Clostridium difficile: Recent Epidemiologic Findings and Advances in Therapy

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Clostridium difficile–associated disease (CDAD) has become an important public health problem. The causative organism is acquired by the oral route from an environmental source or by contact with an infected person or a health care worker who serves as a vector. Disruption of the bowel microflora, generally by antibiotics, creates an environment that allows *C. difficile* to proliferate. Organisms produce toxins A and B, which cause intense inflammation of the colonic mucosa. The syndrome that results includes severe diarrhea, fever, abdominal pain, and leukocytosis. A new strain of *C. difficile* has become prevalent in the United States, Canada, and the United Kingdom. Identified by pulsed-field gel electrophoresis (PFGE), this strain is called North America PFGE type 1, abbreviated as NAP-1. *Clostridium difficile* NAP-1 characteristically generates large amounts of toxins A and B, as well as an additional binary toxin and is associated with enhanced morbidity and a poor response to antibiotic therapy. Mild cases of CDAD may respond to cessation of antibiotic therapy, perhaps related to antibody production by the infected person, but most infected persons require antimicrobial therapy. Vancomycin has been approved by the United States Food and Drug Administration for treatment of CDAD, but reluctance to use this antibiotic in the hospital setting has led to reliance on metronidazole as first-line therapy. Recent studies show a high rate of failure, due either to infection by NAP-1 or to the presence, in hospitals, of older and sicker adults who have been treated with many broad-spectrum antibiotics. Nitazoxanide, bacitracin, teicoplanin, and fusidic acid are additional agents that have published efficacy for this indication in humans. Rifaximin and PAR-101 are under investigation. Other therapies, including polymers that bind *C. difficile* toxin and monoclonal antibodies to toxins, and preventive measures such as toxoid vaccines are also under study.

Key Words: *Clostridium difficile*, *C. difficile*–associated disease, CDAD, infectious diarrhea, metronidazole, vancomycin, nitazoxanide, bacitracin, teicoplanin, fusidic acid, rifaximin, tolevamer, PAR-101.
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OUTLINE

Diarrheal disease due to *Clostridium difficile* has become an important public health concern. With increases in the number of cases,[1–3] the severity of disease,[1, 4] and documented instances of failures to therapy,[1] investigators have been prompted to examine the causes of treatment failure, as well as new treatment modalities.

Clostridium difficile, an anaerobic, gram-positive, spore-forming bacterium, is the most common recognized cause of antibiotic-associated diarrhea,[5] which has become increasingly problematic in hospitals, nursing homes, and other long-term care facilities. Infection by this organism accounts for 10–25% of antibiotic-associated diarrhea, 50–75% of antibiotic-associated colitis, and 90–100% of antibiotic-associated pseudomembranous colitis.[6, 7] The mortality rate of *Clostridium difficile*–associated disease (CDAD) ranges from 6–30% when pseudomembranous colitis is present and can be high even in cases in which colitis is presumed, but not proved.[1, 4, 8] Deaths are often attributed to comorbid conditions, but sometimes to the colitis itself.[4, 8] Although the disease occurs most commonly in the hospital setting, it also occurs in outpatients[9] and has become a large economic burden.[10] The morbidity, together with increased costs related to diagnosis, treatment, and complications, has played an important role in the search for optimal prevention and treatment of CDAD, as well as in instituting policies and procedures for infection prevention and control. Hospital costs related to *C. difficile* infection in the United States and United Kingdom exceed $4000/case.[11, 12]

History of *Clostridium difficile*

In 1935, *C. difficile* was described as part of the normal flora of neonates.[13] By the 1950s, pseudomembranous enterocolitis was thought to occur infrequently and was attributed to either *Staphylococcus aureus* or *Candida albicans*.[14] In 1974, a prospective study of 200 patients treated with clindamycin reported diarrhea in 21% of the patients and pseudomembranous colitis in 10%.[15] In 1977, a toxin produced by a *Clostridium* species was proposed as the cause of clindamycin-induced ileocecitis in hamsters,[16] and in 1978, *C. difficile* was clearly identified as the causal agent of antibiotic-associated colitis in humans.[17]

Microbiology and Epidemiology

Clostridium difficile is transmitted by the fecal-oral route. The spores are acid resistant and can transverse the stomach, ending up in the colon, where they reside; *C. difficile* overgrowth occurs during antibiotic therapy, as the normal intestinal flora is disrupted.[18]

