdC* sequence variation results in considerably higher levels of toxin production (16-fold increase for toxin A and 23-fold for toxin B), and toxin is produced earlier in the course of *C difficile* infection, in the log-growth phase, whereas nonepidemic strains typically do not produce substantial amounts of toxin until the plateau phase.[24] The emergence of this hypervirulent strain has been associated with increasing incidence, higher recurrence rates, and increased severity and mortality.[6,25,26] Studies that have reported that the hypervirulent strain is associated with increased mortality[27,28] are balanced by studies that fail to show this association.[29,30] In addition, most centers in the community do not have the ability to perform strain typing for *C difficile*, and it remains unclear whether treatment recommendations should be made on the basis of strain information.

ARTICLE HIGHLIGHTS

- *Clostridium difficile* is the most common cause of hospital-acquired diarrhea, with an increasing incidence and severity worldwide.
- A substantial percentage of *C difficile* infections (CDIs) occur in the community in individuals not recently hospitalized or exposed to antibiotics.
- Risk factors for CDI include increasing age, systemic antibiotic therapy, use of proton pump inhibitors, hospitalization, residence in a nursing home or long-term care facility, contact with active carriers, and presence of comorbid conditions.
- Testing and treatment for CDI is not recommended in asymptomatic individuals.
- *C difficile* infection can be complicated by treatment failure, sepsis, need for hospitalization, need for surgery, recurrent infection, and death.
- Treatment of CDI is based on severity and number of episodes of recurrence. In patients with severe infection, oral vancomycin should be the initial treatment of choice.
- New and emerging options for treatment of CDI include fidaxomicin, monoclonal antibodies, and fecal microbiota transplantation.

RISK FACTORS FOR CDI

The traditional risk factors for CDI include antibiotic exposure, hospitalization, and increasing age. It is well known that the normal human colonic flora offers protection against colonization by *C difficile*. Exposure to systemic antibiotics leads to disruption of the normal colonic microbiome and increased susceptibility to colonization and toxin production by *C difficile* and increases the risk of symptomatic CDI by 2- to 16-fold.[31,32] Colonization by *C difficile* in early infancy[33] and in the elderly[34] is accompanied by changes in distal gut microbial composition, and alterations in the gut flora as a result of hospitalization or antibiotic exposure can predispose patients to CDI.[35] Treatment with systemic antibiotics can cause persistent alterations in the gut microbial community in some individuals,[36] which may in turn predispose them to recurrent CDI, a problem of major clinical and economic importance. In addition, post hoc analyses of large randomized clinical trials revealed that in patients who received systemic antibiotic therapy concomitant with treatment of

CDI, time to resolution of diarrhea was longer (97 vs 54 hours; $P<.001$), cure rate was lower (84.4% vs 92.6%; $P<.001$), and there was a trend toward more episodes of recurrence (24.8% vs 17.7%; $P=.06$).[37]

The primary means of transmission of CDI are believed to be person-to-person via the fecal-oral route, through environmental contamination, and transmission via fomites and the hands of health care workers.[38,39] Patients with diarrhea secondary to CDI shed spores into the environment, and these spores are resistant to some disinfectants commonly used in hospitals.[40] Production of antitoxin antibody by the host is considered protective against CDI; however, the ability to mount this immune response decreases with age, which could account in part for the increased incidence, severity, and recurrence in the elderly.

Additional potential risk factors for CDI that have been identified include a higher number of comorbid conditions, inflammatory bowel disease, immunodeficiency, hypoalbuminemia, malignant lesions, solid organ transplant, chemotherapy, and the use of PPIs.[41-46] There is some controversy as to the role of stomach acid suppression in CDI pathogenesis. Recent data have suggested that circumventing the potential protective effect of stomach acid, for example, through the use of postpyloric enteral feeding or the use of PPIs or histamine 2 receptor blockers, may lead to a 2- to 3-fold increased risk of acquisition of CDI.[47,48] However, there is conflicting evidence as to whether stomach acid does or does not kill *C difficile* spores.[49,50] Furthermore, studies have found that after controlling for important confounders, the use of PPIs and histamine^2 blockers was not associated with the risk of CDI[51] or adverse outcomes from CDI.[52] Thus, it is not clear whether use of acid-suppressing drugs is an independent risk factor for CDI,[53] although the US Food and Drug Administration (FDA) has recently issued a warning that PPIs are associated with an increased risk of CDI. A summary of risk factors for CDI is given in Table 1.

TABLE 1. Established and Emerging Risk Factors for *Clostridium difficile* Infection

Age >65 y
Previous hospitalization and prolonged length of hospital stay
Nursing home or long-term care facility residence
Contact with active carriers
Antibiotic exposure
Increased risk with prolonged use or multiple antibiotics
Consumption of processed meat
Previous gastrointestinal surgery or endoscopic procedure
Presence of comorbid conditions
Malignancy and chemotherapy
Cystic fibrosis
Diabetes mellitus
Liver cirrhosis
Chronic kidney disease
Inflammatory bowel disease
Immunosuppression, immunodeficiency, or human immunodeficiency virus
Malnutrition
Hypoalbuminemia
Use of proton pump inhibitors
Solid organ or hematopoietic stem cell transplantation
Presence of gastrostomy or jejunostomy tube

DIAGNOSIS OF CDI

The diagnosis of CDI is made on the basis of a combination of clinical features (typically, abdominal pain and diarrhea) and results of stool tests and, rarely, endoscopy or radiologic tests. Several stool tests are available for CDI including stool culture, stool cytotoxin assay, polymerase chain reaction (PCR), enzyme immunoassay, and stool glutamate dehydrogenase assay.[54] Stool culture for *C difficile* is considered the criterion standard because it is highly sensitive (94%-100%) and specific (84%-100%).[55] However, long turnaround time and high cost limits its use in day-to-day practice. Real-time PCR is considered an alternative criterion standard to stool culture because it has excellent sensitivity and specificity; however, it requires technical expertise and does not enable differentiation between asymptomatic carriage and symptomatic infection. Studies using PCR have found high sensitivity and specificity and test-retest reliability.[56,57] Traditionally, the most commonly used test has been enzyme immunoassay, which is based on antigen detection of toxin A and/or toxin B. Enzyme immunoassay has high specificity but is limited by moderate sensitivity. A detailed review of various strategies for stool tests for CDI is beyond the scope of this review and is available elsewhere.[55,58]

Endoscopy is generally not used in making an initial diagnosis of CDI unless there is a high level of suspicion despite normal results of stool tests or if ileus secondary to CDI is suspected. Endoscopic findings of pseudomembranes are specific but not sensitive for a diagnosis of CDI, and if present, indicate severe infection.

