

# New advances in the treatment of *Clostridium difficile* infection (CDI)

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**Abstract:** *Clostridium difficile* infections (CDI) have increased in frequency throughout the world. In addition to an increase in frequency, recent CDI epidemics have been linked to a hypervirulent *C. difficile* strain resulting in greater severity of disease. Although most mild to moderate cases of CDI continue to respond to metronidazole or vancomycin, refractory and recurrent cases of CDI may require alternative therapies. This review provides a brief overview of CDI and summarizes studies involving alternative antibiotics, toxin binders, probiotics, and immunological therapies that can be considered for treatment of acute and recurrent CDI in severe and refractory situations.

**Keywords:** *Clostridium difficile*, antibiotics, probiotics, immunological therapy

## Overview of CDI

*Clostridium difficile* (*C. difficile*) is an anaerobic, Gram-positive, spore-forming bacillus that is known to cause associated diarrhea and pseudomembranous colitis. *C. difficile* infection (CDI) is a serious medical condition, and although heightened awareness of CDI outbreaks has increased surveillance, it appears that the incidence and severity of CDI is increasing around the world (Surowiec et al 2006; Owens 2007). *C. difficile* is reported to cause up to one-third of antibacterial-associated diarrhea cases, 50%–75% of all cases of antibiotic-associated colitis, and 90%–100% of antibiotic-associated pseudomembranous colitis cases (Aslam et al 2005; Owens 2007). Mortality of CDI, as either a direct or indirect cause of death, is quite significant approaching 17% in one trial (Pepin et al 2005). In addition, the cost of hospitalization and treatment of CDI is also significant. It is estimated that the average cost of treatment per case of CDI is about US\$4000 with an average increase in hospital stay of 3.6 days (Aslam et al 2005; Jodlowski et al 2006).

Clinical disease associated with *C. difficile* has a wide range of clinical features (Mylonakis et al 2001). Individuals may be colonized with toxin-producing strains of *C. difficile* and become asymptomatic carriers, or manifest symptoms. Toxin-producing strains of *C. difficile* are carried by 7%–11% of hospitalized inpatients, 5%–7% of those in long-term care facilities, and 2% or fewer of ambulatory adults (Poutanen et al 2004). In neonates, the carriage rate is much higher, approaching 70% (Kelly CP et al 2004; Poutanen et al 2004). Although neonates are common carriers of *C. difficile*, they seldom develop pseudomembranous colitis unless they are suffering from concomitant gastrointestinal motility disorders or other conditions such as neutropenia that increase risk (Kelly et al 2004). Neonatal resistance to *C. difficile* is thought to be primarily related to the inability of toxins to attach to the mucosa of newborns, or protection from the toxins by maternally-acquired antibodies. Carrier rates of neonates drop to levels similar to adults by age 3.

In those developing disease, clinical symptoms vary from mild diarrhea to life-threatening colitis, toxic megacolon, and sepsis (Owens 2007). Most often, clinical

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features of CDI include mild to moderate non-bloody diarrhea, with some abdominal cramping and tenderness. In those with severe CDI, profuse watery diarrhea, abdominal pain, fever, nausea, anorexia, and malaise are frequently seen. In addition, leukocytosis, elevated C-reactive protein, and low albumin levels are often present in severe CDI (Monaghan et al 2008).

Early diagnosis is an essential aspect of managing CDI. A diagnosis of CDI should be considered in patients with an unformed stool and characteristic odor who have received antibiotics within the previous couple of months and/or those with diarrhea arising >72 hours after admission to a healthcare facility (Bartlett et al 2008). A diagnosis of CDI is confirmed with a positive stool test or the presence of pseudomembranes (Cohen et al 2007).

The pathogenesis of disease associated with *C. difficile* is quite complex. *C. difficile* colitis results from a disruption of normal bacterial flora of the colon, ingestion of *C. difficile*, and the release of toxins that lead to mucosal damage and inflammation. Although it is not known why some individuals do not develop disease, it is understood that toxin production is essential for disease to occur. *C. difficile* produces two primary toxins capable of causing colitis: enterotoxin (toxin A), the more potent of the two toxins, and cytotoxin (toxin B) (Surowiec et al 2006; Cloud et al 2007; Durai 2007). These toxins trigger the attraction and adhesion of neutrophils resulting in inflammation of the mucosal lining, and cellular necrosis, as well as increased peristalsis and capillary permeability, leading to diarrhea and colitis (Durai 2007). A strain of *C. difficile*, designated North American pulsed-field gel electrophoresis type 1 (NAP 1), has been linked to several outbreaks of severe disease in North America and Europe. NAP 1 is known to produce 16 times more toxin A and 23 times more toxin B than other strains, as well as an additional toxin known as binary toxin (Kuijper et al 2006). NAP 1 is discussed in more detail in the “Recent CDI Outbreaks” section.

The predominant risk factor associated with acquisition of *C. difficile* is previous antibiotic use (Bartlett et al 2008). In that regard, good antimicrobial stewardship has been an important aspect of CDI risk reduction. Of late, however, the relationship between CDI and antibiotic exposure has been questioned. A recent study of patients with community-acquired CDI showed that 61% of patients did not admit to antibiotic exposure within the previous 90 days of developing disease (Dial et al 2005). Further, an additional study found that 59% of patients with community-acquired CDI did not have documented antibiotic exposure (Kutty et al 2006). While all antimicrobial agents have the potential to alter

colonization and increase risk of CDI, certain antibiotics have been linked to CDI more than others and should be used with caution (Kuijper et al 2007). Among these agents are fluoroquinolones, clindamycin and the beta-lactam agents.

Historically, the risk for infection with *C. difficile* has been greater in elderly and debilitated patients who have little immunity and produce few antibodies against the *C. difficile* toxins (Durai 2007). Additional risk factors for CDI may also include feeding tube use and use of antiulcer medications, although conflicting data exists (Gerding et al 2008b). Studies conducted by Dial and associates have shown proton pump inhibitor (PPI) use as a risk factor for CDI (Dial et al 2005). PPIs have also been identified as an independent risk factor for CDI by other investigators, but not shown as a risk factor in some trials as well (Gerding et al 2008b). Until additional information is gathered through clinical studies, clinicians are encouraged to utilize clinical discretion when considering PPI use for their patients.

Prevention of microbial transmission and reduction of risk factors upon exposure are primary strategies utilized for control of CDI (Owens 2007). Primarily, *C. difficile* is spread via a fecal-oral route. If a patient is suspected of being infected with *C. difficile*, they should be placed in an isolated room or have a dedicated commode (Gerding et al 2008b). If it is not possible to isolate patients in single rooms, such as during an outbreak, patients may be placed in cohorts. Thorough cleansing of patient rooms and equipment following exposure to symptomatic patients is also essential. *C. difficile* is capable of producing highly resistant spores, which are able to survive for extended periods of time. Although resistant to many disinfectants, cleaning agents containing chlorine appear to have some activity against the spores. Disinfection with a 1:10 dilution concentration of concentrated sodium hypochlorite (ie, bleach) has been shown to be effective (Gerding et al 2008b). Vaporized hydrogen peroxide is also being studied as an agent for environmental decontamination of *C. difficile* spores. In contrast, quaternary ammonium-based products are not active against spores and may actually encourage sporulation. Finally, the use of protective clothing (gloves and aprons) and hand hygiene are important aspects of CDI prevention.