The frequency of *C. difficile* carriage is about 1–3% in healthy adults and is higher among hospital employees and caregivers of susceptible patients.[19] Stool carriage of *C. difficile* reaches 16–35% in hospital inpatients, with the percentage proportional to the duration of hospital stay and increasing with exposure to antibiotics.[20, 21] Colonization describes the patient with no clinical symptoms, with positive culture for *C. difficile* organism and/or a positive test for its toxin.[22] *Clostridium difficile*–associated disease, or *C. difficile* infection, describes the condition of patients whose feces test positive for the *C. difficile* organism and especially for its toxin and who exhibit clinical findings of disease.

Causes of *Clostridium difficile*–Associated Disease

This disease has been associated with all classes of antibiotics. The initial antibiotic that led to recognition of CDAD was clindamycin. In more recent years, this infection has been highly related to third-generation cephalosporins and fluoroquinolones,[23–25] a finding that has raised the issue of implementing policies to restrict these drugs in tertiary care hospitals. Despite differential claims by manufacturers of currently used fluoroquinolones, we believe that all fluoroquinolones are implicated, and this belief is supported by recent literature.[25, 26]

In general, broad-spectrum antimicrobial therapy is more likely than narrow-spectrum antibiotic treatment to lead to CDAD.[27] Other specific risk factors for CDAD include repeated

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enemas, prolonged nasogastric tube insertion, gastrointestinal tract surgery, and use of proton pump inhibitors.[28] General risk factors include the presence of other comorbidities, advancing age, debilitation, immunodeficiency (human immunodeficiency virus, chemotherapy), long length of hospital stay, a bedridden state, overuse of broad-spectrum antibiotics, and increased duration of antibiotic therapy.[18, 29]

Clinical Symptoms and Complications

The typical clinical symptoms of CDAD include diarrhea, lower abdominal pain and tenderness, fever, anorexia, nausea, malaise, and leukocytosis.[29] Stools are usually watery, voluminous, and lacking gross blood or mucus. *Clostridium difficile* can cause a variety of complications including pseudomembranous colitis, toxic megacolon, perforations of the colon, sepsis, and death.[29] Severely ill patients who develop toxic megacolon or paralytic ileus may not experience diarrhea.

Pathogenesis and Immunity

Strains of *C. difficile* have a number of virulence factors that assist in adherence and colonization, including flagellar proteins, surface-layer proteins, and surface-exposed adhesion proteins. Pathogenic strains of *C. difficile* express one or two large endotoxins, classified as A and B. Recent epidemiologic evidence indicates the presence of a binary protein toxin that is associated with more severe forms of illness. Purified toxin A shows enterotoxic and proinflammatory activity. Toxin A loosens tight junctions between the epithelial cells that line the colon, which facilitates the entry of toxin B into epithelial cells.[5] A recent study showed more severe disease in patients who are infected with binary toxin-producing strains of *C. difficile*.[23, 30] *Clostridium difficile*–associated disease is characterized by a progression from an uncolonized state to *C. difficile* colonization, followed by toxin production.[31] This process, in part, depends on the specific strain of *C. difficile*.

The immune status of the host is thought to be important in determining the outcome between successful colonization and disease. Individuals without prompt development of circulating antitoxin A immunoglobulin G antibodies are more likely to experience more severe symptoms and higher rates of recurrent diarrhea.[23, 32] Alternatively, higher concentrations of antitoxin A antibody are associated with a shorter duration of illness and a decreased risk of recurrence.

A New Epidemic Strain

Several groups of investigators have reported the emergence of a single strain of *C. difficile* as a major cause of epidemic CDAD in the United States, Canada, and northern Europe.[3, 4, 23] This strain is characterized as a ribotype 27, North American pulsed-field gel electrophoresis type 1 (NAP-1), toxinotype III. The strain has an altered repressor gene and generates approximately 16–23 times more toxin than other strains.[23] Infection by this organism has been associated with a high risk of acute clinical deterioration and a poor response to metronidazole therapy.[1, 33] One report indicated that patients are 3 times as likely to die within 30 days if clinical infection with the NAP-1 strain complicates their hospital stay.[1] At 12 months, the cumulative attributable mortality was 16.7%.[1] This organism, as well as closely related strains, has been discovered in the United Kingdom[34] and the Netherlands.[35]

One group reported that 82% of all cases of CDAD in the province of Ontario, Canada, were due to the NAP-1 strain,[4] and another group found that this strain was predominant in five of eight U.S. medical centers that submitted isolates for analysis.[3] When the latter group of authors studied 22 isolates from our hospital, however, they found that only four (18%) were the NAP-1 strain,[8] a finding that supports the notion that the new, epidemic strain is not solely responsible for the increase in CDAD in the past decade.

