New Antimicrobial Agents for Patients With *Clostridium difficile* Infections

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Current drug treatment of *Clostridium difficile* infection (CDI) focuses on metronidazole and vancomycin. Early studies showed equivalence, but more recent reports indicate that oral vancomycin is preferred for serious CDI. Recent work has demonstrated a need for new drugs due to challenges with the NAP-1 strain, which appears to cause more refractory disease that is more likely to relapse. These two distinctive facets of treatment are the most challenging. This review discusses new agents in development: antibiotics, probiotics, immune response products, and agents to bind *C. difficile* toxins. None are likely to be more effective than oral vancomycin for acute infection. However, several may be as effective, without causing relapse or promoting unnecessary antibiotic use for multiple conditions. The greatest promise is with agents used to interrupt relapses. In this category the leading new agents appear to be antibiotics (rifaximin, nitazoxanide, difimicin, ramoplanin), toxin-binding agents (tolevamer), probiotics (*Saccharomyces boulardii* and *Lactobacillus ramosus*), and immune agents (toxoid vaccine and hyperimmune globulin). The drugs that appear most promising based on recent trials are rifaximin, tolevamer, and difimicin, which appear promising for reducing relapses.

Introduction

Clostridium difficile infection (CDI) has received substantial attention during the past 3 years, reflecting its increased incidence, severity, and refractoriness to standard therapy [1–3]. Many researchers attribute these changes to the emergence of the NAP-1 strain, which appears to be fueled by fluoroquinolone use, and studies suggesting increased toxin production to account for more serious and more refractory disease. Collectively, this work has called attention to deficits in current management strategies for controlling and treating CDI. This report reviews the status of new agents for CDI.

Defining Current Needs

Although relevant, methods to prevent CDI and laboratory methods to facilitate its early and accurate diagnosis are not discussed here. Instead, management of patients with CDI is emphasized, particularly regarding drugs in current development.

Two major challenges in treatment are recognized. The first is management of acute disease, particularly in patients with ileus or toxic megacolon. The presumed reason is that CDI is caused by *C. difficile* producing toxins in the colon, so that effective therapy requires delivering antibiotics or toxin-neutralizing agents to the colonic lumen. Standard therapy assumes that drugs administered will reach the colonic lumen by failure of absorption, enterohepatic circulation, or delivery across the colonic mucosa from the systemic circulation. The major mechanism is nonabsorption with drugs that reach high levels in the colonic lumen by normal peristaltic action. This is obviously stalled with ileus, which becomes a major concern for all standard therapy. The attributable mortality from CDI in recent years has been reported as 6% and higher in some series [1–3]. Virtually all these patients are treated with standard methods according to current recommendations, so elevated mortality reflects deficiencies in current management strategies and defines an area of substantial need. The specific challenge is to deliver an antibiotic that is highly active against *C. difficile* located in the colonic lumen, and achieving this goal in the presence of ileus.

The second challenge is management of relapses. Standard therapy now is associated with a relapse rate after initial therapy in 18% to 20% of cases; patients who are retreated for relapse have a 40% probability of another relapse, and after that the rate is 60% or more. The frequency of relapse appears to be even higher with the NAP-1 strain. Studies of relapses show that about 60% are true relapses, meaning the same strain of *C. difficile* is the putative agent. The assumption in these cases is that antibiotic treatment fails to eradicate the pathogen as a result

Table 1. Drugs in use and in trials for CDI

Agent	Class	In vitro activity MIC, µg/mL	Pharmacology	Comment
Rifampin	Rifamycin	0.002–0.2	Enterohepatic	Resistance issue
Rifaximin	Rifamycin	0.007–0.02	Not absorbed	Resistance issue; phase 3 trial
Rifalazil	Rifamycin	0.007–0.02	Enterohepatic + poor absorption	Resistance issue
Ramoplanin	Lipoglycopeptide	0.1–1.0	Not absorbed	Phase 3 trial
Difimicin	Macrocyclic ester	0.1–0.25	Not absorbed	Phase 3 trial
Nitazoxanide	Nitrothiazole benzamide	0.5	Not absorbed	Dose issue
Fusidic acid	Steroid antibiotic	0.06–64	Poorly absorbed	Resistance issue
Teicoplanin	Glycopeptide		Not absorbed	Vancomycin equivalent
Tolevamer	Anionic polymer			Phase 3 trial
Clostridium difficile vaccine	Toxoid	—	—	
Saccharomyces boulardii	Probiotic	—	—	Concern for fungemia (rare)
Metronidazole	Nitroimidazole	0.03–0.1	See text	Extensive trials
Vancomycin	Glycopeptide	0.02–1.0	Not absorbed	FDA approved for CDI (only agent)