## Diagnosis of CDI

*C. difficile* infection is typically diagnosed by detection of the presence of toxin A and/or toxin B in a stool sample. *C. difficile* toxin detection by cytopathic effect on cells is generally regarded as the best test available for CDI (Bartlett et al 2008). This testing methodology takes up to 48 hours to

obtain a result, which is a disadvantage. Currently, most labs in the US use enzyme immunoassay (EIA) to detect toxin A or toxins A and B (Bartlett et al 2008). EIAs are relatively inexpensive, easy to perform, and have a rapid turnaround time. An additional immunoassay utilized for diagnosis of CDI is the glutamate dehydrogenase (GDH) enzyme test (common-antigen test), which rapidly detects the presence of *C. difficile* in stool samples (Ticehurst et al 2006). Like a culture, the GDH test only detects the presence of *C. difficile*, not the production of toxins. Further, GDH is also produced by other organisms. In considering these points, the GDH test is best utilized as a screening test and coupled with a test for the presence of toxins. Enzyme-linked immunosorbent assay (ELISA) tests for toxin A or toxins A and B are attractive due to rapid turnaround time (about 2 hours) and high specificity (Monaghan et al 2008). The sensitivity of ELISA testing has been shown to vary widely (79%–97%), however (Manabe et al 1995). Given this level of sensitivity, it is prudent to send as many as three samples to rule out disease if initial tests are negative. Assays which detect toxin A and B are preferable since toxin-A negative, toxin-B positive strains of *C. difficile* are known to cause disease (Bartlett et al 2008).

Cultures of stool specimens can also be performed but require additional testing to determine if the isolated *C. difficile* strain produces toxins (Durai 2007; Owens 2007). Results are not available for 3–4 days due to the time needed to perform the tests, limiting the usefulness of this strategy. Cultures are useful when investigating outbreaks of *C. difficile*, conducting susceptibility testing for *C. difficile* strains, and evaluating emerging testing methods.

Finally, flexible sigmoidoscopy can also be utilized to aid diagnosis. This more invasive approach is especially attractive for patients with suspected CDI but negative stool toxin assays (Durai 2007).

## Standard therapy for CDI

Treatment recommendations for disease associated with *C. difficile* include stopping the precipitating antibiotic agents when possible, and providing supportive care by administering fluids and electrolytes as required (Gerding et al 2008a; Surowiec et al 2006). It is important to note that antiperistaltic agents (eg, loperamide, atropine, opiates) should not be included, either alone or in combination, as a therapeutic modality of CDI as they may predispose patients to toxic megacolon (Gerding et al 2008). Antibiotics directed against *C. difficile* are a mainstay of CDI therapy. Oral vancomycin was the first antimicrobial agent shown effective for treatment of CDI. Following several

studies that demonstrated treatment equivalence between metronidazole and vancomycin, metronidazole emerged as the consensus first-line treatment for patients other than pregnant and lactating women, and those intolerant of metronidazole (Aslam et al 2005; Surowiec et al 2006; Durai 2007; Owens 2007). The primary reasons for metronidazole becoming the agent of choice for CDI are reduced cost compared with that of oral vancomycin and concern that vancomycin use could lead to increased spread of vancomycin-resistant enterococci. Reports describing metronidazole failures and questions of the equivalence of metronidazole and vancomycin for CDI have been raised (Musher et al 2005; Pepin et al 2005a). Pepin and colleagues recently compared metronidazole and vancomycin treatment outcomes in patients separated into the time period before identification of the BI/NAP1 epidemic *C. difficile* strain (1991–2002) and after the strain was identified (2003–2006) (Pepin et al 2007). From 1996 to 2002, patients receiving vancomycin demonstrated improved outcomes compared to those receiving metronidazole. During the 2003–2006 time period, the odds ratio for the comparison between vancomycin and metronidazole was 1.0, showing no difference between the treatments. If evaluating performance in patients stratified by disease severity, data from clinical trials does suggest, however, that vancomycin is superior to metronidazole for those with severe disease (Gerding et al 2008a).

Recently revised treatment guidelines for CDI are stratified into three groups: mild to moderate disease, severe disease (white blood cell count  $\geq 15,000$  cells/mm<sup>3</sup> or creatinine level  $\geq 1.5$  times the level prior to CDI), and severe complicated disease (severe disease and admission to an intensive care unit, need for colectomy, toxic megacolon, ileus, hypotension or, colonic perforation) (Cohen et al 2007). For patients with mild to moderate CDI, oral metronidazole at a dose of 500 mg 3 times per day is recommended as first-line therapy. Oral vancomycin 125 mg 4 times daily for 10–14 days is now recommended for severe cases of CDI. Finally, for those diagnosed with severe complicated CDI, vancomycin 500 mg orally or via nasogastric tube 4 times per day and/or intravenous metronidazole 500–750 mg every 8 hours is recommended. If a patient with severe complicated CDI has complete ileus, intravenous metronidazole is used with rectal administration of vancomycin.

The latest CDI therapy guidelines also suggest that recurrent CDI be treated with the same drug used as initial therapy, unless the severity of the infection has increased (Cohen et al 2007). Metronidazole should not be used for a second recurrence. In CDI patients with a second or greater

recurrence, an oral vancomycin taper, with or without pulse dosing, is utilized.

## Recent CDI epidemics

As stated above, overall rates of CDI have increased in recent years and the number of severe cases has increased as well (Aslam and Musher 2006; Kuijper et al 2006; Owens 2007). Although the exact reason for the increase is not fully understood the discovery of a highly virulent strain of *C. difficile* has been associated with recent outbreaks (Kuijper et al 2006). In 2002, a *C. difficile* epidemic occurred in hospitals in Quebec, Canada (Warny et al 2005). The outbreak was primarily caused by a *C. difficile* strain identified as a toxinotype III. This strain was further identified and genotyped through pulse-field gel electrophoresis (PFGE) and PCR-ribotyping and classified as a North American PFGE type 1 (NAP1) and PCR-ribotype 027. In vitro data showed this particular strain, NAP1/027, to produce 16 times the amount of toxin A and 23 times the amount of toxin B, compared to a control strain, toxinotype 0. The NAP1/027 strain has also shown greater spore producing capacity compared to strains not associated with CDI outbreaks (Owens 2007). In addition to the outbreaks in Canada, NAP1/027 has been associated with recent outbreaks in the US, Netherlands, and UK (Warny et al 2005; McDonald et al 2005). A hypervirulent PCR-ribotype 027 strain was associated with outbreaks in Belgium and France (Kuijper et al 2006; Cookson 2007). Although these particular strains were not specifically mentioned as being identified as NAP1 it has been proposed that all ribotype 027, toxinotype III strains belong to this PFGE group (Kuijper et al 2006). Of note, the NAP1/027 strain exhibits increased resistance to the fluoroquinolone antibiotics and a cohort study of the epidemic at one Quebec hospital identified prior fluoroquinolone use as the antibiotics most highly correlated with the development of CDI (Pépin et al 2005b). It has been proposed that the widespread use of fluoroquinolones has also lead to the selection of the resistant strain and contributed to outbreaks in the US (McDonald et al 2005).