Abdominal radiographs or computed tomographic scans are uncommonly used to make the initial diagnosis. Computed tomographic findings suggestive of CDI include bowel wall thickening, pericolonic stranding, and fold thickening. Radiologic findings of a dilated colon may indicate severe-complicated CDI, and in the presence of severe abdominal pain, leukocytosis, fever, and hypotension likely indicate toxic megacolon.

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IDENTIFICATION OF SEVERE CDI

The spectrum of CDI ranges from mild to severe or severe-complicated. Severe CDI has been defined by the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) as peripheral leukocytosis of 15,000 cells/μL or more or an increase in serum creatinine concentration of 1.5-fold or more above baseline.[13] Severe-complicated infection is defined by hypotension, shock, sepsis, ileus, megacolon, perforation, or death secondary to CDI.[13] Studies have identified additional predictors of severe CDI[59,60] that include increasing age; concomitant antibiotic therapy, narcotic use, and antimotility drug use; hypoalbuminemia; comorbid conditions such as chronic kidney disease; increased number of bowel movements; and the presence of fever or pseudomembranes.[59,61-64] It is important to identify severe or severe-complicated infection because treatment recommendations are made on the basis of disease severity.[13] A summary of risk factors associated with severe CDI is given in Table 2.

TREATMENT OF CDI

General Measures

Patients who are asymptomatic carriers of *C difficile* should not receive treatment because there are no data to suggest that treating these individuals would prevent symptomatic infection or transmission.[13] As for any diarrheal illness, initial therapy should include attention to fluid and electrolyte status, with replacement as necessary. The use of antimotility agents such as narcotics and loperamide in active *C difficile* infection is discouraged because use of these agents may result in more severe colitis. In patients with CDI, unnecessary antibiotic therapy should be discontinued, and if ongoing antibiotic therapy is needed, targeted narrow-spectrum agents should be used. In patients with severe diarrhea and risk factors for CDI such as increasing age, antibiotic exposure, or recent hospitalization, it may be reasonable to initiate empiric antibiotic therapy for CDI while stool test results are pending.

Measures for infection control include strict implementation of isolation precautions with the use of gloves and gowns, hand washing with soap and water, and use of hypochlorite-based agents for environmental disinfection.[7,65] Daily cleaning of hospital rooms using germicidal bleach wipes in wards with a high incidence of hospital-acquired CDI reduces the incidence of CDI and prolongs the time between hospital-acquired CDI cases.[65] Detailed guidelines for infection prevention have been published by the SHEA and IDSA.[13,40]

TABLE 2. Risk Factors for and Predictors of Severe *Clostridium difficile* Infection

Age >65 y
Antiperistaltic or narcotic medication use
Underlying comorbid conditions
Immunosuppressive medication use
Acute kidney injury or chronic kidney disease
Chronic obstructive pulmonary disease
Altered mental status
Fever
Hypotension
Severe abdominal pain and/or distention
Ten or more bowel movements per day
Leukocytosis
Hypoalbuminemia
Ascites
Ileus
Presence of pseudomembranes

Metronidazole and Vancomycin

Metronidazole is an inexpensive, effective, off-label treatment recommended for mild to moderate CDI. The usual dose is 500 mg 3 times a day for 10 to 14 days.[13] Metronidazole has similar efficacy as vancomycin for treatment of mild to moderate CDI.[61] However, there is recent evidence that metronidazole may be less effective against CDI than in the past.[66] From 1991 to 2002 in Quebec, the rate of metronidazole failure was 9.6%; however, during an outbreak in 2003-2004, that rate rose to almost 26%,[66] close to that reported from Houston, where 22% of patients who received metronidazole had continued symptoms after 10 days or more of therapy.[67] Lack of response to initial therapy with metronidazole has been associated with increased mortality.[67] However, at this time, there are no known predictive factors to determine in which patients metronidazole therapy is likely to fail. After adjusting for appropriate confounders, metronidazole may be associated with more complications than vancomycin[6] and more adverse effects including nausea, disulfiram-like reaction when drinking alcoholic beverages, metallic taste, and peripheral neuropathy, and it is not recommended for use in children or in women during lactation or pregnancy.

Oral vancomycin is FDA approved for treatment of CDI but is more expensive than metronidazole. In a study by Zar et al,[61] vancomycin was found to be superior to metronidazole in patients with severe CDI (cure rate of 97% for vancomycin vs of 76% for metronidazole). Factors defining severity in that study included age older than 60 years, tem-

perature higher than 38.3°C, serum albumin concentration less than 2.5 mg/dL, peripheral white blood cell count more than 15,000 cells/μL, presence of pseudomembranous colitis at endoscopy, or treatment in the intensive care unit. Of note, the relapse rate was not considerably different between the 2 treatment groups.[61] Because oral vancomycin is poorly absorbed, a high stool concentration can be achieved without systemic adverse effects. The recommended dose is 125 mg 4 times a day for 10 to 14 days. In patients with severe-complicated CDI (eg, those with hypotension, sepsis, ileus, or megacolon secondary to CDI), the recommended treatment is intravenous metronidazole supplemented with high-dose vancomycin (250 to 500 mg 4 times a day) either orally or via nasogastric tube in patients who cannot take oral medications (eg, those with ileus) and/or a vancomycin enema.[13] Patients in whom CDI does not improve promptly with oral vancomycin therapy should be reassessed for other causes of diarrhea because failure of vancomycin therapy is unusual and additional therapy including surgery may be indicated.

However, because of the cost of oral vancomycin and concerns about development of vancomycin resistance in other organisms, and on the basis of studies that reported similar efficacy as vancomycin in mild to moderate CDI,[61] the IDSA/SHEA guidelines recommend metronidazole as the first-line therapy in patients with the first or first recurrent episode of mild to moderate CDI in the absence of contraindications to its use or indicators of severe infection.[13] Patients in whom CDI does not improve in 72 to 96 hours should be reassessed for other causes of diarrhea. If other diseases have been ruled out, treatment should be switched from metronidazole to vancomycin.[13] In patients who do not tolerate metronidazole or develop worsening diarrhea while receiving metronidazole, treatment should also be switched to vancomycin. In patients with severe disease, as defined by leukocytosis or renal failure, or who have a second or additional episodes of recurrence (see subsequent discussion), vancomycin should be the treatment of choice.