CDI—*Clostridium difficile* infection; FDA—US Food and Drug Administration; MIC—minimum inhibitory concentration.

of sporulation. However, about 40% appear to represent new infections with *C. difficile*, because it involves a different strain. This presumably reflects that the major drugs to treat *C. difficile*—oral vancomycin or metronidazole—also are inducing agents. Thus, the paradox that drugs used to treat the disease also cause it. This was demonstrated in studies of CDI in 1977 using the hamster model, which showed that vancomycin protected hamsters challenged with clindamycin, but all animals died of lethal colitis when oral vancomycin was discontinued; death occurred with or without antecedent clindamycin. The challenge with relapses apparently is to control *C. difficile*, but also to permit reestablishment of the normal colonic flora that presumably is responsible for population control in the colon and the reason why carriers of *C. difficile* do not have CDI in the absence of antibiotic exposure.

This review defines two quite different challenges for CDI management strategies. The first is to get effective drugs to the infection site in patients with advanced disease and ileus. The second challenge is relapsing disease and the need for drugs to control *C. difficile* replication or neutralize toxin without perturbing normal flora and its reestablishment.

Current Status of Management

Important observations in the past 3 years have redefined some relevant management issues. These are discussed in the next two sections.

Acute CDI

Multiple antibiotics appear to be effective, including oral vancomycin, bacitracin, metronidazole, teicoplanin, fusidic acid, and possibly linezolid. All have the property of almost uniform in vitro activity against *C. difficile* and demonstrated benefit for treating CDI. Two—metronidazole and vancomycin—have emerged as standards and multiple drugs are being evaluated (Table 1). Early comparative studies showed that these two drugs were comparably effective in response rates [2,4,5]. However, more recent studies consistently showed oral vancomycin was superior in patients with severe disease. This is based on a meta-analysis of reported trials, two prospective studies with randomization in patients stratified by disease severity [6,7], and retrospective analysis of cases to define time to recovery of normal bowel function and time to eradicate cultivable *C. difficile* [8]. The presumed explanation is possible resistance, which has been reported but not supported by most studies. The real problem is delivery of metronidazole to the colonic lumen [9]. This agent is virtually completely nonabsorbed when given orally, although variable levels in the colon have sometimes been found in patients with colonic inflammation, as with Crohn's disease or in the presence of diarrhea [9]. By contrast, vancomycin is almost completely absorbed so that serum levels with oral administration are nil and levels achieved in the colon lumen are several hundred-fold higher than the highest minimum inhibitory concentration (MIC) recorded (16 µg/mL). Thus, many authorities now

recommend metronidazole for mild cases of CDI based on comparable activity compared with oral vancomycin for patients with mild or moderate CDI, substantially lower cost for the oral preparations, and concern for promotion of vancomycin-resistant enterococci (which is probably fallacious reasoning) [8].

As noted earlier, a major concern with vancomycin in seriously ill patients with ileus is the inability to deliver the drug to the infection site. This has been achieved with intracolonic delivery by colonoscope or retention enema, but these methods of drug delivery are unconventional and the reported experience is limited. Other interventions for the patient with ileus include intravenous immunoglobulin (IVIG; discussed later), intravenous metronidazole (based on the assumption that colonic levels are achieved in the presence of an inflamed colon), or colectomy. Colectomy is now done in 0.5% to 2% of cases with a mortality rate of about 25% to 35% in five reported series with 102 cases [10].

In summary, it seems hard to envision a new drug that will have superior performance compared with oral vancomycin in treating the initial infection based on pharmacologic properties of that drug and activity against *C. difficile*. However, it seems highly plausible that there will be better agents in terms of inducing relapses. The potential exists for alternative, nonantimicrobial treatment for seriously ill patients, including better definition of the role of IVIG and systemic antimicrobials.

Relapsing disease

The rate of relapses is about 20% with initial treatment and increases in frequency with subsequent recurrences. The presumed reason is that the drugs used to treat are also inducing agents. Multiple methods have been used to "break the cycle," especially in those with multiple relapses who may have almost continual dependence on oral vancomycin. Metronidazole plays a lesser role here due to concern about neuropathy with long-term use. Other options are probiotics, primarily *Saccharomyces boulardii* and *Lactobacillus rhamnosus*. Although commonly used, no consensus exists regarding their efficacy and neither drug is approved for this indication by the US Food and Drug Administration (FDA) [11,12]. Another potential intervention is IVIG, based on the assumption that relapses reflect the inability to mount an antigenic response to toxin A as indicated by circulating levels of IgG. An additional option is a tapering dose of vancomycin over a 2-week period combined with "pulse therapy" using 125 mg, by mouth, on alternate days for 4 to 6 weeks [13,14]. The theory for this approach is that the higher dose is required to control *C. difficile* and the low-dose pulse treatment maintains *C. difficile* as a spore until the normal flora is reestablished, with the assumption that this usually requires at least 1 month.