A follow-up finding of the epidemic in a Quebec hospital showed that vancomycin was not superior to metronidazole in reducing post-infection complications from 2003 to 2006 (Pépin et al 2007). This was in contrast to a prior study conducted at the same hospital from 1991 to 2003 in which vancomycin demonstrated the ability to decrease complications vs metronidazole for CDI (Pépin et al 2004; Pépin et al 2007). The hypervirulent strain, which was suspected to arrive at the institution in 2003, might account for this

difference (Pépin et al 2007). It has been proposed that due to the increased amounts of toxin produced by the hypervirulent strain, antibiotics such as vancomycin, which takes approximately 24 hours to arrive at the colon, do not work quickly enough to prevent the toxins from saturating binding sites in the colon. The antibiotics still may be utilized to control further damage by reducing *C. difficile* producing toxin contained in the intestine; however, the toxin already bound and causing intestinal inflammation will be dependent on the immune system. Although more data are needed to confirm this hypothesis, it reinforces the need for the development of preventative procedures or agents having a quick onset of action. Therapies such as toxin-binding medications, immunoglobulins or a vaccine are potential strategies that should be investigated to control this aggressive strain.

## Relapse rates and resistance

Recurrence rates of CDIs have typically ranged from 5% to 20%; however, Musher et al (2005), described 50% of the subjects tested as being refractory to treatment or having either documented or clinical recurrence of disease (Musher et al 2005; Segarra-Newnham 2007). *C. difficile* resistance to metronidazole or vancomycin therapy has been theorized as a reason for treatment failures, however current data does not support this theory (Surowiec et al 2006). Unfortunately, regular susceptibility testing of *C. difficile* strains is not conducted in microbiology laboratories, as *C. difficile* is generally considered to be susceptible to metronidazole and vancomycin (Peláez et al 2002). Although documented widespread susceptibility data are limited, resistant cases have been reported and documentation of this phenomenon is important (Peláez et al 2002; Kuijper et al 2006). Peláez and colleagues (2002) conducted *C. difficile* susceptibility tests over an eight-year period and reported 6.3% of isolates as resistant to metronidazole (minimum inhibitory concentration [MIC]  $\geq 32$   $\mu\text{g/mL}$ ), 3.1% of isolates intermediately resistant (MIC 4–16  $\mu\text{g/mL}$ ) to vancomycin and 0 isolates resistant to vancomycin (MIC  $\geq 32$   $\mu\text{g/mL}$ ) (Peláez et al 2002). The rates of resistance were higher in the HIV infected population, perhaps explained by the likely increased prior use of the antimicrobial drugs in these patients.

Although the reported resistance may bring about general concern, the clinical significance of these reports is unknown. MIC breakpoints are not established for colonic concentrations and it is possible that the concentrations reached at the local site would be high enough to overcome and effectively treat the resistant strains (Peláez et al 2002). Other data in which treatment failures to metronidazole were reported as



high as 50% suggest that antimicrobial resistance did not play a part in the treatment failures based on the lack of any isolate at the institution being identified as resistant (Musher et al 2005). Another issue needing further analysis is the effect the hypervirulent strain associated with recent epidemics will have on treatment failures. In the recent Quebec outbreak, during 2003–2004 the hypervirulent strain was associated with an increase in recurrent infections after treatment with either vancomycin or metronidazole when compared to recurrent infection rates from 1991 to 2002 (Pepin et al 2005b; Pepin et al 2007). However, the recurrence rate decreased in the following years (2005–2006) prompting the researchers to suspect the recurrences were due to reinfection from continued exposure vs actual relapse (Pepin et al 2007). The reason for reinfections was estimated by the total number of new hospital-acquired CDIs during this time. The number of new cases from 1991 to 2002 ranged from 37 to 65, but increased in 2003 to 303, and further increased in 2004 to 363. In 2005, the number of new cases declined to 173 and only 54 cases were documented halfway through 2006. The researchers further proposed that increased use of sporicidal cleaners in patients' rooms during the hospitalization rather than only upon discharge may reduce the recurrence rate of CDI.

Although it is difficult to precisely determine the cause of the increasing rates and severity of CDI, it is likely due to a combination of factors. The continued use of antibiotics known to increase the risk for CDI (beta-lactams, clindamycin, and more recently fluoroquinolones), the recent appearance of a hypervirulent strain, as well as other environmental factors all likely contribute to the increased incidence. Increased awareness of the complications and outbreaks of CDIs may increase surveillance, which further increases the reported rates of CDIs. Due to the increasing number of overall and severe cases of CDI and reported treatment failures with current agents, there is a need for more effective therapeutic treatment options as well as preventative treatments. Current research involves treatment of acute disease, as well as treatment and prevention of recurrent disease. The following sections provide an overview of new discovery involving various agents being evaluated for acute and recurrent CDI.

## Adjunctive and alternative therapeutic options for CDI

The literature was reviewed for alternative and investigational agents. The majority of the agents investigated for CDI fall into the following categories: antimicrobial agents, toxin binding agents, immune modifying agents and probiotics.

Although many agents have in vitro data, this discussion will focus primarily on those products that have human clinical trials. Currently, only in vitro data has been published for XRP 2868, telavancin (TD-6424), daptomycin, rifalazil, lacticin 3147, and tinidazole (Bannatyne and Jackowski 1987; Goldstein et al 2003; Rothstein et al 2003; Anton et al 2004; Goldstein et al 2004; Citron et al 2005; Fung and Doan 2005; Goldstein et al 2005; Tyrrell et al 2006; Hecht et al 2007; Rea et al 2007). Tinidazole is a structural analogue of metronidazole and like metronidazole has good in vitro activity against *C. difficile* (Fung and Doan 2005). A unique and promising finding is that tinidazole was recently found to have low minimum inhibitory concentrations against six NAP1 strains (Hecht et al 2007). Even though promising clinical trials were performed with bacitracin, no recent evidence has been published regarding its use in CDI (Young et al 1985; Dudley et al 1986).