Fidaxomicin

Fidaxomicin is a macrocyclic antibiotic with little or no systemic absorption after oral administration and a narrow spectrum of activity against gram-positive aerobic and anaerobic bacteria including *C difficile*.[68] In in vitro studies, fidaxomicin was more active than vancomycin against *C difficile*.[69-71] In a clinical trial, the response rate with fidaxomicin (200 mg twice daily) was similar to that with vancomycin (125 mg 4 times daily) after 10 days of treatment (88.2% with fidaxomicin vs 85.8% with vancomycin).[72] However, significantly fewer patients in the fidaxomicin group had a recurrence (15.4% vs 25.3%; $P=.005$).[72] In addition, subgroup analyses revealed that rates of recurrence were significantly lower with fidaxomicin than with vancomycin in patients with the nonhypervirulent strain of *C difficile* (7.8% vs 25.5%; $P<.001$) but were not significantly different in patients infected with this strain (24.4% vs 23.6%; $P=.93$). In another trial, fidaxomicin was not inferior to vancomycin in achieving clinical cure.[73] Major reported adverse events were uncommon and were comparable with those reported with oral vancomycin. Subsequent post hoc analyses of these trials found that when patients received systemic antibiotics concurrent with CDI treatment, the cure rate was significantly higher for fidaxomicin compared with vancomycin (90% vs 79.4%; $P=.04$), and recurrence rates were lower for fidaxomicin (16.9% vs 29.2%; $P=.048$).[37]

These data demonstrate that fidaxomicin is well tolerated, is not inferior to oral vancomycin for clinical cure in mild to moderate CDI, and is associated with lower rates of recurrence than is vancomycin in patients infected with nonhypervirulent strains of *C difficile*. Fidaxomicin might be favored over oral vancomycin in patients who require additional concomitant systemic antibiotics after a diagnosis of CDI. The FDA has approved fidaxomicin for treatment of CDI. However, there are no randomized data comparing fidaxomicin with metronidazole for treatment of a first episode of mild to moderate CDI, for which metronidazole remains the initial treatment of choice. In addition, fidaxomicin has not been studied for efficacy in recurrent CDI and in special populations including children or individuals with inflammatory bowel diseases.

There are several pharmacoeconomic considerations for the use of fidaxomicin. The current average wholesale cost of fidaxomicin is $135.00 for each 200-mg dose, compared with $0.72 for a 500-mg dose of metronidazole and $31.81 for a 125-mg capsule of oral vancomycin.[74] The average cost of a 10-day course of fidaxomicin would be 125-fold higher than a 10-day course of metronidazole 3 times daily and 2 times higher than a 10-day course of oral vancomycin 4 times daily. To save on cost, some institutions administer oral vancomycin solution (using the intravenous solution) rather than capsules.

With these cost considerations, fidaxomicin is often restricted to use in patients with an initial episode of CDI who are at high risk of recurrence (eg, individuals of advanced age, patients with severe CDI, and those receiving concomitant antibiotic therapy[75,76]) and who are infected with the nonhypervirulent strain or in those who have had multiple episodes of recurrence. However, currently there are no robust clinical models to predict recurrence in

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patients with CDI. Furthermore, it should be noted that the efficacy of fidaxomicin compared with vancomycin (or any other treatment) has not been specifically studied in these patient groups. Fidaxomicin is also sometimes used in patients who have a severe intolerance of or allergic reaction to oral vancomycin.

Fecal Microbiota Transplantation

A major risk factor for CDI is systemic antibiotic use, which disrupts normal gut flora and leads to increased predisposition to CDI. The risk of CDI recurrence after initial treatment is approximately 20% to 25%[4,7] and is further increased with the use of additional systemic antibiotics and with subsequent CDI recurrences[75]. The pathophysiologic features of recurrent CDI are incompletely understood but likely involve ongoing disruption of the normal fecal flora and inadequate host immune response. Standard treatment of CDI using antibiotics such as metronidazole and vancomycin further disrupts colonic microbial communities that normally keep expansion of *C difficile* populations in check. Because *C difficile* spores are resistant to antibiotics, they can germinate to vegetative forms after antibiotic therapy has been discontinued. These factors can perpetuate CDI recurrence after discontinuation of therapy. Therefore, a high percentage of patients experience multiple recurrences of CDI.

Although it is hoped that the emerging narrow-spectrum antibiotics such as fidaxomicin will permit restoration of the gut microbiota in patients with the chronic relapsing form of CDI, this hypothesis has not been tested in these patients.

Fecal microbiota transplantation (FMT) is being studied as an alternative to standard antibiotic therapy to treat recurrent CDI, to restore colonic flora with the use of intestinal microorganisms from a healthy donor (via infusion of a liquid suspension of stool), and to restore the intestinal microbiota in patients with recurrent CDI.

A systematic review of 27 studies and case reports including 317 patients with recurrent CDI treated via FMT found an overall success rate of 92%, with 89% of patients responding after a single treatment.[77] In those studies, 35% of patients received FMT via enema, with a response rate of 95%; 23% via the nasogastric route, with a response rate of 76%; and 19% via colonoscopy, with a response rate of 89%.[77]

A study from the University of Minnesota reported initial experience with FMT in 43 patients with recurrent CDI including patients with underlying inflammatory bowel disease.[78] These patients received FMT via colonoscopy from either individual patient-identified donors or a standard donor pool. The overall rate of infection clearance was 86% in response to a single infusion, there were no differences in outcomes relative to donor source, and no serious adverse effects were reported.[78] Another recent study reported experience with FMT via colonoscopy in 70 patients with recurrent CDI.[79] During the initial 12-week follow-up, FMT resulted in resolution of symptoms in all patients with the nonhypervirulent strain of *C difficile* and in 89% of those with the hypervirulent strain.[79] There were no evident complications attributable to FMT. Another group reported their experience with FMT via enema and found a similar response rate and no adverse events.[80] There have been no studies of FMT for prophylaxis in patients at high risk of recurrence after a first episode of CDI, and there has been no head-to-head comparison of FMT with conventional treatments for CDI.

There are several considerations for FMT that include donor selection, including the use of a standard donor pool vs a related donor, the need to screen donors for transmissible infectious diseases, standardization of stool preparation techniques, insurance reimbursement for donor testing, and long-term safety and efficacy of FMT in this population.[81] Hence, the present uncontrolled evidence suggests that FMT may be an option in patients with multiple episodes of CDI recurrence to prevent future episodes, although further larger studies are needed to support this recommendation and to compare FMT with other methods of treatment of recurrent CDI.

