Clinical Management of Clostridium difficile–Associated Disease

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The incidence of Clostridium difficile–associated disease (CDAD) and its serious complications (including colectomy and death) have been increasing worldwide. This phenomenon is strongly associated with the appearance of a new “hypervirulent” strain in several countries. More-effective strategies are needed for the prevention and treatment of this entity. This article will review the current approaches using antimicrobials, probiotics, immunomodulation, surgery, and miscellaneous adjuvants to prevent and treat this infection.

In the past few years, there have been increasing reports of nosocomial epidemics of Clostridium difficile–associated disease (CDAD) in the United States [1] and Canada [2], along with documentation of increased morbidity, mortality, complications (e.g., colectomy), need for intensive care, and relapses. Similar reports have emanated from France [3], The Netherlands [4], Poland [5], and a myriad of other countries [6–8]. Typing of the isolates involved in these outbreaks has revealed a preponderance of so-called North American Pulsefield type 1, which has been similarly described as ribotype 027 and toxino type III and is now popularly called the “hypervirulent” strain (NAP1/027). This hypervirulent strain is known for its production of binary toxin [1, 2], as well as for the presence of a tcdC gene mutation associated with enhanced synthesis of both toxin A and toxin B [9]. In addition, compared with historical strains obtained, in some cases, from the same geographic areas, this strain has recently developed high-level fluoroquinolone resistance [1, 2].

Along with the reports of epidemic CDAD have emerged anecdotal impressions or small-series substantiation of decreased responsiveness to metronidazole therapy [10–12]. High colectomy and case-fatality rates have prompted clinicians to seek better approaches to this disease—specifically, better ways of preventing disease and identifying treatments that will more effectively and quickly reverse the symptoms and signs of CDAD before the onset of severe disease or death.

Prevention of CDAD can be conceptualized as being subdivided into 3 categories: (1) probiotics, (2) immunomodulation, and (3) “early preventative therapy.” Similarly, treatment of CDAD can also be subdivided into therapeutic categories: (1) antibiotics, (2) immunomodulation, (3) probiotics, (4) surgery, (5) miscellaneous adjuvant therapies, and (6) the approach for patients with multiple relapses. Each of these categories will be dealt with in turn.

PREVENTION OF CDAD

Probiotics. Of the 3 CDAD prevention categories mentioned, probiotics have probably been touted for the longest time as a plausible means of preventing this disease. However, despite the plethora of studies, some of which included double-blind, randomized methodology, no probiotic has reproducibly and convincingly emerged as an effective strategy for CDAD prophylaxis. In addition, caution should be exercised before probiotics are endorsed on a wide scale, because bloodstream infection due to orally administered probiotics has been reported in both immunocompetent [13] and severely ill [14] individuals.

Some of the probiotics evaluated in comparative studies of CDAD prevention include Lactobacillus rhamnosus GG, Lactobacillus acidophilus, Lactobacillus
bulgaricus, Lactobacillus plantarum 299v, Saccharomyces boulardii, and mixtures of these probiotics. A recent meta-analysis of such studies suggested some overall efficacy of probiotics [15], but this evaluation of dissimilar patients and outcomes has been criticized [16, 17]. At present, the role of probiotics in the prevention of CDAD is dubious, and it has been very appropriately summarized by Dendukuri and colleagues, in a large meta-analysis, as follows: "Studies conducted to date provide insufficient evidence for the routine clinical use of probiotics to prevent or treat CDAD" [18, p. 167].

A new type of “probiotic”—genetically modified toxin-negative C. difficile—has recently been characterized and seems to prevent CDAD in hamsters when given prophylactically [19]. Data on the use of this agent in humans are not yet available.

Immunomodulation. The preponderance of severe CDAD in elderly and immunocompromised individuals has suggested that host resistance plays a major role in prevention and modulation of disease. Indeed, fascinating data from early studies suggest that C. difficile colonization of hospitalized patients does not progress to CDAD in the presence of a host response to the toxins—specifically, in the presence of high levels of antitoxin A, which can be measured in the serum of such individuals [20]. These data suggest that passive immunity (i.e., administration of antitoxin immunoglobulins) or active immunity (i.e., vaccination with an effective C. difficile toxin-derived vaccine) might prevent CDAD. Although no direct prospective evidence exists to support these concepts as yet, vaccine trials for the prevention of CDAD are currently being planned.