Finally, the most successful method of managing relapsing CDI is a fecal transplant using stool from a healthy donor delivered by nasogastric (NG) tube or by retention enema [15]. This is consistently shown to be the most predictably effective method for treating relapses. However, this treatment is not readily available because it is administratively difficult and aesthetically displeasing; reimbursement is questionable; and using biologics with largely unknown ingredients raises liability concerns.

In treating relapses, multiple options are available but none are easily accomplished and consistently effective. This area offers the probability of successful new drug development for controlling *C. difficile* while allowing reestablishment of normal flora, which is the ultimate mechanism to control *C. difficile*. This area appears to offer substantial promise for new drug development with drugs that have very selective antibiotic activity or bind toxin.

New Drugs and Tactics

Rifamycins

Three members of the rifamycin class have been used extensively to treat *C. difficile* [16]. The first, rifampin, was reported in 1982 to be the most active in vitro among 32 antibiotics tested, with 73% sensitive at 0.06 μg/mL and 98% sensitive at 2 μg/mL [17]. The drug is well absorbed, but gives high colonic levels as a result of enterohepatic circulation [18]. The initial studies were reported in 1987, when it was used in combination with oral vancomycin for patients with multiple relapses following vancomycin treatment. The combination was successful in six of seven patients, but all seven were recolonized with *C. difficile*. None of these strains were resistant to rifampin [19]. Two concerns were the extensive drug interactions as a result of inducing *CYP3A4* by rifampin, and the high frequency of high-level resistance with this agent when used alone for almost any pathogen. Few reports have been published of rifampin use for CDI since this early report.

Subsequent studies have been done with rifaximin, which also shows excellent in vitro activity against *C. difficile* [20–25]. One report of 93 strains showed a MIC_{50} of 0.004 μg/mL, which is far more active than either metronidazole at 0.125 μg/mL or vancomycin at 1 μg/mL, but the MIC_{90} for rifaximin was 128 μg/mL [17]. The pharmacokinetic studies of rifaximin showed that it is nearly completely nonabsorbed, giving plasma levels that are usually undetectable and stool concentrations with 200-mg doses as high as 8000 μg/g [22]. Two case series have been reported with rifaximin using oral doses of either 400 mg once daily or 200 mg twice daily for relapsing disease [22,23•]. Both reports show high frequency of response with no further episodes, but of the combined total of 14 patients, one showed the stool isolate with a MIC pretreatment of 0.0075 μg/mL, which increased after treatment to 256 μg/mL. Two comparative trials of rifaximin versus vancomycin have been reported in patients with initial infections with *C. difficile*; both

showed comparable clinical response, but the time to negative toxin test was substantially shorter in vancomycin recipients (5 vs 8 days) [24,25].

The third rifamycin is rifalazil, which is an oral agent with a prolonged half-life permitting once-daily administration; it is well absorbed, but high colonic levels are achieved as a result of enterohepatic circulation [26]. This drug also shows extraordinarily good in vitro activity with MIC_{50} of 0.0075 μg/mL [27]. To our knowledge, no reports exist of clinical trials with rifalazil, although it has been tested in the hamster model and, unlike vancomycin, did not result in relapses.

Collectively, these studies show that agents in this class have promise based on high colonic levels and good in vitro activity against *C. difficile*. The Achilles heel of the class is the high level of resistance noted for many bacteria (including *C. difficile*) challenged with rifamycins as monotherapy.

Ramoplanin

Ramoplanin is a new lipoglycodepsipeptide with good activity against gram-positive, but not gram-negative, organisms [28,29]. The drug is poorly absorbed, has excellent activity in vitro against *C. difficile*, and had activity comparable to oral vancomycin in the hamster model [30]. The single clinical trial comparing vancomycin with ramoplanin—200 mg, twice daily or 400 mg, twice daily, for 10 days—showed a response rate comparable to vancomycin in 86 patients with cure rates of 86% in each group and a 20% to 26% relapse rate in ramoplanin recipients [31]. The study authors concluded that the drug was comparable to vancomycin given orally for initial therapy of CDI, but has the potential advantage of activity against vancomycin-resistant enterococci; moreover, it does not intrude on any currently used antibiotics in terms of promoting clinically important resistance.