Other Options for Treatment of CDI

Additional potential options for treatment of CDI include rifaximin, nitazoxanide, cholestyramine, intravenous immunoglobulin (IVIG), monoclonal antibodies, vaccines, and probiotics.

Rifaximin is a gastrointestinal-selective antibiotic characterized by a broad antimicrobial spectrum that has activity against most gram-negative and gram-positive bacteria and anaerobes and aerobes and has excellent in vitro activity against *C difficile*.[82] Despite being a broad-spectrum antibiotic, rifaximin does not cause significant alterations to the gut microbiome; however, there may be concern for development of resistance against rifaximin in *C difficile* and other gut microbes with widespread use of this agent.[83] Rifaximin has been effective for treatment of CDI in smaller clinical studies and case reports.[84-86] A recent randomized controlled trial found that rifaximin was similar to vancomycin (57% vs 64%, respectively) in attaining clinical success (resolution of fever, abdominal pain, or diarrhea) and was not inferior in resolution of diarrhea (80% vs 81%) and recurrence (9% vs 14%).[87] These data suggest that rifaximin may be an alternative to vancomycin for treatment of CDI, although the published article is awaited. Rifaximin is currently not

recommended as monotherapy for CDI, but can be used for recurrent CDI after treatment with oral vancomycin (125 mg 4 times a day for 14 days) in the form of a "rifaximin chaser" (400 mg orally twice daily for 14 days).[7,88]

Nitazoxanide is an antiparasitic drug that is also active against *C difficile* and is as effective as vancomycin and metronidazole for treatment of CDI.[89,90] However, nitazoxanide has no clear benefits over other available drugs, and long-term safety and efficacy data are lacking. At present, nitazoxanide can be considered an alternate therapy in patients with multiple episodes of recurrence despite several courses of vancomycin and metronidazole and who are not candidates for FMT or other therapies.

Anion exchange resins such as cholestyramine work by binding toxin and may help decrease symptoms in mild disease. However, there is no evidence that adding cholestyramine to the treatment regimen decreases the risk of recurrence, and these resins also bind vancomycin and therefore should not be used simultaneously.[13,91] Overall, the role of these drugs in the management of CDI is unclear.

Intravenous immunoglobulin has been used to treat recurrent and severe CDI with variable success, and there are no randomized controlled trials reporting a benefit of IVIG therapy in CDI.[92] Intravenous immunoglobulin contains antibodies against *C difficile* toxins A and B and may be a useful option to decrease the risk of disease recurrence[93] in patients in whom other therapies have failed or as an adjunctive treatment in seriously ill patients with fulminant CDI.[94] In a large, randomized, controlled study of monoclonal antibodies against *C difficile* toxins A and B in addition to antibiotic therapy, the rate of CDI recurrence was lower in patients who received treatment with monoclonal antibodies (7% vs 25%; $P<.001$).[95] The recurrence rate in patients with the hypervirulent strain was 8% in the antibody group and 32% in the placebo group ($P=.06$). In patients with a history of recurrent CDI, another episode of recurrence occurred in 7% and 38%, respectively ($P=.006$). A phase 3 study is under way to further establish the safety and efficacy of monoclonal antitoxin antibody treatment of CDI. Therefore, IVIG may have a role as an adjunct treatment in patients with multiple episodes of CDI recurrence or in those with fulminant CDI.

Preliminary trials of a parenteral vaccine containing toxoids A and B found excellent serum antibody responses in healthy adults.[96] Of 3 patients given the vaccine who required continuous vancomycin therapy to manage recurrent CDI, all were able to discontinue vancomycin, and 2 patients had substantial increases in concentrations of serum antibodies to toxins A and B.[97] Another phase 1 study enrolled adults and elderly volunteers and randomized them to receive 3 different doses of *C difficile* toxoid vaccine or placebo. A 100% seroconversion rate was observed in the younger volunteers with all dosages of toxin A and a variable response dependent on dosage in elderly participants.[98] Of note, the seroconversion rate for toxin B was lower than for toxin A in both age groups. No serious adverse effects were reported. Phase 2 trials are ongoing to further evaluate the efficacy of this toxoid vaccine for prevention of CDI recurrence.

Probiotics are preparations of live microorganisms that have been used to prevent and treat CDI, with a suggested objective to repopulate the colonic microflora. The various probiotics commonly used include species of *Lactobacillus, Bifidobacterium,* and *Saccharomyces*. There is currently no role for probiotics in the primary prevention of CDI because of limited data and the potential risk of bloodstream infection with these agents.[13,99] *Saccharomyces boulardii* produces an enzyme that inhibits the effects of *C difficile* toxins A and B.[100] *S boulardii* has been studied for treatment of CDI in conjunction with antibiotic therapy and has been associated with a decreased risk of CDI recurrence.[101,102] Owing to the lack of large randomized controlled trials that found probiotics beneficial for the treatment of CDI, these agents are currently not recommended in practice guidelines.[13]

SURGICAL MANAGEMENT OF CDI

Surgery is indicated for treatment of refractory CDI not responding to medical therapy or for fulminant colitis, which is a relatively rare complication of CDI. Clinical features of fulminant CDI include systemic inflammatory response syndrome, severe abdominal pain and tenderness, and colonic distention observed on radiographs. Diarrhea may be absent because of ileus. The traditional surgical approach to CDI is subtotal or total colectomy and is associated with poor outcomes, with mortality as high as 50%.[103] Factors predictive of increased mortality after colectomy to treat fulminant CDI include age older than 65 years, renal failure, leukocytosis, increased serum lactate concentration, low albumin level, sepsis, multiple organ failure, and immunosuppression.[104-106] Recently, a colon-sparing approach including loop ileostomy with intraoperative colonic lavage using warmed polyethylene glycol solution via the ileostomy and instillation of vancomycin flushes postoperatively via the ileostomy has been described, with decreased mortality compared with that in historical control patients who underwent traditional surgery.[107]

The timing of surgical consultation for CDI remains controversial, more so because patients with fulminant CDI are generally poor surgical candidates because of age and comorbid conditions.[108] However, delaying surgery in early fulminant colitis leads to increased adverse outcomes including

TABLE 3. Risk Factors for Recurrent *Clostridium difficile* Infection

Age >65 y
Previous episodes of *C difficile* infection
History of severe *C difficile* infection
Increasing peripheral leukocyte count
Hypoalbuminemia
Fever
Presence of comorbid conditions
Inflammatory bowel disease
Ongoing or recurrent antibiotic exposure
Decreased serum anti–toxin A IgG
Use of acid suppression medications (controversial)

death. It is therefore recommended that a surgical consultation be obtained early if a patient has worsening diarrhea despite optimal medical therapy, symptoms of megacolon, or sepsis.[109-111]