Early preventative therapy. In this article, the term “early preventative therapy” is used to denote the use of CDAD therapeutic agents (i.e., metronidazole or vancomycin) at the same time that CDAD-inciting antibiotics are used, to prevent the development of symptomatic CDAD in high-risk patients. Such high-risk patients would include, for instance, individuals who are known to be colonized with C. difficile, who are at high risk for CDAD for epidemiological reasons (e.g., because they are elderly and have been admitted to a hospital where CDAD is endemic), or who recently had CDAD. For these individuals, administration of an essential antibiotic (e.g., as treatment for pneumonia) would be associated with a high probability of developing CDAD. On the basis of no prospective evidence but, often, a large body of clinical experience, some clinicians now start a parallel course of oral metronidazole or vancomycin along with treatment with the potentially CDAD-inducing antimicrobial, to prevent the appearance of symptomatic CDAD. Despite the absence of guidelines for this approach, there is remarkable homogeneity in the approaches used by most clinicians, in that clinicians who practice this prophylactic strategy use oral metronidazole or vancomycin during the entire course of antimicrobial therapy and for an additional 7 days after the end of its administration. Although this approach is logical in its intent, we must await documented proof of its effectiveness before it can be endorsed.

TREATMENT OF CDAD

Antibiotics. Standard therapy for CDAD consists of oral administration of either metronidazole or vancomycin. Although vancomycin remains the only licensed therapy for CDAD in the United States, a recent poll substantiated that a vast majority of infectious diseases clinicians use metronidazole as first-line therapy for this disease [21]. Current guidelines support this approach, citing the much reduced cost of metronidazole, compared with that of vancomycin; the reduced risk of acquiring vancomycin-resistant enterococci when vancomycin is avoided; and the comparable clinical effectiveness of both agents against CDAD [22–25]. However, all of these guidelines are based on clinical effectiveness documented in the medical literature before the appearance of the current hypervirulent strain. Indeed, recent reports of decreased responsiveness of CDAD to conventional therapy, as well as increased relapse rates associated with CDAD caused by the hypervirulent strain and treated with metronidazole [11], have prompted some authorities to endorse oral vancomycin as the preferred therapy for moderate or severe disease caused by this epidemic strain [26]. Large-scale prospective comparisons of vancomycin and metronidazole for the treatment of CDAD caused by the hypervirulent strain do not exist, but a current 3-arm study investigating the usefulness of tolevaner (a styrene sulfonate polymer that specifically binds C. difficile toxins A and B) in the treatment of CDAD is using metronidazole and vancomycin in the 2 comparative arms. This should allow a side-by-side comparison of these 2 agents for the treatment of CDAD caused by the hypervirulent strain as well as CDAD caused by other C. difficile types.

The reasons or mechanisms behind the perceived diminished effectiveness of metronidazole (compared with vancomycin) have not been elucidated [27]. Thousands of C. difficile isolates have now been tested in at least 3 countries (the United States, the United Kingdom, and Canada), and no resistance to metronidazole has been found [1, 2]. A recent cross-Canada surveillance study of CDAD resulted in the collection and testing of >1800 infecting isolates and found no strain that had resistance to metronidazole (M. Mulvey, personal communication). However, some recent in vitro studies have suggested that “heteroresistance” to metronidazole may explain the clinical phenomenon of a slow or incomplete response to this antimicrobial agent [28, 29]. This finding remains to be substantiated.

Additional small studies using bacitracin, teicoplanin, and fucidin for the treatment of CDAD have been published, with each study showing promising results [30–34]. However, the number of patients treated in each study was small, and the infecting strains were not typed. The latter 2 agents are not licensed in the United States, although they are available in
other countries. Some clinicians use combinations of drugs to treat CDAD (e.g., metronidazole and vancomycin or metronidazole and rifampin); however, none of these modalities has been subjected to adequate scientific scrutiny. A recent analysis of patients who received rifampin in addition to metronidazole showed no benefit whatsoever from this approach, when compared with patients who received metronidazole alone [35].

An additional therapeutic dilemma exists for patients with severe disease who cannot take oral CDAD therapy because of the presence of an ileus or severe nausea and/or abdominal pain. For these individuals, a reasonable approach involves intravenous administration of metronidazole, in an effort to achieve diffusion into the inflamed colon, along with enteral administration of vancomycin via a gastric tube (with suction discontinued for 60 min after administration of each dose every 6 h). Intracolonic administration of vancomycin via a Foley catheter (with 500–1000 mg of vancomycin given in varying volumes of saline every 4–12 h and with the catheter clamped for 60 min after administration of each dose) has also been described [36, 37].