Difimicin (OPT-80 and PAR101)

Difimicin is an 18-membered macrocyclic antibiotic that is poorly absorbed, gives very high colonic levels, and has a limited spectrum with good activity against several anaerobic bacteria, including clostridial species [32]. Activity against *C. difficile* shows MIC values of 0.1 to 0.25 μg/mL [33,34]. The drug is well tolerated with oral administration and showed promising results in a phase 1 trial with a dose of 400 mg/d [33–35]. The drug is currently in a phase 3 clinical trial versus oral vancomycin for CDI.

Fusidic acid

Fusidic acid is a steroid with a narrow spectrum including activity against gram-positive bacteria, but no activity against gram-negative agents. It has been used in Europe and Canada as a topical agent for skin and eye infections since the 1960s. The drug shows good activity against *C. difficile* [36–39], but evolution of resistance is a problem [38]. A comparative trial with metronidazole showed about 50% of strains became highly resistant to fusidic acid; nevertheless, these patients had clinical responses comparable to those with metronidazole [38]. The drug also compared favorably with vancomycin and metronidazole in comparative trials of CDI [39]. Concern about resistance has resulted in uncertainty about the future of this drug as a CDI treatment.

Nitazoxanide

Nitazoxanide is used for parasitic infections of the gastrointestinal tract, but has in vitro activity against *C. difficile* [40]. This drug was tested in the hamster model with clindamycin challenge [41•] and proved as effective as vancomycin and metronidazole in preventing acute lethality; however, unlike the comparators, it did not induce CDI. A subsequent randomized, double-blind trial of metronidazole (250 mg, four times daily for 10 days) versus nitazoxanide (500 mg, twice daily for 7 days, and 500 mg, twice daily for 10 days) showed comparable 7-day response rates (82% vs 89%) and relapse rates (43% vs 30%) [41•]. A subsequent open-label trial was reported with nitazoxanide in 35 patients who had metronidazole failure (no response to treatment for ≥ 14 days) or more than two relapses [42••]. The response rate to nitazoxanide was 26 of 35 (74%) and the relapse rate in responders was 7 of 26 (27%).

Anion exchange resins

Anion exchange resins bind toxin A and toxin B and consequently are candidates to neutralize the toxins of CDI [43]. Initial trials with cholestyramine were done before *C. difficile* was known to be the putative agent of CDI and showed efficacy in patients with antibiotic-associated pseudomembranous colitis due to clindamycin [44]. A subsequent study with colestipol was unsuccessful, and these binding agents lost favor [45]. More recently, tolevamer was developed; this is a large anionic polymer that also binds *C. difficile* toxins A and B with no apparent antibiotic activity [46••]. The drug was tested in a phase 3 trial versus vancomycin and metronidazole with patients during their first episode of CDI. The results are summarized in Table 2, which shows tolevamer was significantly inferior to metronidazole and vancomycin for primary response rates, but the relapse rate was significantly less [47••]. These results might be anticipated because this drug has no inherent antimicrobial activity and thus is unlikely to prompt reinfection.

Probiotics

The substantial interest in probiotics is fueled in part by a recent report of significant benefit of *Lactobacillus* in preventing CDI [48]. Two products are available commercially, but neither has been approved by a regulatory agency for treatment of CDI. *Lactobacillus rhamnosus* (commercially available as the dietary supplement Culturelle; Amerifit

Table 2. Tolevamer clinical trial for CDI

	Tolevamer, 3 g tid, *n* = 278	Metronidazole, 375 mg qid, *n* = 140	Vancomycin, 125 mg qid, *n* = 126
Response	73%*	95%	96%
Recurrence	6%*	18%	18%

*Significant difference compared with metronidazole and vancomycin.
qid—four times daily; tid—three times daily.

Brands, Cromwell, CT) is an organism that, unlike most *Lactobacillus*, can colonize the GI tract [49•]. The limited clinical experience for this agent in relapsing CDI has been favorable [50]. One clinical trial was performed in 15 patients with recurrent CDI, with a therapeutic response in three of eight given *Lactobacillus plantarium* [51]. There are seven reported cases of infections, primarily bacteremia, associated with *L. rhamnosus* given to prevent antibiotic-associated diarrhea or recurrent CDI [52•]. The data are too limited for any conclusions regarding the potential use of this drug for CDI.