## Antimicrobial agents

### Ramoplanin

As a lipoglycopeptide antibiotic, ramoplanin has demonstrated activity against aerobic and anaerobic gram-positive bacteria such as *Enterococcus* and *C. difficile* (Farver et al 2005; Fulco and Wenzel 2006). Its bactericidal activity is by blocking peptidoglycan synthesis by binding to lipid II. Lack of cross-resistance with ramoplanin to vancomycin has been proposed due to its unique mechanism of action. High concentrations of ramoplanin have been observed in the feces. In vitro and in vivo hamster gut evaluations have shown that ramoplanin has similar efficacy in reducing cytotoxin production compared to vancomycin but may be more effective in killing spores and preventing spore recrudescence (Freeman et al 2005). Oscient Pharmaceuticals, the developer of ramoplanin, has stated that the antibiotic has FDA Fast Track status and Special Protocol Assessment for Phase III trials (Oscient Pharmaceuticals 2007).

A Phase II trial evaluated the efficacy of ramoplanin to that of vancomycin in the treatment of hospital acquired CDI (Pullman et al 2004). As a multi-centered, randomized, open-label, 3 arm trial, patients received either ramoplanin at 200 mg twice a day (n = 28) or 400 mg twice a day (n = 29) for 10 days or vancomycin 125 mg 4 times a day (n = 29) for 10 days. An end-of-therapy assessment evaluated the clinical response as a complete cure or partial resolution of symptoms. The end-of-therapy clinical cure was 83% in patients receiving ramoplanin 200 mg and 85% in the ramoplanin 400 mg group as compared to 86% in the vancomycin group. The rate of relapses was 26.3% with the ramoplanin 200 mg

group, 21.7% with the ramoplanin 400 mg group and 20.8% with the vancomycin treated group. Common adverse effects associated with ramoplanin were nausea (22.8%), vomiting (14.1%) and diarrhea (10.5%). Serious adverse effects with ramoplanin were respiratory failure, gastrointestinal bleeding, angina, aspiration, hypoxia, ileus, pancreatitis, proctitis, small bowel obstruction, emesis, sepsis and cholelithiasis but these were similar to that of the vancomycin treated group. The serious adverse effects related to vancomycin use were respiratory failure, aspiration, hypoxia, gastrointestinal hemorrhage, deep venous thrombosis, aortic stenosis, cardiac failure, cardiogenic shock, multiple-organ failure, pyrexia, and sickle cell anemia crisis. The mortality rate was similar between the treatment groups and deaths were not attributed to the medications. The authors stated that ramoplanin demonstrated acceptable efficacy with limited toxicity but there was insufficient power to establish non-inferiority to vancomycin.

## Rifaximin

Rifaximin is a poorly absorbed rifamycin derivative, which acts by inhibiting bacterial RNA synthesis (Marchese et al 2000). It is active against gram-negative and gram-positive anaerobic and aerobic bacteria. The drug is used primarily for travelers' diarrhea (Gerard et al 2005). Based on the available information rifaximin appears to be safe and well tolerated and lack any clinically significant CYP3A4 drug interactions. Encouraging results on in vitro data for rifaximin were recently published by Hecht et al (2007). They tested 110 isolates of *C. difficile* collected from 1983–2004. Rifaximin was one of the most active agents tested with lower minimum inhibitory concentrations than other agents. However, three of the isolates demonstrated resistance (high MICs). Two of the isolates were from Argentina in 1998 and 1 was from Chicago in 1995. This does raise the concern about possible clinical implications if resistance became more widespread. Six of the isolates that had low MICs were of the NAP1 type (implicated in recent outbreaks), and thus rifaximin may be a potential treatment option in such situations.

In a small clinical trial of twenty patients, nine of ten patients who received rifaximin 200 mg three times a day for 10 days were successfully treated (Boero et al 1990). In the vancomycin group ten of ten patient receiving 500 mg twice daily for 10 days were successfully treated.

In one case report rifaximin, vancomycin and a probiotic were found successful in treating a refractory case of CDI (Berman 2007). The patient required several courses of this combination for a total of seven weeks to achieve resolution

of his symptoms. Initially the probiotic used was Culturelle® (ConAgra Functional Foods, Inc, Omaha, NE, USA) but in the later courses was changed to Flora-Q (Kenwood Therapeutics, Fairfield, NJ, USA). Culturelle® contains *Lactobacillus rhamnosus* GG (LGG) (Amerifit Brands Inc. 2008). Flora-Q® contains *Lactobacillus acidophilus*, *Bifidobacterium*, *Lactobacillus paracasei*, *Streptococcus thermophilus* (Kenwood 2008). Jadlowski and colleagues (2006) also reported successful use of rifaximin to treat CDI in patients who were unable to take other agents or had failed with other agents (Jadlowski et al 2006).

Recently Johnson and colleagues (2007) published a series on 8 women with recurrent CDI (Johnson et al 2007). Patients received a 14-day course of oral rifaximin immediately following a course of vancomycin while asymptomatic. Six of the 8 patients received rifaximin at a dose of 400 mg orally twice daily. In the remaining 2 patients, 1 received 200 mg orally 3 times a day and 1 received 200 mg orally twice a day. Seven of the patients had no further episodes of diarrhea after 1 course of rifaximin. One patient did require a second 14-day course of rifaximin to resolve the diarrhea. This patient was also found to have a *C. difficile* isolate still present after her second treatment and the isolate demonstrated resistance by having a high MIC. The authors were concerned about the potential for resistance based on this finding. However, 1 study found a low incidence of spontaneous development of rifaximin-resistant organisms (Marchese et al 2000).

A study is currently being conducted by Salix Pharmaceuticals to evaluate rifaximin for CDI (Salix Pharmaceuticals 2007a). It is a phase III clinical trial assessing the safety and efficacy of rifaximin compared to vancomycin. An estimated 300 patients will be enrolled in this trial. In a May 2007 news release Salix Pharmaceuticals anticipated a new drug application for CDI by mid 2008 (Salix Pharmaceuticals 2007b).

## Nitazoxanide

Nitazoxanide is a nitrothiazolide antiparasitic used to treat cryptosporidiosis and giardiasis (McVay and Rolfe 2000). Its mechanism of action is to interfere with pyruvate-ferredoxin oxidoreductase enzyme-dependent electron transfer reaction, which is necessary for anaerobic metabolism. The inhibition of *C. difficile* occurs with low concentrations of nitazoxanide or with its metabolite, tizoxanide (Musher et al 2006).

Nitazoxanide was compared to metronidazole in a prospective, randomized, double-blind study of hospitalized patients with CDI (Musher et al 2006). The primary endpoint was defined as normal bowel habits and no other clinical

symptoms after 7 days of treatment. The response rate was 36/40 (90%) patients with the 7-day course of nitazoxanide, 32/36 (88.9%) with the 10-day course of nitazoxanide and 28/34 (82.4%) with metronidazole. The sustained response rate was not statistically significant between the treatment groups at 31 days.