**Immunomodulation.** Since publication of the previously discussed study [20], in which antitoxin immunoglobulins seemed to play an important role in preventing or modulating disease, maneuvers intent on boosting this aspect of an individual’s immunity have been attempted. Active immunization with a vaccine containing denatured C. difficile toxins (“toxoids”) has been shown to elicit high levels of antitoxin antibodies [38, 39]. This preparation was administered to 3 individuals with chronic relapsing CDAD, all of whom remained symptom-free after administration [40]. A substantive review of this vaccine was recently published by Giannasca and Warny [41]. Passive immunization using intravenous immunoglobulin (IVIG) has been used in small case series [42–45], as well as in selected patients with severe disease, during the large outbreak in Montreal, Canada. In the published series involving small numbers of patients, the responses seem to be dramatic, but a large comparative study has yet to be undertaken. In Montreal, during the large multi-institutional outbreak there, anecdotal evidence from clinicians suggested that improved outcomes were obtained for patients with severe CDAD when they received IVIG in addition to conventional therapy with or without colectomy. Doses of IVIG used in Montreal varied from clinician to clinician, but they usually consisted of either a single administration of 0.3 g/kg or 5 daily infusions of the same dose. A retrospective and comparative analysis of the use of IVIG in Montreal is currently under way.

Another method of delivering antitoxin and antibacterial immunoglobulins to patients with CDAD has involved creating hyperimmune bovine colostrum (after inoculation of cows with an appropriate C. difficile vaccine) and refining the collected product for use as an enteral therapy [46–48]. One such product has been shown to prevent CDAD in hamsters, whereas another has not only prevented disease in hamsters but has also eliminated relapsing disease in 15 of 16 human subjects [49].

**Probiotics.** As summarized above in Prevention of CDAD, there exists no clear-cut evidence that probiotics are useful in the treatment of established CDAD. The only exception remains the single study of S. boulardii for the prevention of relapses when used sequentially after therapy with high-dose (i.e., 2-g/day) oral vancomycin [50], although this has not been substantiated for patients with multiple relapses due to the hypervirulent strain. The same probiotics listed above in Prevention of CDAD have been evaluated for the treatment of CDAD. The 2 meta-analyses cited above [15, 18] do not provide much conclusive evidence supporting their use, other than the possible mentioned benefit of S. boulardii in the treatment of relapsing disease.

**Surgery.** Colonic surgery remains an important aspect of care for the patient with severe CDAD. Although the type of surgery that is necessary seems to be clear, the optimal timing of surgery remains undefined.

The type of surgery to perform for patients with CDAD who are deemed to need surgery has been clinically well substantiated: only a total colectomy appears to be the procedure of choice to save these patients’ lives. One recent report demonstrated a mortality rate of 100% if a hemicolectomy (rather than a total colectomy) is performed for these severely ill individuals [51]. Colorectal surgeons usually report that the pancolitis associated with severe CDAD makes in colorectal anastomosis virtually impossible, thereby necessitating performance of a total colectomy and ileostomy for all such patients.

The best time to perform a total colectomy for a patient with severe CDAD remains an elusive issue. One older study suggested that the “best practice” is to undertake rapid surgery if the patient has a perforated bowel, has severe disease without response to medical therapy after 48 h, or has already demonstrated multiple-organ damage [52]. These criteria, however, remain too nebulous and undefined. Also, in the presence of disease caused by the hypervirulent strain, some patients experience progression from severe disease to death in less than the suggested 48-h waiting period after the initiation of medical therapy. An additional factor to consider is that many patients with severe disease cannot receive enteral therapy because of the presence of ileus or severe nausea and/or abdominal pain, rendering medical therapy suboptimal and leading to predictably progressive disease. The timing of surgery (i.e., total colectomy) for this latter patient group is especially crucial.

Attempts to standardize indications for optimal timing of surgery have shown that patients fare better if they undergo colectomy before they develop the need for vasopressors and if certain clinical and laboratory parameters fall within a “dangerous” range (i.e., a WBC count of 20,000–50,000 cells/mm³,
a serum lactate level of 2.2–5.0 mmol/L, an Acute Physiologic and Chronic Health Evaluation score >27, and patient age >74 years) [53]. It is only through analyses of such patients that we will be able to pinpoint the best time to use surgical intervention for these seriously ill patients.