We believe that the apparent virulence of *C. difficile*, the high morbidity and mortality from infection, and the substantial failure rate after treatment are more related to host factors than to the infecting organism, reflecting the presence, in hospitals, of patients who are older and sicker than in the past, and who have been treated with many antibiotics.

Diagnosis

The Infectious Diseases Society of America[36] and the Society for Hospital Epidemiology of America (SHEA)[37] have established guidelines for diagnosing *C. difficile* infection. The diagnosis is generally based on the detection of toxin A or B in stool filtrates. A toxin-specific enzyme-linked immunosorbent assay (ELISA) is most often used.[38] Detection of cytotoxin B in diarrheal stool filtrates with tissue-culture cytotoxicity assay is regarded as the gold standard for diagnosis and is thought to be the most sensitive test, but the results may take up to 3 days.[38] There are new rapid immunoassays that can be

done individually and provide results in less than 1 hour.

The ELISAs have good specificity, but 100–1000 pg of either toxin A or toxin B must be present for the test to be positive; therefore, a false-negative rate of 10–20% can occur[29]; this false negativity can be overcome, in part, by repeating the study. Early reports on detection of toxins A and/or B by ELISA suggested that the diagnosis of CDAD could be made in about 80% of cases if three fresh diarrheal stools were provided. Currently available ELISA kits measure antibody to both toxins and have undoubtedly been improved. In our experience, there have been very few cases in which a discrepancy occurred between the results of ELISA and that of the cytotoxicity assay.[39] Nevertheless, there are many patients in whom epidemiologic and clinical findings point strongly toward a clinical diagnosis of CDAD and who respond to therapy, yet all assays for toxin remain negative. Such cases may occur because the toxin, for whatever reason, is not released into the feces, or they may reflect a different disease process altogether. The current thinking is to treat such patients as if they have CDAD, even if the assays are negative.

Commercially available reagents that detect both toxin A and toxin B are preferred, as 1–2% of cases involve strains of *C. difficile* that only produce toxin B.[40] Results of this test are generally reported within hours or within 1 day.[41–43] Culturing stool, if done correctly, has a high degree of sensitivity for identifying the organism, but lacks specificity in relating the presence of *C. difficile* to disease. Many patients may be colonized with *C. difficile* and yet remain free of disease.[31]

Other nonspecific laboratory findings indicative of CDAD include leukocytosis,[44, 45] hypoalbuminemia,[29] and fecal leukocytes.[36, 46] Abdominal radiography, computed tomography, and colonoscopy may aid in the detection of colitis. However, the imaging studies are relatively insensitive and yield nonspecific results, and colonoscopy is invasive; all of these studies are expensive.

Treatment

The drugs available or under investigation for treatment of CDAD are listed in Table 1. The initial treatment of CDAD involves discontinuation of the offending antibiotic, fluid replacement, and initiation of specific antimicrobial therapy.[19] Early studies suggested that 15–23% of patients with CDAD had spontaneous resolution of symptoms once the offending antibiotic was discontinued.[40, 47] In practice, however, discontinuation of antibiotics is often not possible, and most clinicians are reluctant to do so without administering specific therapy, as there is no assurance that the symp-toms will resolve. Most important, discontin-uation of antibiotics in most hospitalized patients does not lead to symptomatic improvement.

Table 1. Treatment Options for *Clostridium difficile*–Associated Disease

Characteristic	Drug
Approved by FDA	Vancomycin
Widely used	Metronidazole
Published efficacy in humans	Nitazoxanide, bacitracin, teicoplanin, and fusidic acid
Under investigation	Rifaximin, PAR-101, and tolevamer

FDA = U.S. Food and Drug Administration.