AN APPROACH TO TREATMENT OF RECURRENT CDI

A major problem in management of CDI is recurrent infection, which occurs in 20% to 25% of patients after the first episode of CDI.[4,7] Risk factors for recurrent CDI are given in Table 3. Clinically, recurrent CDI is defined as occurrence of symptomatic diarrhea or abdominal pain, with positive results of a stool test within 56 days of a previous episode after interim symptom resolution.[13] Episodes occurring after 56 days are likely due to reinfection; however, to differentiate true recurrence from reinfection, genotypic analysis is required. This definition is important because positive stool test results without diarrhea should not be considered a recurrence of CDI, and recurrent diarrhea with normal findings on a stool test should lead the clinician to consider a broader differential diagnosis including postinfectious irritable bowel syndrome, although false-negative stool test results in a patient with true recurrent CDI is a possibility. However, the practice of repeat stool testing for CDI is discouraged because the yield is low.[56] In patients with severe symptoms suggestive of recurrence, treatment can be initiated while awaiting stool assay results.

There are no randomized controlled trials of patients with multiple CDI recurrences, and treatment options and recommendations are often made on the basis of findings of small studies and case reports. In a patient with a confirmed first recurrence, initial therapy should consist of a 2-week course of oral metronidazole therapy for mild to moderate CDI (if the first infection responded to this treatment) or oral vancomycin for severe CDI. For a second recurrence, a 6- to 7-week tapering regimen with oral vancomycin is recommended (Table 4).[7,13] For a subsequent relapse, a 10- to 14-day course of a standard dosage of oral vancomycin is recommended, followed by a 14-day course of oral rifaximin (400 mg twice daily). At this stage, oral fidaxomicin or fecal microbiota transplant also may be considered,

TABLE 4. Treatment Options for Recurrent *Clostridium difficile* Infection

First recurrence
Mild to moderate *C difficile* infection (CDI)
Oral metronidazole, 500 mg 3 times a day for 14 d
Mild to moderate CDI (no response to oral metronidazole previously)
Severe CDI
Oral vancomycin, 125 mg 4 times a day for 14 d
Second recurrence
Oral vancomycin tapered over 6 wk
125 mg 4 times daily for 14 d
125 mg 2 times daily for 7 d
125 mg once daily for 7 d
125 mg once every other day for 8 d
125 mg once every 3 d for 15 d
Future recurrences
Oral vancomycin, 125 mg 4 times a day for 14 d, followed by rifaximin, 400 mg twice daily for 14 d
Consider fecal microbiota transplantation
Consider intravenous immunoglobulin, 400 mg/kg, repeated up to 3 times at 3-wk intervals
Consider combination therapy with oral vancomycin and oral rifaximin

although fidaxomicin has not been studied in patients with multiple recurrent episodes of CDI. Additional treatment options for multiple relapses include 400 mg/kg IVIG, repeated up to 3 times if needed, or combination therapy with oral vancomycin and rifaximin. In some patients, long-term treatment with oral vancomycin (125 mg daily or every other day) may be needed to control symptoms and prevent episodes of recurrence.

CONCLUSION

The incidence and severity of CDI are increasing, and the condition can be associated with significant morbidity. CDI is now being increasingly described in patients previously thought to be at low risk, and several novel risk factors have been identified. Recurrent CDI continues to be a major management challenge. The emergence of newer therapies including fidaxomicin and fecal microbiota transplant has added options for the management of CDI. Additional research is ongoing to identify other CDI treatment options including newer antibiotics, monoclonal antibodies, vaccines, and probiotics.

Abbreviations and Acronyms: **CDI** = *Clostridium difficile* infection; **FDA** = Food and Drug Administration; **FMT** = fecal microbiota transplantation; **IDSA/SHEA** = Infectious Diseases Society of America/Society for Healthcare Epidemiology of America; **IVIG** = intravenous immunoglobulin; **PCR** = polymerase chain reaction; **PPI** = proton pump inhibitor

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REFERENCES

1. Bartlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing Clostridia. *N Engl J Med*. 1978;298(10):531-534.
2. Khanna S, Pardi DS. The growing incidence and severity of Clostridium difficile infection in inpatient and outpatient settings. *Expert Rev Gastroenterol Hepatol*. 2010;4(4):409-416.
3. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality [published correction appears in *N Engl J Med*. 2006;354(20):2200]. *N Engl J Med*. 2005;353(23):2442-2449.
4. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired Clostridium difficile infection: a population-based study [published correction appears in *Am J Gastroenterol*. 2012;107(1):150]. *Am J Gastroenterol*. 2011;107(1):89-95.
5. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of Clostridium difficile-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol*. 2005;26(3):273-280.
6. Pépin J, Valiquette L, Alary ME, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. *CMAJ*. 2004;171(5):466-472.
7. Kelly CP, LaMont JT. Clostridium difficile: more difficult than ever [published correction appears in *N Engl J Med*. 2010;363(16):1585]. *N Engl J Med*. 2008;359(18):1932-1940.
8. Ricciardi R, Rothenberger DA, Madoff RD, Baxter NN. Increasing prevalence and severity of Clostridium difficile colitis in hospitalized patients in the United States. *Arch Surg*. 2007;142(7):624-631; discussion 631.
9. Zilberberg MD, Shorr AF, Kollef MH. Increase in Clostridium difficile-related hospitalizations among infants in the United States, 2000-2005. *Pediatr Infect Dis J*. 2008;27(12):1111-1113.
10. Zilberberg MD, Shorr AF, Kollef MH. Increase in adult Clostridium difficile-related hospitalizations and case-fatality rate, United States, 2000-2005. *Emerg Infect Dis*. 2008;14(6):929-931.
11. McDonald LC, Owings M, Jernigan DB. Clostridium difficile infection in patients discharged from US short-stay hospitals, 1996-2003. *Emerg Infect Dis*. 2006;12(3):409-415.
12. McDonald LC, Coignard B, Dubberke E, et al; Ad Hoc Clostridium difficile Surveillance Working Group. Recommendations for surveillance of Clostridium difficile-associated disease. *Infect Control Hosp Epidemiol*. 2007;28(2):140-145.
13. Cohen SH, Gerding DN, Johnson S, et al; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431-455.
14. Khanna S, Pardi DS, Aronson SL, Kammer PP, Baddour LM. Outcomes in community-acquired Clostridium difficile infection. *Aliment Pharmacol Ther*. 2012;35(5):613-618.
15. Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of Clostridium difficile-associated disease among inpatients at children's hospitals in the United States, 2001-2006. *Pediatrics*. 2008;122(6):1266-1270.
16. Benson L, Song X, Campos J, Singh N. Changing epidemiology of Clostridium difficile-associated disease in children. *Infect Control Hosp Epidemiol*. 2007;28(11):1233-1235.
17. Enoch DA, Butler MJ, Pai S, Aliyu SH, Karas JA. Clostridium difficile in children: colonisation and disease. *J Infect*. 2011;63(2):105-113.
18. Langley JM, LeBlanc JC, Hanakowski M, Goloubeva O. The role of Clostridium difficile and viruses as causes of nosocomial diarrhea in children. *Infect Control Hosp Epidemiol*. 2002;23(11):660-664.
19. Klein EJ, Boster DR, Stapp JR, et al. Diarrhea etiology in a children's hospital emergency department: a prospective cohort study. *Clin Infect Dis*. 2006;43(7):807-813.
20. Boenning DA, Fleisher GR, Campos JM, Hulkower CW, Quinlan RW. Clostridium difficile in a pediatric outpatient population. *Pediatr Infect Dis*. 1982;1(5):336-338.
21. Otten AM, Reid-Smith RJ, Fazil A, Weese JS. Disease transmission model for community-associated Clostridium difficile infection. *Epidemiol Infect*. 2010;138(6):907-914.