A double-blind, randomized study evaluated patients who had failed conventional therapy of metronidazole and/or oral vancomycin for *C. difficile* colitis (Musher et al 2007). Failure was defined as a persistence of fever, diarrhea, abdominal pain, unexplained leucocytosis and a positive EIA for *C. difficile* toxin after 14 days of treatment or at least two infections that responded to treatment but recurred within 30 days. Patients received either nitazoxanide 500 mg orally twice a day for 10 days or metronidazole. The study results were revealed after 22 patients and an additional open label study followed with 13 patients receiving nitazoxanide after conventional therapy failure. The results were that 74% (26/35 patients) had rapid resolution of symptoms with nitazoxanide. Twenty out of the 28 patients (71%) with persisting infection after failure to metronidazole responded and 6/7 patients (86%) with recurrent disease responded to nitazoxanide ( $p = 0.65$ ). The major study limitation was that it was open labeled and non-comparative.

## OPT-80

OPT-80, also known as PAR-101 and tiacumicin B, is a macrocyclic antibiotic. As a member of the tiacumicin family, OPT-80 is an antibiotic naturally produced by *Dactylosporangium aurantiacum*. The spectrum of activity is against gram-positive aerobic and anaerobic bacteria including *C. difficile* (Ackerman et al 2004). Phase I clinical trials have reported minimal absorption of OPT-18 and high concentrations in the feces when administered orally (Johnson 2007).

A phase II open-label, dose-ranging study evaluated 45 adults receiving either 50, 100, or 200 mg of OPT-18 every 12 hours for 10 days (Johnson 2007). The results were that the higher doses were more efficacious in the median time-to-cessation of diarrhea. Two patients had recurrence of symptoms. Another phase II trial was an open-label, proof-of-principle study of 32 patients receiving 50, 100, or 200 mg every 12 hours of OPT-18 for 10 days. The conclusion was that the *C. difficile* counts decreased by day 10 in all but one patient. Adverse effects were unrelated to the drug in both trials.

Phase III clinical trials are ongoing to access the cure rate and rate of recurrence of OPT-18 as compared to vancomycin

in randomized, double-blind studies. Completion of the trials is anticipated in March 2008 (Johnson 2007).

## Fusidic acid

Fusidic acid, also known as fucidin, is in the class of polysaccharides commonly referred to as sulfated fucans. The antibacterial action of fusidic acid is by inhibiting protein synthesis with preventing translocation on the ribosome. Its current use is in treating staphylococcal infections. (Leo Pharmaceutical, Medsafe). Adverse effects reported have been primarily gastrointestinal with rare cases of skin rashes and hematologic disorders. Drug-drug interactions to with fusidic acid include; antibiotics that are biliary excreted, oral anticoagulants, and HMG-CoA reductase inhibitors.

Barreti et al (2007) proposed that fusidic acid is considered to be an L-selectin blocker when inhibiting *C. difficile*. The proposed mechanism of action is by inhibiting L-selectin, which is an adhesion molecule, fusidic acid inhibits the leukocyte rolling. Leukocyte rolling is part of the process of leukocyte extravasation into inflamed sites. This can result in the reduction of tissue injury and inflammation associated with *C. difficile* (Barreto et al 2007). The pharmacodynamics of fusidic acid were compared to that of metronidazole and vancomycin. The conclusions were that fusidic acid has the longest postantibiotic effect and postantibiotic sub-minimum inhibitory concentration compared to the other two antibiotics but that the greatest bactericidal effect was with metronidazole (Odenholt et al 2007). The first non-blinded study establishing the response of fusidic acid, when treating CDI, was reported by Cronberg et al (1984).

Wenisch et al (1996) conducted a prospective, randomized comparative study of first episode CDI with fusidic acid, metronidazole, vancomycin, and teicoplanin. The definition of clinical cure was the lack of the following symptoms; loose stools, gastrointestinal symptoms or fever and the normalization of C-reactive protein and leukocyte counts. If the diarrhea persisted after 6 days, the treatment was defined as clinical failure. Clinical cure with fusidic acid was 93% (27/29 patients), metronidazole was 94% (29/31), vancomycin was 94% (29/31) and teicoplanin was 96% (27/28) ( $p > 0.05$ ). Recurrence of symptoms was 28% with fusidic acid, 16% with metronidazole, 16% with vancomycin and 7% with teicoplanin. The authors concluded that although fusidic acid had a high clinical cure rate, it also had the highest rate of recurrence and adverse effects, especially gastrointestinal discomfort (31%).

Fusidic acid was compared to metronidazole in treating the first episode of CDI in a double-blind randomized

trial (Wullt and Odenholt 2004). The cure rate at the first follow-up clinic visit was 83% with fusidic acid as compared to 93% with metronidazole ( $p = 0.116$ ). The recurrence of symptoms was 27% with fusidic acid and 29% with metronidazole while the reappearance of the *C. difficile* toxin was 13% with fusidic acid and 10% with metronidazole. The evaluation of symptoms and presence of toxin was done on days 35–40 after receiving the medications.

The use of fusidic acid for CDI was reviewed in three patients with ulcerative colitis, one patient with Crohn's disease and one patient who was later diagnosed with Crohn's disease (Bektas et al 2007). All of the patients received fusidic acid at 1,500 mg/day orally for 10 days. Four of the five patients had been previously treated with metronidazole. The *C. difficile* toxin A was negative in all of the cases on day 10 along with clinical symptoms. No recurrences were documented.

## Teicoplanin

Structurally related to vancomycin, teicoplanin is a non-absorbable glycopeptide antibiotic (Wistrom 1994; Citron et al 2003). Teicoplanin has exhibited lower minimal inhibitory concentrations against *C. difficile* compared to vancomycin. A previous clinical trial resulted in a high initial cure rate with teicoplanin but 33% of the patients had clinical recurrence of CDI and bacteriological elimination rate at 4 weeks was only 59% (Wistrom 1994). A more recent clinical study completed by Wenisch et al (1996) compared teicoplanin to fusidic acid, metronidazole and vancomycin (Wenisch et al 1996). The results as previously discussed, revealed that teicoplanin was promising with a clinical cure rate of 96% and a recurrence rate of 7%.

## Rifampin

As an anti-tubercular antibiotic, rifampin also has demonstrated in vitro activity against *C. difficile* (Fekety et al 1983; Buggy et al 1987). High rifampin concentrations in the intestinal lumen have been reported but concentrations in the stool were not documented (Fekety et al 1983).

A prospective, single-blinded, randomized study of 39 hospitalized patients with CDI, were given either metronidazole 500 mg three times a day for 10 days or metronidazole with rifampin 300 mg twice a day for 10 days (Lagrotteria et al 2006). A clinical cure was if the patient was asymptomatic during the treatment course or had a microbiological response. The group receiving metronidazole with rifampin had a clinical cure rate of 63% as compared to metronidazole at 65% ( $p = 0.91$ ). The metronidazole and rifampin

group had a 17% rate of laboratory-confirmed relapse, while metronidazole was 31%. The authors halted the study early due to 6 deaths in the metronidazole and rifampin treatment group and one death in the metronidazole treatment group. The high mortality rate was attributed to the enrollment of elderly patients with numerous comorbidities such as diabetes, renal failure, cancer, and heart disease. The authors concluded that rifampin does not have a routine role as an adjunct to metronidazole in the treatment of hospitalized CDI due to a low cure rate.