Vancomycin

Vancomycin was the first drug to be widely used to treat CDAD and is the only agent approved by the U.S. Food and Drug Administration (FDA) for this indication.[48] This drug must be given orally; it is not absorbed in the bowel, nor is parenteral drug excreted into the bowel lumen in any appreciable amount. In vitro, *C. difficile* is susceptible to vancomycin; the minimum inhibitory concentration (MIC) for 90% of tested strains (MIC_{90}) is 0.75–2 µg/ml.[41, 49–54] A single study found that 3% of *C. difficile* isolates had intermediate resistance to vancomycin (MIC 4–16 µg/ml), but the clinical implications were not reported, and the in vitro findings have not been reproduced.[55] Since oral vancomycin leads to stool concentrations of up to 3100 µg/ml,[56] results of this study are not likely to be clinically significant.[48] A dose-ranging study showed that oral vancomycin 125 mg 4 times/day is as effective as higher doses.[57] Although some experts have recommended a tapering dosage of vancomycin, there is little rationale and only minimal anecdotal data to support such a regimen.

Metronidazole

Soon after vancomycin was shown to treat CDAD, reports of efficacy of metronidazole began to appear. Two randomized controlled trials

Table 2. Treatment Failure and Recurrence Rates in Studies of Antibiotic Treatment of *Clostridium difficile*–Associated Disease

Year of Study	No. (%)		Follow-up Duration (days)	Failure + Recurrence Rate (%)
	Treatment Failures	Recurrences		
Metronidazole				
1982	0/13 (0)	2/13 (15)	30	15
1983	2/42 (5)	2/39 (5)	21	10
1994	14/632 (2)	39/632 (6)	30	8
1996	2/31 (6)	5/31 (16)	30	22
2001	—	22/44 (50)	60	—
2004	38/99 (38)	—	—	—
2005	46/207 (22)	58/207 (28)	90	50
2005	178/1123 (16)	243/845 (29)	60	45
Vancomycin				
1980	3/79 (4)	11/79 (14)	30	18
1981	0/16 (0)	2/16 (13)	42	13
1983	0/52 (0)	6/51 (12)	21	12
1984	6/189 (3)	46/189 (24)	25	27
1985	8/42 (19)	11/30 (37)	30	56
1986	0/15 (0)	3/15 (20)	60	20
1989	2/25 (8)	3/25 (12)	30	20
1989	0/46 (0)	9/46 (20)	42	20
1992	0/20 (0)	4/20 (20)	30	20
1994	1/122 (1)	12/122 (10)	30	11
1996	2/31 (6)	5/31 (16)	30	22
2005	—	31/112 (28)	60	—
Metronidazole + vancomycin				
1994	8/33 (24)	8/33 (24)	60	48
1998	9/36 (25)	7/36 (19)	90	44
2004	—	68/267 (25)	60	—

Adapted from reference 61.

compared oral metronidazole with oral vancomycin; both demonstrated statistically equivalent, high cure rates and low rates of recurrence.[47, 58] As a result, oral metronidazole 500 mg 3 times/day or 250 mg 4 times/day came to be considered first-line treatment for CDAD, with the usual duration of therapy being 10 days.[46] Metronidazole also achieves potentially effective concentrations in the intestinal lumen after intravenous administration and is therefore an option for patients who cannot tolerate oral drugs.[59]

Even though vancomycin remains the only approved drug, the Infectious Diseases Society of America,[60] SHEA,[37] the Centers for Disease Control and Prevention,[12] and the American Gastroenterology Association[57] all suggest metronidazole as the preferred therapy for the following reasons: in comparative studies in the 1980s, results of treatment appeared to be similar with the two drugs; vancomycin is far more expensive; and there is concern that oral vancomycin will select vancomycin-resistant bacteria in the gastrointestinal tract.[29, 61]

Metronidazole versus Vancomycin

Table 2 presents a comparison of failure and recurrence rates between metronidazole and vancomycin. Either metronidazole or vancomycin has been thought to lead to a rapid resolution of symptoms. The fever generally begins to respond within 24–48 hours and the diarrhea within 48–96 hours.[57] In a comparative study, vancomycin appeared to lead to a more rapid resolution of symptoms than did metronidazole.[12] As noted previously, treatment of CDAD with metronidazole has increasingly been associated with an increased rate of failure and recurrence,[1, 8] perhaps as high as 25% in each category. One group related this failure to the prevalence of the putatively more virulent NAP-1 strain,[1] but another group, most of whose patients were infected by other strains, attributed it to the presence, in hospitals, of older patients who have

more severe underlying illnesses and to the increased use of multiple broad-spectrum antibiotics.[48]