22. Viscidi R, Willey S, Bartlett JG. Isolation rates and toxigenic potential of Clostridium difficile isolates from various patient populations. *Gastroenterology*. 1981;81(1):5-9.
23. MacCannell DR, Louie TJ, Gregson DB, et al. Molecular analysis of Clostridium difficile PCR ribotype 027 isolates from Eastern and Western Canada. *J Clin Microbiol*. 2006; 44(6):2147-2152.
24. Merrigan M, Venugopal A, Mallozzi M, et al. Human hypervirulent Clostridium difficile strains exhibit increased sporulation as well as robust toxin production. *J Bacteriol*. 2010; 192(19):4904-4911.
25. Kuijper EJ, Barbut F, Brazier JS, et al. Update of Clostridium difficile infection due to PCR ribotype 027 in Europe, 2008. *Euro Surveill*. 2008;13(31):pii:18942.
26. Kuijper EJ, Coignard B, Brazier JS, et al. Update of Clostridium difficile-associated disease due to PCR ribotype 027 in Europe. *Euro Surveill*. 2007;12(6):E1-E2.
27. Miller M, Gravel D, Mulvey M, et al. Health care-associated Clostridium difficile infection in Canada: patient age and infecting strain type are highly predictive of severe outcome and mortality. *Clin Infect Dis*. 2010;50(2):194-201.
28. Hubert B, Loo VG, Bourgault AM, et al. A portrait of the geographic dissemination of the Clostridium difficile North American pulsed-field type 1 strain and the epidemiology of C. difficile-associated disease in Quebec. *Clin Infect Dis*. 2007; 44(2):238-244.
29. Goorhuis A, Van der Kooi T, Vaessen N, et al. Spread and epidemiology of Clostridium difficile polymerase chain reaction ribotype 027/toxinotype III in The Netherlands. *Clin Infect Dis*. 2007;45(6):695-703.
30. Morgan OW, Rodrigues B, Elston T, et al. Clinical severity of Clostridium difficile PCR ribotype 027: a case-case study. *PLoS One*. 2008;3(3):e1812.
31. Thibault A, Miller MA, Gaese C. Risk factors for the development of Clostridium difficile-associated diarrhea during a hospital outbreak. *Infect Control Hosp Epidemiol*. 1991;12(6): 345-348.
32. Shah K, Pass LA, Cox M, Lanham M, Arnold FW. Evaluating contemporary antibiotics as a risk factor for Clostridium difficile infection in surgical trauma patients. *J Trauma Acute Care Surg*. 2012;72(3):691-695.
33. Rousseau C, Levenez F, Fouqueray C, Doré J, Collignon A, Lepage P. Clostridium difficile colonization in early infancy is accompanied by changes in intestinal microbiota composition. *J Clin Microbiol*. 2011;49(3):858-865.
34. Rea MC, O'Sullivan O, Shanahan F, et al. Clostridium difficile carriage in elderly subjects and associated changes in the intestinal microbiota. *J Clin Microbiol*. 2012;50(3):867-875.
35. Manges AR, Labbe A, Loo VG, et al. Comparative metagenomic study of alterations to the intestinal microbiota and risk of nosocomial Clostridum difficile-associated disease. *J Infect Dis*. 2010;202(12):1877-1884.
36. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci U S A*. 2011;108(suppl 1):4554-4561.
37. Mullane KM, Miller MA, Weiss K, et al. Efficacy of fidaxomicin versus vancomycin as therapy for Clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections [published correction appears in *Clin Infect Dis*. 2011;53(12):1312. Dosage error in article text]. *Clin Infect Dis*. 2011;53(5):440-447.
38. Dubberke ER, Reske KA, Noble-Wang J, et al. Prevalence of Clostridium difficile environmental contamination and strain variability in multiple health care facilities. *Am J Infect Control*. 2007;35(5):315-318.
39. Kim KH, Fekety R, Batts DH, et al. Isolation of Clostridium difficile from the environment and contacts of patients with antibiotic-associated colitis. *J Infect Dis*. 1981;143(1):42-50.
40. Dubberke ER, Gerding DN, Classen D, et al. Strategies to prevent Clostridium difficile infections in acute care hospitals. *Infect Control Hosp Epidemiol*. 2008;29(suppl 1):S81-S92.
41. Khanna S, Pardi DS. IBD: Poor outcomes after Clostridium difficile infection in IBD. *Nat Rev Gastroenterol Hepatol*. 2012; 9(6):307-308.
42. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with Clostridium difficile in patients with inflammatory bowel disease. *Gut*. 2008; 57(2):205-210.
43. Patriarchi F, Rolla M, Maccioni F, et al. Clostridium difficile-related pancolitis in lung-transplanted patients with cystic fibrosis. *Clin Transplant*. 2011;25(1):E46-E51.
44. Kyne L, Sougioultzis S, McFarland LV, Kelly CP. Underlying disease severity as a major risk factor for nosocomial Clostridium difficile diarrhea. *Infect Control Hosp Epidemiol*. 2002; 23(11):653-659.
45. Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent Clostridium difficile infection [published correction appears in *Arch Intern Med* 2010;170(13):1100]. *Arch Intern Med*. 2010;170(9):772-778.
46. Lowe DO, Mamdani MM, Kopp A, Low DE, Juurlink DN. Proton pump inhibitors and hospitalization for Clostridium difficile-associated disease: a population-based study. *Clin Infect Dis*. 2006;43(10):1272-1276.
47. Dial S, Delaney JA, Schneider V, Suissa S. Proton pump inhibitor use and risk of community-acquired Clostridium difficile-associated disease defined by prescription for oral vancomycin therapy. *CMAJ*. 2006;175(7):745-748.
48. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired Clostridium difficile-associated disease. *JAMA*. 2005;294(23): 2989-2995.
49. Rao A, Jump RL, Pultz NJ, Pultz MJ, Donskey CJ. In vitro killing of nosocomial pathogens by acid and acidified nitrite. *Antimicrob Agents Chemother*. 2006;50(11):3901-3904.
50. Wilson KH, Sheagren JN, Freter R. Population dynamics of ingested Clostridium difficile in the gastrointestinal tract of the Syrian hamster. *J Infect Dis*. 1985;151(2):355-361.
51. Pépin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis*. 2005;41(9):1254-1260.
52. Khanna S, Aronson SL, Kammer PP, Baddour LM, Pardi DS. Gastric acid suppression and outcomes in Clostridium difficile infection: a population-based study. *Mayo Clin Proc*. 2012; 87(7):636-642.
53. Khanna S, Pardi DS. Gastric acid suppression and Clostridium difficile infection: is there a causal connection [letter]? *Clin Gastroenterol Hepatol*. 2012;10(5):564; author reply 564.
54. Kufelnicka AM, Kim TJ. Effective utilization of evolving methods for the laboratory diagnosis of Clostridium difficile infection. *Clin Infect Dis*. 2011;52(12):1451-1457.
55. Carroll KC. Tests for the diagnosis of Clostridium difficile infection: the next generation. *Anaerobe*. 2011;17(4):170-174.