## Toxin-binding agents Cholestyramine/colestipol

Cholestyramine and colestipol have been shown to bind *C. difficile* toxins A and B in vitro and also vancomycin (Taylor and Bartlett 1980). Several case reports exist of both pediatric and adult patients who had several relapses and failed to respond to traditional treatments that were successfully treated with extended courses of cholestyramine (Kunimoto and Thomson 1986; Pruksananonda and Powell 1989; Moncino and Falletta 1992). However, a randomized in vivo controlled trial of colestipol failed to show any impact on the fecal excretion of *C. difficile* or its toxin from patients (Mogg et al 1982).

## Tolvamer

Tolvamer, formerly known as GT160-246 and GT267-004, is an investigational styrene sulfonate polymer that has the ability to non-covalently bind *C. difficile* toxins A and B (Braunlin et al 2004). The active ingredient is poly (4-styrenesulfonate) that contains as counter ions either 100% sodium (tolvamer sodium) or a combination of 63% sodium and 37% potassium (tolvamer potassium-sodium) (Barker et al 2006). In animal studies, tolvamer was compared to cholestyramine in reducing fluid accumulation caused by toxin A in rat ileal loops and mortality rates in a hamster model (Kurtz et al 2001). Tolvamer was found to be at least 80 times more effective at inhibiting the fluid accumulation due to toxin A and 16 times more effective at blocking intestinal permeability compared to cholestyramine in the rat model. This study also found that 80% of tolvamer and 10% of cholestyramine treated hamsters were protected from mortality due to *C. difficile* infection.

Louie and colleagues compared tolvamer sodium with vancomycin in mild to moderate CDI in a Phase II clinical trial involving 289 patients (Louie et al 2006). Patients received either vancomycin 125 mg per day for 10 days or tolvamer 1 g 3 times a day or 2 g 3 times per day for 14 days.



The primary end point was time to resolution of diarrhea which was defined as the first of 2 consecutive days when the patient had  $\leq 2$  stools which were loose or watery or if the patient had hard or formed stools. Non-inferiority was defined as 2 days or less difference in resolution of diarrhea. In the per protocol group, tolevamer 6 g per day group was found to be non-inferior to vancomycin ( $p = 0.02$ ). The most common side effect in this study was hypokalemia.

A Phase III clinical trial of more than 1,100 patients compared tolevamer to standard treatment (Genzyme 2007a; Genzyme 2007b; Genzyme 2007c). The study was a non-inferiority trial of tolevamer potassium-sodium (GT267-004) compared to vancomycin and metronidazole. In a press release by Genzyme, the company stated that tolevamer did not prove to be non-inferior to vancomycin (Genzyme 2007c). Genzyme also noted that they expected results of a second Phase III clinical trial late in 2007. Currently, no clinical trials for tolevamer use in CDI could be identified.

## Immune-modifying agents

### Monoclonal antibodies

Research has begun on human monoclonal antibodies directed against *C. difficile* toxins A or B and the impact this may have on CDI (Babcock et al 2006). Based on animal data, two antibodies are being explored in clinical trials. CDA1 is directed against toxin A and MDX-1388 is directed against toxin B. Currently a Phase II study is being conducted to evaluate if the addition of the human monoclonal antibodies GS-CDA1 and MDX-1388 to standard treatment for CDI reduces the risk of recurrent CDI compared to standard treatment plus placebo (University of Massachusetts 2007). Patients will receive a single intravenous solution of GS-CDA1 combined with MDX-1388 or placebo (normal saline). The study plans to enroll 100 patients in each of the study arms.

### Immunization

High levels of anti-toxin A IgG are associated with protection against CDI (Aboudola et al 2003). An anti-*C. difficile* toxoid has been developed to determine if it is possible to induce an immune response in patients with multiple episodes of recurrent CDI (Sougioultzis et al 2005). Sougioultzis et al (2005) evaluated 3 patients with recurrent CDI treated with 4 doses of intramuscular *C. difficile* toxoid vaccine (days 0, 7, 28, 56) and oral vancomycin daily until the day of the last dose of vaccine. Vancomycin doses ranged from 125 mg twice daily to 250 mg 4 times a day. The vaccine consisted of formalin-detoxified *C. difficile* toxins A and B which was believed to

induce anti-*C. difficile* toxin IgG. In 2 of the 3 subjects, serum IgG antitoxin antibodies increased and all three subjects were able to stop vancomycin and remain disease free. Prior studies with this vaccine in healthy individuals found it to be well tolerated and able to produce antibody response (Kotloff et al 2001; Aboudola et al 2003).

Results of a phase I trial of the vaccine containing inactivated *C. difficile* toxins A and B were recently reported (Acambis 2007). This study found that four doses of the vaccine were well tolerated and produced an immune response in young healthy adults (Acambis 2006, 2008). The company stated that the majority of the side effects seen in the trial were similar to most intramuscular vaccine injections (pain, redness, and mild tenderness at the site of injection, and headache). A second phase I trial in patients 65 and older also found the vaccine to be well tolerated and to produce an immune response at various doses (Acambis 2008). In December of 2007, Acambis reported that it had completed work on reformulating the vaccine to improve stability over the vaccine used in the Phase I trials (Acambis 2007). They plan to begin a proof-of-concept study by the end of 2008.

Ghose and colleagues (2007) found that transcutaneous immunization with formalin-treated *C. difficile* toxin A resulted in anti-*C. difficile* toxin A IgG and IgA responses in serum and anti-*C. difficile* toxin A IgA in stool in mice (Ghose et al 2007). These findings suggest that transcutaneous administration may be a viable option.

### Immune globulin

Intravenous immune globulin (IVIG) has been documented as a therapeutic tool for the treatment of CDI in several case reports. Juang et al (2007) conducted a retrospective analysis of patients who had severe *C. difficile* positive disease during a 2-year time frame (Juang et al 2007). They identified 79 patients of which 18 had received IVIG in addition to standard therapy and matched them with 18 patients who had not received IVIG. IVIG was given at a dose of 200–300 mg/kg for a single dose. They did not find a beneficial response in patients who were treated with IVIG compared to standard therapy alone in the primary endpoints of all-cause mortality, length of stay or colectomies. This data is in conflict with many case reports of success with IVIG therapy. Leung et al (1991) was one of the first to report the successful use of IVIG 400 mg/kg every 3 weeks in 6 children with relapsing CDI (Leung et al 1991). A retrospective review of 14 patients with severe, refractory, recurrent *C. difficile* found that IVIG may be effective in this group (McPherson et al 2006). Patients received 1 to 5 courses of standard antibiotics prior to IVIG

therapy. Doses of IVIG ranged from 150 to 400 mg/kg. Nine of the 14 patients had resolution of diarrhea, 1 had a partial response but died later after a recurrence and 4 died of other causes. Wilcox (2004) reported a series of 5 cases of CDI treated with IVIG in doses of 300–500 mg/kg for 1, 2, or 6 doses. Of the 5 patients, 3 were considered successfully treated; however, 1 did relapse within 6 weeks (Wilcox 2004). Beales (2002) reported successful treatment of 4 cases of refractory recurrent CDI with IVIG 400 mg/kg given twice, 21 days apart along with a tapering dose of vancomycin (Beales 2002). Several other individual case reports also reported successful treatment with varying regimens involving IVIG (Salcedo et al 1997; Murphy et al 2006; Hassoun and Ibrahim 2007).