Miscellaneous adjuvant therapies. The interesting concept of using “prebiotics” to stimulate the growth of normal intestinal flora as a means of treating CDAD has been suggested recently [54]. The use of oral oligofructose led to an increase in intestinal bifidobacteria and a decreased relapse rate among treated patients. These data obviously require corroboration before wide-scale acceptance.

Cholestyramine seems to be attractive because of its nonspecific binding capacity and the suggestion that it might therapeutically bind *C. difficile* toxins, thereby speeding recovery and/or decreasing the risk of relapse. However, the only complete studies using cholestyramine are from the 1970s or 1980s (long before the appearance of the hypervirulent strain) and included small groups of patients. Since then, at least 2 publications have documented that cholestyramine not only binds *C. difficile* toxins but will also bind teicoplanin and vancomycin in the gut, leading to reduced or absent free fecal concentrations [55, 56]. These latter data, the lack of controlled trials using this agent, and the frequent intestinal adverse effects associated with the use of cholestyramine by patients with CDAD are strong arguments against its use.

Fecal flora “transplantations” have shown remarkable effectiveness in abrogating recurrent disease in patients with multiple relapses of CDAD [57, 58]. The need for adequate screening of stool donors, unpleasant manipulation of large quantities of stool, and technically difficult administration to achieve pan-colonic distribution has made this therapy extremely difficult to implement. Tvede and Rask-Madsen [57] replaced the stool mixture with a “synthetic stool” blend of 10 aerobic and anaerobic bacteria and documented impressive success with this approach. It remains unknown which bacterial species are most necessary or important for therapeutic colon repopulation and whether this approach has any propensity for causing bacteremia or any other adverse events if used in a large enough group of patients. Other creative ways of repopulating the gut with “normal flora” have been reported, including administration of stool via a nasogastric tube [59]. This latter approach purportedly achieved positive relapse-free results for 18 subjects.

Approach for the patient with multiple relapses of CDAD. One of the most difficult issues related to CDAD is the treatment approach for patients with multiple relapses of CDAD. Studies of such individuals show that multiple relapses are more common in elderly individuals and in those with initially severe CDAD, as well as in patients with renal insufficiency, those who have recently undergone gastrointestinal surgery, and those taking additional antibiotics and antacid drugs [60–62]. Interesting serologic studies show that patients with relapses of CDAD have lower circulating antitoxin A antibody titers than patients without multiple relapses of CDAD, suggesting an impaired immune response as at least one of the underlying causes [63]. Because of this, immunomodulation, as discussed above, might be key in preventing such relapses.
At the present time, no single therapy has been shown to be superior in the prevention of further relapses in patients who have already experienced multiple recurrences of CDAD. Some success has been described with the use of high-dose (i.e., 2-g/day), tapering-dose, and pulsed-dose oral vancomycin [64]. In one series, additional benefit was noted with the addition of *S. boulardii* [65], but this experience occurred before the appearance of the hypervirulent strain, and the experience during the Montreal epidemic was disappointing in terms of the ability of this probiotic to prevent relapsing disease caused by this strain.

For a few investigational drugs, such as OPT-80 [66] and tolevaran [67], lower relapse rates have been demonstrated in small case series, but these data require substantiation, and larger trials are currently under way. A recent approach using vancomycin followed by rifaximin displayed impressive effectiveness in 8 women with multiple relapses of CDAD; however, the development of in vitro rifaximin resistance after treatment is worrisome [68].

Clinicians remain without an effective evidence-based approach for the patient with multiple relapses of CDAD. Although some algorithms consist of high-dose or tapered-dose oral vancomycin, with concomitant or sequential IVIG and/or such probiotics as *L. rhamnosus* GG and *S. boulardii*, no single regimen can be recommended at this time.

**CURRENT STATUS OF INVESTIGATIONAL THERAPIES FOR CDAD**

At the present time, in part because of the appearance of the hypervirulent form of CDAD and the increasingly frequent reports of severe disease and death resulting from this disease worldwide, a number of initiatives have been undertaken to find alternative and improved antimicrobials, probiotics, immunomodulating agents, and adjuvant measures for preventing and controlling this disease. Table 1 presents most of the current research endeavors, although this field is advancing rapidly. It is certainly the fervent hope of most physicians who deal with this disease, along with the desire of those patients who have CDAD, that one or more approaches will be shown to be highly effective in preventing the disease itself, decreasing the associated serious morbidity and high mortality, and preventing the frequent relapses that make so many patients ill for such a long period.

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