56. Khanna S, Pardi DS, Rosenblatt JE, Patel R, Kammer PP, Baddour LM. An evaluation of repeat stool testing for Clostridium difficile infection by polymerase chain reaction [published online ahead of print]. *J Clin Gastroenterol*. 2012.
57. Sloan LM, Duresko BJ, Gustafson DR, Rosenblatt JE. Comparison of real-time PCR for detection of the tcdC gene with four toxin immunoassays and culture in diagnosis of Clostridium difficile infection. *J Clin Microbiol*. 2008;46(6):1996-2001.
58. Peterson LR, Mehta MS, Patel PA, et al. Laboratory testing for Clostridium difficile infection: light at the end of the tunnel. *Am J Clin Pathol*. 2011;136(3):372-380.
59. Fujitani S, George WL, Murthy AR. Comparison of clinical severity score indices for Clostridium difficile infection. *Infect Control Hosp Epidemiol*. 2011;32(3):220-228.
60. Lungulescu OA, Cao W, Gatskevich E, Tlhabano L, Stratidis JG. CSI: a severity index for Clostridium difficile infection at the time of admission. *J Hosp Infect*. 2011;79(2):151-154.
61. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45(3):302-307.
62. Belmares J, Gerding DN, Parada JP, Miskevics S, Weaver F, Johnson S. Outcome of metronidazole therapy for Clostridium difficile disease and correlation with a scoring system. *J Infect*. 2007;55(6):495-501.
63. Keddis MT, Khanna S, Noheria A, Badour LM, Pardi DS, Qian Q. *Clostridium difficile* infection in patients with chronic kidney disease. *Mayo Clin Proc*. 2012. [In Press]
64. Shivashankar R, Khanna S, Kammer PP, et al. Clinical predictors of severe complicated *Clostridium difficile* infection. *Am J Gastroenterol*. 2011;106(S2):S162.
65. Orenstein R, Aronhalt KC, McManus JE Jr, Fedraw LA. A targeted strategy to wipe out Clostridium difficile. *Infect Control Hosp Epidemiol*. 2011;32(11):1137-1139.
66. Pepin J, Alary ME, Valiquette L, et al. Increasing risk of relapse after treatment of Clostridium difficile colitis in Quebec, Canada. *Clin Infect Dis*. 2005;40(11):1591-1597.
67. Musher DM, Aslam S, Logan N, et al. Relatively poor outcome after treatment of Clostridium difficile colitis with metronidazole. *Clin Infect Dis*. 2005;40(11):1586-1590.
68. Gerber M, Ackermann G. OPT-80, a macrocyclic antimicrobial agent for the treatment of Clostridium difficile infections: a review. *Exp Opin Investig Drugs*. 2008;17(4):547-553.
69. Finegold SM, Molitoris D, Vaisanen ML, Song Y, Liu C, Bolaños M. In vitro activities of OPT-80 and comparator drugs against intestinal bacteria. *Antimicrob Agents Chemother*. 2004;48(12):4898-4902.
70. Ackermann G, Löffler B, Adler D, Rodloff AC. In vitro activity of OPT-80 against Clostridium difficile. *Antimicrob Agents Chemother*. 2004;48(6):2280-2282.
71. Karlowsky JA, Laing NM, Zhanel GG. In vitro activity of OPT-80 tested against clinical isolates of toxin-producing Clostridium difficile. *Antimicrob Agents Chemother*. 2008;52(11):4163-4165.
72. Louie TJ, Miller MA, Mullane KM, et al; OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for Clostridium difficile infection. *N Engl J Med*. 2011;364(5):422-431.
73. Cornely OA, Crook DW, Esposito R, et al; OPT-80-004 Clinical Study Group [Collaborators (82)]. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis*. 2012;12(4):281-289.
74. Lancaster JW, Matthews SJ. Fidaxomicin: the newest addition to the armamentarium against Clostridium difficile infections. *Clin Ther*. 2012;34(1):1-13.
75. Hu MY, Katchar K, Kyne L, et al. Prospective derivation and validation of a clinical prediction rule for recurrent Clostridium difficile infection. *Gastroenterology*. 2009;136(4):1206-1214.
76. Johnson S. Recurrent Clostridium difficile infection: a review of risk factors, treatments, and outcomes. *J Infect*. 2009;58(6):403-410.
77. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. *Clin Infect Dis*. 2011;53(10):994-1002.
78. Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent Clostridium difficile infection. *Am J Gastroenterol*. 2012;107(5):761-767.
79. Mattila E, Uusitalo-Seppälä R, Wuorela M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. *Gastroenterology*. 2012;142(3):490-496.
80. Kassam Z, Hundal R, Marshall JK, Lee CH. Fecal transplant via retention enema for refractory or recurrent Clostridium difficile infection. *Arch Intern Med*. 2012;172(2):191-193.
81. Bakken JS, Borody T, Brandt LJ, et al; Fecal Microbiota Transplantation Workgroup. Treating Clostridium difficile infection with fecal microbiota transplantation. *Clin Gastroenterol Hepatol*. 2011;9(12):1044-1049.
82. Koo HL, DuPont HL. Rifaximin: a unique gastrointestinal-selective antibiotic for enteric diseases. *Curr Opin Gastroenterol*. 2010;26(1):17-25.
83. DuPont HL, Jiang ZD, Okhuysen PC, et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea [published correction appears in *Ann Intern Med*. 2005;143(3):239]. *Ann Intern Med*. 2005;142(10):805-812.
84. Berman AL. Efficacy of rifaximin and vancomycin combination therapy in a patient with refractory Clostridium difficile-associated diarrhea. *J Clin Gastroenterol*. 2007;41(10):932-933.
85. Johnson S, Schriever C, Galang M, Kelly CP, Gerding DN. Interruption of recurrent Clostridium difficile-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. *Clin Infect Dis*. 2007;44(6):846-848.
86. Rubin DT, Sohi S, Glathar M, Thomas T, Yadron N, Surma BL. Rifaximin is effective for the treatment of Clostridium difficile-associated diarrhea: results of an open-label pilot study. *Gastroenterol Res Pract*. 2011;2011:106978.
87. Pardi DS, Brennan R, Spinnell M, et al. The efficacy and safety of rifaximin vs. vancomycin in the treatment of mild to moderate C. difficile infection: a randomized double-blind active comparator trial. *Gastroenterology*. 2012;142(5):S-599.
88. Garey KW, Ghantoji SS, Shah DN, et al. A randomized, double-blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with Clostridium difficile infection. *J Antimicrob Chemother*. 2011;66(12):2850-2855.
89. Musher DM, Logan N, Bressler AM, Johnson DP, Rossignol JF. Nitazoxanide versus vancomycin in Clostridium difficile infection: a randomized, double-blind study. *Clin Infect Dis*. 2009;48(4):e41-e46.