Despite multiple case reports of successful treatment with IVIG, good sound clinical trials are lacking and thus make it difficult to recommend this for treatment of CDI at this time. High cost and low product availability also limit the potential use of this therapy.

## Colostrum

Human colostrum has been found to have neutralizing activity against *C. difficile* toxins A and B and thus is thought to potentially protect newborns against these toxins (Wada et al 1980; Kim et al 1984; Dallas and Rolfe 1998). In recent years technology has allowed the development of “immune milk” from bovine colostrum (Kelly et al 1997). Cows can be immunized with specific pathogens or antigens to produce colostrum that is higher in concentration of specific antibodies against those pathogens. Fractionation techniques have also been developed that allow isolation of immunoglobulins (Ig) from bovine colostrum and milk. IgG immunoglobulins are the predominate immunoglobulins in bovine colostrum (92%). IgM and IgA are also found in bovine colostrum. Animal models have found both protection from CDI and treatment of CDI with IgG concentrate from colostrum of hyperimmunized cows (Lyerly et al 1991; Kelly et al 1996). Warny et al (1999) were able to prove that bovine immunoglobulin concentrate containing high concentrations of IgG from colostrum of cows immunized against *C. difficile* resisted digestion and inactivation in the upper gastrointestinal tract of humans (Warny et al 1999). This finding is important since toxin-neutralizing activity in the human colon is needed to have therapeutic benefit. Kelley and colleagues (1997) also found data to support that a similar bovine immunoglobulin concentrate when taken orally by humans had the ability to neutralize activity of *C. difficile* toxins A and B in their stools (Kelly et al 1997).

## Whey protein concentrate

More recent studies of milk-derived preparations have centered on whey protein concentrates (van Dissel et al 2005; Numan et al 2006; Young et al 2007). Anti-*C. difficile* whey protein concentrate (anti-CD-WPC) is made from mature milk (immune milk), not colostrum. In mature bovine milk IgA is the predominate immunoglobulin with lesser amounts of IgG and IgM. To produce anti-*C. difficile* whey protein, milk is collected from cows that have been immunized against *C. difficile* to produce immunoglobulins which are primarily of the IgA class. Anti-CD-WPC has been found to decrease relapse in patients with CDI when given after a course of standard antibiotics in two clinical trials (Van Dissel et al 2005; Numan et al 2006). In both trials whey protein concentrate 40% was used at a dose of 5 g (added to uncarbonated mineral water) three times a day for 14 days starting after patients had completed at least a 10-day course of metronidazole and/or vancomycin. The safety of anti-CD-WPC was also evaluated in clinical trials and based on the data collected the product was well tolerated (Numan et al 2006; Young et al 2007).

## Probiotics

CDIs are frequently attributed to antibiotics altering the normal gut flora thus allowing *C. difficile* to flourish (Katz 2006). The World Health Organization and Food and Agricultural Organization define probiotics as, “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (FAO and WHO 2002, p 8). Probiotics serve as a potential method of restoring normal microbes in the gastrointestinal tract, which theoretically prevents or treats CDIs. Bacterial strains of *Lactobacillus* and *Bifidobacterium* and the yeast *Saccharomyces* are commonly utilized probiotics and have been used for the prevention and treatment of CDI (Boyle et al 2006; Katz 2006).

Overall reviews of the studies analyzing lactobacillus for CDI determined there are limited, inconclusive results on its effectiveness for preventing or treating CDI and suggest more clinical studies are needed (Katz 2006; Segarra-Newnham 2007). Recently a randomized double-blind, placebo controlled study by Hickson et al (2007) further analyzed the effectiveness of lactobacillus as a prophylactic agent. Although the primary outcome of the study was the prevention of antibiotic associated diarrhea, the prevention of CDI was included as a secondary outcome. One hundred fifteen hospitalized patients over the age of 50 who were receiving antibiotics were included in the final analysis. The probiotic was administered as a 100 g liquid given twice daily

and included *Lactobacillus casei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*. Probiotic administration began within 2 days of antibiotic therapy and continued for 7 days after antibiotics were discontinued. The study found an absolute risk reduction of 17% for the prevention of CDI, which was statistically significant ( $p = 0.001$ ). The estimated cost of preventing one case of CDI secondary to antibiotic use was estimated at US\$120 (£60; €89) and the authors concluded that regular use could result in significant cost savings. These results are potentially promising, however the study was criticized for excluding patients taking clindamycin, cephalosporins and aminopenicillins, all antibiotics associated with a high risk of causing *C. difficile* (Billyard 2007).

Although there are no controlled studies supporting *Saccharomyces* for the primary prevention of CDI, two randomized controlled trials support its use for recurrent CDI (McFarland et al 1994; Surawicz et al 2000). McFarland and colleagues (1994) conducted a randomized, placebo-controlled trial utilizing *S. boulardii* 500 mg twice daily in 124 patients with active CDI (McFarland et al 1994). Approximately half ( $n = 60$ ) of the patients had at least one prior CDI. Patients were also treated with metronidazole and/or vancomycin, with the *S. boulardii* therapy beginning within four days of the start of antibiotics. Patients were excluded if they had acquired immunodeficiency syndrome or if they were immunosuppressed secondary to chemotherapy within the past 3 months. CDI recurrence rates were followed for 4 weeks after discontinuing the *S. boulardii*. Overall the treatment failure rate was 26.3% in the *S. boulardii* group vs 44.8% in the placebo group ( $p = 0.05$ ). Upon further analysis researchers discovered that the significant difference occurred in patients with at least one previous episode of CDI. In the patients with at least one prior CDI, 34.6% of the *S. boulardii* treatment group failed therapy versus 64.7% of placebo patients ( $p = 0.04$ ). Of the patients being treated for their first CDI, 19.3% failed *S. boulardii* treatment compared to 24.2% of placebo treated patients ( $p = 0.86$ ). Although the treatment groups were small, this data suggests that patients experiencing at least 1 recurrent episode of CDI may benefit from *S. boulardii* treatment.

Surawicz et al (2000) also conducted a randomized, double-blind, placebo controlled study utilizing *S. boulardii* for the treatment of recurrent CDI ( $n = 168$ ) (Surawicz et al 2000). *S. boulardii* 500 mg BID or placebo was administered in addition to either metronidazole 1 g daily, vancomycin 500 mg daily, or vancomycin 2 g daily. *S. boulardii* was started on day 7 of the 10 day course of

antibiotic and continued for a total of 28 days. Results of the study showed that patients treated with *S. boulardii* in addition to vancomycin 2 g daily had a 16.7% recurrence rate versus a 50% recurrence rate in the patients treated with vancomycin 2 g daily and placebo ( $p = 0.05$ ). *S. boulardii* did not significantly decrease the recurrence rate in either the vancomycin 500 mg daily group or the metronidazole group. A limitation to the results of this trial included the small number of patients ( $n = 32$ ) included in the vancomycin 2 g daily group.