Metronidazole also is recommended for treatment of an initial recurrence, even if it was the original agent used.[27] If patients continue to have diarrhea after 2–5 days of treatment with metronidazole, it is reasonable to consider switching to vancomycin.[29, 62] If the patient is unable to tolerate oral drugs, a nasogastric tube should be used to administer antibiotics, as an enteral route is desirable to treat the infection[5]; there is always concern, however, that because of ileus the drug will not reach the colon. When ileus appears, metronidazole (but not vancomycin) may be given intravenously, as moderate concentrations appear in the colon.[57] Colectomy may be necessary in severe cases of toxic megacolon with or without perforation.[18] Treatment with antiperistaltic agents (e.g., loperamide, diphenoxylate) has been discouraged in case reports that describe patients who have toxic megacolon.[63, 64]

Oral vancomycin, rather than metronidazole, is indicated for pregnant or lactating patients and for patients who exhibit intolerance to metronidazole or who fail to respond to metronidazole after 3–5 days of treatment.[29] Some authorities suggest that patients with copious diarrhea may require higher doses of oral vancomycin, for example, 500 mg 4 times/day, to achieve adequate concentrations in the colonic lumen.[29]

Bacitracin

Bacitracin was found to be successful in the treatment of isolated cases of *C. difficile* colitis in the 1980s and, in two randomized trials,[65, 66] compared favorably with vancomycin.[61] In one of these studies,[66] the authors reported that, after completion of therapy, 55% of patients receiving bacitracin and 14% of those receiving vancomycin still had *C. difficile* toxin in the stool ($p<0.05$), but this result did not affect the number of clinical recurrences.

Teicoplanin and Fusidic Acid

Teicoplanin and fusidic acid, neither of which is available in the United States, have both been shown to have similar efficacy to oral vancomycin[67] or metronidazole.[68] One group compared oral vancomycin 500 mg, oral metronidazole 500 mg, and oral fusidic acid 500 mg, each given 3 times/day for 10 days, with oral teicoplanin 400 mg twice/day for 10 days, yielding an initial response of 93–96%.[58] However, treatment with fusidic acid was associated with a significantly higher recurrence rate (28%) compared with that of the other drugs.

Another group carefully reviewed nine studies to determine the most effective antibiotic therapy for CDAD in adults.[69] The authors looked at initial outcome and recurrence up to 6 weeks after treatment. They found that metronidazole, bacitracin, and fusidic acid were no less effective than vancomycin in terms of symptomatic cure. Teicoplanin may have been slightly more effective than vancomycin, which exhibited a relative failure risk of 1.21 (95% confidence interval 1–1.46, p=0.06).

Nitazoxanide

Nitazoxanide is a nitrothiazolide that was approved in the United States in December 2003 for the treatment of protozoan and helminthic infections.[70] This agent blocks anaerobic metabolic pathways of microorganisms.[6, 71] In vitro, low concentrations (e.g., 0.06–0.5 µg/ml) of nitazoxanide or its metabolite, tizoxanide, inhibit *C. difficile*.[6, 71] In humans, approximately two thirds of the oral dose is excreted in feces as the active metabolite, tizoxanide, which has an MIC_{90} of 0.06 µg/ml for *C. difficile*.[6, 7] The metabolite has been found at a concentration of 200 µg/ml in human bile after a 1000-mg oral dose, allowing high intraluminal concentrations to be achieved.[72]

In a multicenter, double-blind, controlled trial comparing metronidazole with nitazoxanide, 34 patients received metronidazole 250 mg 4 times/day for 10 days, 40 patients received nitazoxanide 500 mg twice/day for 7 days, and 36 patients received nitazoxanide at the same dosage for 10 days.[73] After 7 days of treatment, 82.4% of patients had responded to metronidazole versus 89.5% of patients who responded to nitazoxanide. Thirty-one days after start of treatment, sustained responses were observed in 57.6%, 65.8%, and 74.3% of patients who had received metronidazole for 10 days, nitazoxanide for 7 days, and nitazoxanide for 10 days, respectively. The study was designed to show equivalence, and none of these differences was statistically significant. Adverse events were similar in all treatment groups. The authors concluded that nitazoxanide is at least as effective as metronidazole and may be useful in treating CDAD or recurrence that has failed metronidazole therapy. This concept was

supported in a subsequent open-label study of patients who failed treatment with metronidazole.[39] In that study, 75% responded to nitazoxanide, although one third of these patients later relapsed. A study comparing nitazoxanide and vancomycin is in progress.