90. Young JD, Mangino E, Stevenson KB, Koletar SL. Nitazoxanide versus metronidazole for Clostridium difficile-associated colitis [letter]. *Clin Infect Dis*. 2007;44(1):152; author reply 152-154.

91. Taylor NS, Bartlett JG. Binding of Clostridium difficile cytotoxin and vancomycin by anion-exchange resins. *J Infect Dis*. 1980;141(1):92-97.

92. Abougergi MS, Broor A, Cui W, Jaar BG. Intravenous immunoglobulin for the treatment of severe Clostridium difficile colitis: an observational study and review of the literature. *J Hosp Med*. 2010;5(1):E1-E9.

93. Leav BA, Blair B, Leney M, et al. Serum anti-toxin B antibody correlates with protection from recurrent Clostridium difficile infection (CDI). *Vaccine*. 2010;28(4):965-969.

94. Abougergi MS, Kwon JH. Intravenous immunoglobulin for the treatment of Clostridium difficile infection: a review. *Dig Dis Sci*. 2011;56(1):19-26.

95. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against Clostridium difficile toxins. *N Engl J Med*. 2010;362(3):197-205.

96. Kotloff KL, Wasserman SS, Losonsky GA, et al. Safety and immunogenicity of increasing doses of a Clostridium difficile toxoid vaccine administered to healthy adults. *Infect Immun*. 2001;69(2):988-995.

97. Sougioultzis S, Kyne L, Drudy D, et al. Clostridium difficile toxoid vaccine in recurrent C. difficile-associated diarrhea. *Gastroenterology*. 2005;128(3):764-770.

98. Greenberg RN, Marbury TC, Foglia G, Warny M. Phase I dose finding studies of an adjuvanted Clostridium difficile toxoid vaccine. *Vaccine*. 2012;30(13):2245-2249.

99. Dendukuri N, Costa V, McGregor M, Brophy JM. Probiotic therapy for the prevention and treatment of Clostridium difficile-associated diarrhea: a systematic review [published correction appears in *CMAJ*. 2005;173(4):345]. *CMAJ*. 2005;173(2):167-170.

100. Castagliuolo I, Riegler MF, Valenick L, LaMont JT, Pothoulakis C. Saccharomyces boulardii protease inhibits the effects of Clostridium difficile toxins A and B in human colonic mucosa. *Infect Immun*. 1999;67(1):302-307.

101. Surawicz CM, McFarland LV, Elmer G, Chinn J. Treatment of recurrent Clostridium difficile colitis with vancomycin and Saccharomyces boulardii. *Am J Gastroenterol*. 1989;84(10):1285-1287.

102. Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent Clostridium difficile disease: use of high-dose vancomycin combined with Saccharomyces boulardii. *Clin Infect Dis*. 2000;31(4):1012-1017.

103. Longo WE, Mazuski JE, Virgo KS, Lee P, Bahadursingh AN, Johnson FE. Outcome after colectomy for Clostridium difficile colitis. *Dis Colon Rectum*. 2004;47(10):1620-1626.

104. Markelov A, Livert D, Kohli H. Predictors of fatal outcome after colectomy for fulminant Clostridium difficile colitis: a 10-year experience. *Am Surg*. 2011;77(8):977-980.

105. Byrn JC, Maun DC, Gingold DS, Baril DT, Ozao JJ, Divino CM. Predictors of mortality after colectomy for fulminant Clostridium difficile colitis. *Arch Surg*. 2008;143(2):150-154; discussion 155.

106. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. *Ann Surg*. 2011;254(3):423-427; discussion 427-429.

107. Synnott K, Mealy K, Merry C, Kyne L, Keane C, Quill R. Timing of surgery for fulminating pseudomembranous colitis. *Br J Surg*. 1998;85(2):229-231.

108. Hall JF, Berger D. Outcome of colectomy for Clostridium difficile colitis: a plea for early surgical management. *Am J Surg*. 2008;196(3):384-388.

109. Ali SO, Welch JP, Dring RJ. Early surgical intervention for fulminant pseudomembranous colitis. *Am Surg*. 2008;74(1):20-26.

110. Seder CW, Villalba MR Jr, Robbins J, et al. Early colectomy may be associated with improved survival in fulminant Clostridium difficile colitis: an 8-year experience. *Am J Surg*. 2009;197(3):302-307.