Another probiotic is *Saccharomyces boulardii*, which has been the subject of two randomized trials [53,54]. One used *S. boulardii*, 500 mg, starting on day 7 of high-dose vancomycin treatment and continuing for 28 days. Results of this trial showed a recurrence rate of 17% in recipients of the probiotic versus 50% in the placebo group ($P = 0.05$) [53]. A second trial used 500 mg, twice daily for 4 weeks, combined with antibiotics for *C. difficile*. The recurrence rate among 124 participants was 26% in probiotic recipients and 45% in a placebo group ($P = 0.05$). These results, although statistically significant, were not sufficiently compelling for FDA approval. It should be noted that *S. boulardii* has been reported as the cause of fungemia, with 40 reported cases [54]. Of these, three apparently had this complication associated with treatment using the probiotic. A review of probiotics, including *S. boulardii* and *Lactobacillus*, concluded that available data are insufficient to endorse this tactic for recurrent CDI and that the potential for bacteremia and fungemia may outweigh the benefits [55]. Another meta-analysis summarized six randomized trials and concluded that probiotics showed efficacy for CDI (RR 0.59; $P = 0.005$) [12]. A Cochrane Library review concluded there was no evidence to support probiotics alone as treatment of CDI, and inadequate evidence to support their use as an adjunct to antibiotic treatment [56•].

Immune treatment

The scientific rationale of the immune treatment of CDI is based on the study by Kyne et al. [57], who reported results of studies in 44 patients with CDI, including 22 with a single episode and 22 with recurrent disease. The former group demonstrated a systemic anamnestic response to toxin A with elevated levels of serum IgG. The conclusion from this report is that clinical expression of CDI reflects the failure of an immune response. This provides the rationale for treatment with IVIG, hyperimmune serum, and the pursuit of a vaccine.

Multiple reports exist of IVIG treatment for CDI, including its use for refractory cases of acute disease associated with ileus and as potential definitive treatment of patients with multiple recurrences. Unfortunately, the results are anecdotal, uncontrolled, and variable [57–60]. A variant of this form of treatment is oral administration of whey protein concentrate from milk of cows immunized with *C. difficile*–inactivated toxin A and toxin B [61,62•]. This is in the early stage of development. Another product is MDX-1388, which represents human monoclonal antibodies against toxins A and B [63•]. Studies in hamsters show efficacy in preventing lethal CDI and relapses, but studies in patients have not yet started. Finally, a *C. difficile* toxoid vaccine has undergone a pilot trial to prevent recurrent disease with anticipation of an active vaccine for high-risk patients [64]. All this work is either anecdotal or in early development.

Fecal biotherapy

Ultimate control of *C. difficile* in the colon is attributed to the normal flora, and its disturbance is the presumed mechanism of antibiotic-associated colitis. Thus, fecal transplantation is a rational approach to treating CDI [65–67]. The source of stool in these cases is a healthy donor, usually related to the patient. Installation is from below by retention enema or from above by NG tube. The largest published experience is with NG infusion in 18 patients with multiple occurrences [15]. All but one of these patients had definitive cure as a result of treatment. Of all methods of managing relapse, this one seems to have the best outcome reported. However, as noted earlier, this approach is not readily available and concerns exist regarding the use of biomaterial despite screening for enteric pathogens and recognized viral pathogens (eg, human T-lymphotropic virus types 1 and 2, HIV, hepatitis viruses). This tactic is undergoing a randomized, controlled trial versus vancomycin for patients with recurrent CDI in The Netherlands.

Conclusions

This review shows three major challenges for CDI therapy. The first is a method to deal with fulminant disease often associated with ileus and difficulty in getting therapeutic agents to the infection site in the colon. Vancomycin has

ideal properties in terms of pharmacology and in vitro activity versus virtually all strains of *C. difficile*. Finding a more effective alternate therapy will be difficult, although it is likely that a suggested intervention might be an alternative to vancomycin that is as effective but costs less, poses less concern for abuse and resistance, and/or presents a lower probability of relapse. With regard to relapsing disease, some agents appear promising, such as tolevamer, difimicin, and possibly rifaximin or ramoplanin. The most successful therapy used for relapsing disease appears to be fecal transplant, but this is not likely ever to have widespread acceptance despite almost uniformly successful clinical experience. Immune control is attractive for a prevention strategy, if the thesis of Kyne et al. [57] is correct, but new products with hyperimmune globulin and toxoid vaccine are several years away.

Disclosure

Dr. Bartlett has served as HIV consultant and on advisory boards for Abbott, Bristol-Myers Squibb, GlaxoSmithKline, and Tibotec. He has served as an infectious disease consultant and on advisory boards for Arpida and Johnson & Johnson.

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