Rifaximin

Rifaximin is a nonabsorbed rifamycin drug that effectively treats travelers' diarrhea. This drug is active in vitro against aerobic and anaerobic gram-positive and gram-negative organisms and is being studied in humans with CDAD.[74]

PAR-101

PAR-101 is a naturally occurring, nonabsorbable, 18-membered macrocyclic antimicrobial that is being investigated for the treatment of *C. difficile* infection. This drug has a relatively narrow antimicrobial spectrum, being inactive against facultative gram-negative bacilli and against many anaerobic non-*Clostridium* organisms while exhibiting excellent activity against *C. difficile*.[75, 76] Based on this activity, PAR-101 is being studied in humans for the treatment of CDAD.

Combination Therapy

To our knowledge, there are no systematic studies of regimens that use more than one antibiotic for the treatment of CDAD, despite the tendency of some providers to prescribe them. Based on a noncontrolled study of seven patients, rifampin in combination with vancomycin has been reported as helpful for some patients with recurrent CDAD[27]; no additional studies have, to our knowledge, been reported, and based on this kind of report, it does not seem appropriate to recommend such usage.

Nonantimicrobial Agents

Anion-Binding Resins

Anion exchange resins, such as colestipol and cholestyramine, bind to the toxin produced by *C. difficile* but lack clinical efficacy.[17, 77, 78] The use of anion-binding resins in combination with vancomycin was effective for some patients with recurrent CDAD.[27] However, these agents can also bind orally administered antibiotics directed against *C. difficile*.[79] Tolevamer is a polymer that preferentially binds and inactivates *C. difficile* toxin. In animal studies, this drug effectively prevented mortality due to CDAD and did not interfere with the activities of most antibiotics in vitro.[80] In a phase II study, tolevamer was shown to be effective for resolution of diarrheal symptoms.[81]

Probiotics

Evidence is inadequate to support the use of prebiotics (nutrients that facilitate normal colonic bacterial flora) or probiotics (live microbial supplements) for treating patients with established CDAD.[5] A meta-analysis found that probiotic agents may be effective in preventing antibiotic-associated diarrhea, but little evidence supports their role in the treatment of CDAD.[82] In addition, information regarding the most beneficial species and effective dosages is lacking. Clinicians should be aware of reports of fungemia both in immunocompromised and immunocompetent patients treated with *Saccharomyces boulardii*.[82]

Other Therapies

Short courses of intravenous methylprednisolone[83] or pooled human immunoglobulin 200–500 mg/kg have been used with variable success in treating patients with CDAD, including those who are immunocompetent.[12, 84] A recent report of intravenous immunoglobulin describes treatment of 14 patients, some of whom improved with therapy.[85] However, this study was not controlled, and patients continued to receive vancomycin or metronidazole until symptoms subsided. Based on the low levels of antibody to toxins A and B in the population at large, and on the minimal anecdotal information that is available, we do not believe the use of intravenous immunoglobulin to be justified, although a beneficial effect due to some other mechanism cannot, a priori, be excluded. Anti–*C. difficile* bovine immunoglobulin neutralizes the effects of toxin B in the cell cytotoxicity assay and has been used to treat and prevent CDAD in rodents.[1, 86] Use of monoclonal antibody to toxin A has shown promising results in animals, and phase II studies in humans are in progress[87] using CDA1 and MDX-1388, human monoclonal antibodies to toxin A and toxin B. Surgical intervention is reserved for patients who do not respond to medical treatment or when colonic perforation or toxic megacolon is suspected.[88, 89]

Recurrence

Recent studies have consistently shown that CDAD recurs in up to 50% of patients receiving treatment.[39, 90, 91] Independent risk factors for recurrence include age older than 65 years, increased severity of underlying disease, and exposure to additional antibiotics after treatment.[32] Other factors that influence risk of recurrence include low serum albumin concentrations (< 2.5 g/dl),[91] intensive care unit admissions,[92] and length of stay of 16–30 days.[1] Treatment recommendations for patients who have recurrence after initial treatment with metronidazole include a repeat course of metronidazole, oral vancomycin, or nitazoxanide. To our knowledge, no prospective comparative studies have been reported.