The use of probiotics presents several potential concerns. Probiotics are usually considered dietary supplements and do not undergo as rigorous of testing compared to pharmaceutical agents (Boyle et al 2006). Therefore the assurance of purity, amount, and safety of the probiotics may be in question. In certain countries, regulation of these products occurs by varying governing organizations if the product is marketed for a specific health benefit or use. Side effects of *Lactobacillus* and *Bifidobacterium* include bloating and flatulence, which may be a transient effect of the probiotics eliminating the infectious bacteria (Karpa 2007). *S. boulardii* has been associated with constipation and increased thirst (McFarland et al 1994).

Bacteremia and endocarditis caused by *Bifidobacteria* and *Lactobacillus* have been reported and *S. boulardii*, is a rare cause of fungemia (Borriello et al 2003; Segarra-Newnham 2007). While infections may be caused by these organisms, there are no data stating the risk of developing an infection secondary to consuming lactobacillus or bifidobacteria is any higher than the risk of infection due to a commensal organism (Borriello et al 2003). The overall reported risk of bacteremia due to these organisms is less than one case per one million people. A study in Finland demonstrated that increased consumption of *lactobacilli* was not associated with an increase in blood stream infections (Salminen et al 2002).

Despite the reports demonstrating the safety of probiotics, there are several case reports of *Lactobacillus* infections associated with probiotic use and even more reports of *Saccharomyces* fungemia related to consumption of *S. boulardii* (Muñoz et al 2005; Boyle et al 2006). These infections have occurred in immunocompromised, critically ill, or in patients with a chronic disease or debilitation, and no reports have associated these agents with causing infections in healthy individuals (Boyle et al 2006). A review of 60 cases of *Saccharomyces* fungemia showed 26 of the cases were directly associated with the administration of *S. boulardii* (Muñoz et al 2005). The majority of these cases involved critically

ill patients, which calls into question the safety of this yeast in the critically ill or immunosuppressed population.

The reported infections associated with probiotics did not necessarily involve patients utilizing the therapy specifically for *C. difficile*. However, the rare potential for infection needs to be considered given that patients who are afflicted with *C. difficile* frequently have a chronic disease or may be immunocompromised. Although the case reports suggest the immunocompromised are at risk there are studies demonstrating the safe use of *lactobacillus* in transplant patients as well as those with documented HIV (Rayes et al 2002; Salminen et al 2004). Infections secondary to the use of *Bifidobacterium* have not been reported, which may reflect a safer bacteria or its relatively lower use rate in marketed products compared to *lactobacillus* (Boyle et al 2006).

## Fecal transplantation

Aas et al (2003) describe a retrospective cases series of 18 patients receiving stool transplant for the treatment of recurrent CDI. This method has been proposed to restore bacterial flora and reduce the growth of *C. difficile*. The 18 patients reviewed had a range of two to seven positive *C. difficile* toxin tests prior to the transplant, and had received an average of 3.2 courses of antibiotic treatments consisting of metronidazole and/or vancomycin. The average time between the diagnosis of CDI and fecal transplantation ranged from 25 to 497 days. The fecal transplant was administered via a nasogastric tube and the details of the preparation and administration are described in the report. Of note all patients were treated with vancomycin 250 mg every 8 hours starting 4 days prior to transplant and discontinued the night before the procedure. Of the 18 patients receiving the transplant, 15 had a resolution of CDI. Thirteen of these patients tested negative for *C. difficile* toxin with the other 2 patients reporting no diarrhea recurrence in the 3-month follow up. Of the 3 patients unsuccessfully treated, two patients died within 2 weeks of transplant with both patients having critical illnesses present at the time of transplantation. The remaining patient experienced a recurrent case of CDI confirmed with a positive *C. difficile* toxin test and was successfully treated with a 10-day course of vancomycin.

Although no adverse effects were reported with the stool transplants, the potential risk of acquiring a disease secondary to the transplant does exist (Aas et al 2003). In the study by Aas et al (2003), this risk was minimized by preferably obtaining stool donation from an individual with a close physical connection to the recipient. If a spouse or significant other was not available then another family member or a

healthy individual was utilized. All donors were screened for hepatitis, A, B, and C, HIV-1, HIV-2, syphilis, *C. difficile*, and other gastrointestinal pathogenic bacteria, ova and parasites. The patient acceptability of such a procedure may also be in question. Currently the limited data available regarding stool transplant only warrant its use in severe, recurrent cases that are refractory to other therapies. If the patients experiencing these types of infections determine that the disease is significantly impairing their quality of life then the idea of a stool transplant potentially providing a cure may be given serious consideration.

## Surgery

Because of high mortality rates associated with severe CDI, surgical consultation is recommended. Indications for surgery as a treatment modality include toxic megacolon, bowel perforation, and colonic-wall thickening (Gerding et al 2008a.) Overall post-surgical mortality rates are often high, with total colectomy being reported to have a lower mortality rate than partial colon resection (Koss et al 2006). A retrospective observational cohort trial of CDI patients was recently published which evaluated emergency colectomy versus medical therapy alone in those admitted to the intensive care unit (Lamontagne et al 2007). In the trial, independent predictors of 30-day mortality were leukocytosis  $\geq 50 \times 10^9/L$ , lactate  $\geq 5$  mmol/L, age  $\geq 75$  years of age, immunosuppression, and shock requiring vasopressors. After adjusting for these confounders, the trial showed a reduction of mortality in the surgical intervention group. Colectomy appeared to be most beneficial in immunocompetent patients, those with leukocytosis  $\geq 20 \times 10^9/L$ , those with a lactate level between 2.2 and 4.9 mmol/L, and patients age 65 years and greater.

## Conclusion

Metronidazole and vancomycin have historically been regarded as the primary therapy options for *C. difficile* infection. Metronidazole is still regarded as the agent of choice for initial therapy and first recurrence for most patients with mild to moderate CDI. Vancomycin use should be minimized when possible over concerns related to vancomycin-resistant enterococci and staphylococci, and relatively higher costs when compared to treatment with metronidazole. Vancomycin use is recommended for those that do not respond to metronidazole, have severe CDI, and those with multiple recurrences of CDI. Difficulty associated with treatment of severe CDI, multiple recurrences of CDI and the emergence of a hypervirulent strain of *C. difficile* have



led to investigation into new CDI treatments. If faced with CDI treatment dilemmas, clinicians should consider these therapies based on their pros and cons. As additional clinical data involving these alternative treatment options become available, modifications to treatment algorithms is likely.

## Disclosures

None of the authors has any conflicts of interest to disclose.

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