Prevention

Hospital Policies

The SHEA guidelines include recommendations for controlling *C. difficile* infection in hospitals and long-term care facilities.[92] Prevention of nosocomial transmission of *C. difficile* depends on careful attention to hand washing, isolation and barrier precautions, and cleaning of the physical environment.[27] Cross-infections can be decreased with proper hygiene, bed spacing, and reduced sharing of toilet facilities, but isolation precautions are likely to be most effective.[5]

Health care facilities can play a large part in prevention of CDAD by ensuring early diagnosis and reinforcing good hygiene practices.[10] Health care facilities should also promote good hand hygiene by requiring staff to use soap and water for cleaning[93]; alcohol-based hand rubs may not be as effective against spore-forming bacteria.[10] Contact precautions must be in place for affected patients, as well as environmental cleaning and disinfection policies.[10] Efforts to contain *C. difficile* infection also require careful monitoring of the incidence and severity of disease.

The following is a list of guidelines for controlling *C. difficile* infection[94]:

- Frequent hand washing with soap and water
- Use of gloves when caring for patients
- Cleaning of environmental surfaces with sporicidal agents
- Isolation of symptomatic patients in private rooms
- Restriction of antibiotics when outbreaks occur
- Avoidance of rectal thermometers

The following is a list of practices that are not recommended for *C. difficile* infection control[95]:

- Routine stool culture for *C. difficile* in asymptomatic patients or health care providers, even during outbreaks
- Culturing of health care providers' hands for *C. difficile*
- Treating a patient empirically for *C. difficile* before completion of toxin results, unless the patient is very sick with a compatible syndrome or there is a hospital-wide high prevalence of *C. difficile*.

Vaccines

Vaccines against *C. difficile* toxins have been successful in animal models, and early safety trials in humans have been satisfactory. However, active immunization may not be effective in people most at risk for *C. difficile*, who characteristically fail to mount an immune response to *C. difficile* infection. In light of these factors, passive immunization may be a more promising strategy.[5] However, neither of these approaches would address the possibility that local colonic immunoglobulin A production may be more important in protecting against CDAD than humoral immunoglobulin G.

Patient Care Recommendations

Based on the above discussion, the following outline summarizes the recommended treatment of CDAD[48]:

- Discontinue the offending antibiotic, if possible
- Replace fluids and electrolytes
- Avoid antimotility agents
- Provide treatment
  - First line: oral metronidazole 500 mg every 6–8 hours for 10 days; if patient cannot tolerate oral therapy, use intravenous metronidazole and switch to oral once tolerable
  - Second line: oral vancomycin 125 mg every 6 hours (recommend use only when metronidazole seems ineffective, the patient is pregnant, the patient is allergic to metronidazole, or true resistance is shown); nitazoxanide can also be considered second line (and certainly if oral vancomycin fails)
  - Recurrence: retrial of agent used to treat initial episode of *C. difficile* colitis, usually metronidazole; for second recurrences, use oral vancomycin or nitazoxanide

- Multiple recurrences of refractory disease: consider probiotics, immunoglobulin, or steroids
- Ileus or toxic megacolon: intravenous metronidazole, option of adding vancomycin retention enemas 500 mg mixed in 100 ml of normal saline
- Ensure strict contact isolation
- Do not treat symptom-free carriers

Conclusion

Clostridium difficile–associated disease is increasing in frequency and severity and has become a major focus of the medical literature. Emerging resistant strains have forced health care organizations and governments to recognize the need to reinforce practice standards for infection control and to focus on formulary containment of widespread use of broad-spectrum antibiotics. Treatment with vancomycin is thought to be effective, but concern over emergence of vancomycin-resistant bacteria in the hospital environment limits its use. Metronidazole, favored for its low cost and lesser concern over bacterial resistance, is associated with lack of response and relapse. Nitazoxanide may be an alternative for patients who fail metronidazole and/or oral vancomycin therapy. Experimental agents, such as rifaximin and PAR-101, and novel approaches to therapy, including tolevamer, antibodies to toxins, and toxoid vaccines, are under study.

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