Clostridium difficile Colitis

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• *Clostridium difficile* • Colitis • Diarrhea • Infection

Clostridium difficile is an anaerobic, gram-positive, spore-forming bacillus capable of producing significant diarrhea or colitis in the hospitalized patient, particularly one previously exposed to antibiotics. Even though no microbial pathogen is identified in most patients with antibiotic-associated diarrhea, *C difficile* accounts for 15% to 25% of such cases and is the most common pathogen associated with infectious diarrhea in hospitalized patients.[1] *C difficile*–associated disease (CDAD) is common in the surgical population because of the frequent use of prophylactic and therapeutic antimicrobial agents. Although uncommon, a *C difficile* infection can progress to fulminant colitis that requires surgical intervention.[2–5] In recent years, *C difficile* infections have been increasing in incidence and severity. This may be caused by the emergence of a more pathogenic strain of *C difficile*, the BI/NAP1/027 strain, which has been implicated in several outbreaks of CDAD in North America and Europe.[2–5]

CDAD is associated with significant morbidity, some mortality, and significant health care costs. Although it may only be a marker of patient illness, the all-cause death rate of patients infected with *C difficile* was reported to be about 10% greater than the overall hospital death rate of 3.4%.[6] In the United States, each case of CDAD was found to be associated with additional costs of more than $3600 in 1998, and total costs of CDAD may have exceeded $1 billion dollars that year.[7] Because of the frequency of CDAD in the surgical population and the possible need for surgical therapy in those patients, the surgeon should have a good understanding of this disease, including its pathogenesis, clinical features, diagnosis, and medical and surgical treatment.

PATHOGENESIS

In the absence of exposure to the health care setting, acquisition of *C difficile* is uncommon. Less than 5% of the healthy adult population is colonized with this bacterium.[8] A total of 20% to 30% of hospitalized patients become colonized with *C difficile*, although most of these patients remain asymptomatic.[9–11] Because of its

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ability to form resistant spores, *C difficile* is not easily eradicated from the hospital environment with standard cleansing procedures.[9,12] Medical staff may transmit the spores after contact with an infected patient; the most common sites of contamination include fingernails, fingertips, palms, and the undersides of rings.[13]

Colonic proliferation of *C difficile* is thought to occur when the bacterial environment has been altered by current or previous exposure to an antibiotic.[14–16] The association of any specific antibiotic with CDAD may be related to the capacity of that agent to suppress commensal bacterial growth, the concentration that the drug reaches in the colonic lumen, and the resistance of *C difficile* to the antibiotic.[2,15,17,18] *C difficile* infection can also occur in the absence of exposure to antibiotics; in many such cases, CDAD is associated with the use of antineoplastic medications.[15]

Only *C difficile* strains that produce exotoxins, specifically toxins A and B, are pathogenic. Toxin B is approximately 10 times more potent than toxin A.[19–22] Since 2000, a *C difficile* strain known as "BI/NAP1/027" has progressively emerged. This strain produces increased amounts of toxins A and B. A deletion in this strain's *tcdC* gene, which is a negative regulator of toxin production, causes production of both toxins A and B to increase by 16- to 23-fold.[2,23,24] This strain is also more resistant to fluoroquinolones, has hypersporulation capacity, and produces an additional binary toxin.[25] The hypersporulation capacity potentially accounts for the enhanced transmission of this strain in hospitals as compared with previous strains.

The BI/NAP1/027 strain has now spread throughout the United States, Canada, and Europe.[26] It is associated with an increased severity of disease; patients infected with this strain more frequently have pseudomembranous colitis.[27–29] In the United States, the incidence of *C difficile* infection has more than doubled and *C difficile*–related mortality has quadrupled since the emergence of the BI/NAP1/027 strain.[30–32] There is no evidence, however, that this strain is any more resistant to standard medical therapy than are other *C difficile* strains.[5,33–35]

RISK FACTORS

Major risk factors for CDAD include antibiotic exposure, hospitalization, and advanced age.[1] Previous antibiotic exposure was reported to increase the risk for the development of *C difficile* diarrhea sixfold.[17] Although a single dose of antibiotics can lead to *C difficile* colonization and proliferation, prolonged antibiotic exposure further increases the risk of a *C difficile* infection.[36,37]

Almost any antibiotic can predispose a patient to a *C difficile* infection. Historically, such drugs as clindamycin, cephalosporins, and certain penicillins were the ones most commonly associated with CDAD.[15,17,18] More recently, fluoroquinolones have been implicated as a cause of this infection.[3,33,38,39] There is some controversy regarding the role of specific antibiotics in the current outbreak of the BI/NAP1/027 strain. A prospective study of 12 hospitals in Quebec, Canada found exposure to fluoroquinolones or cephalosporins to be risk factors for CDAD because of this strain.[33] Fluoroquinolone use was also cited as a risk factor for BI/NAP1/027 CDAD outbreaks in various geographic areas in the United States.[38] In a subsequent review of the 2001 to 2004 outbreak of BI/NAP1/027 in Quebec, Canada, however, it was concluded that there was no direct link between the outbreak and specific antibiotics. Instead, the CDAD outbreak was thought to be secondary to poor infection control.[24]

Exposure to the health care setting also increases the risk of acquiring CDAD. The spores are more prevalent in hospital and long-term care facilities, and colonization is greater among patients in those locales, thereby facilitating transmission.[9,40,41] Within

the hospital setting, patients housed in an intensive care unit and those having a prolonged hospital stay are more likely to become infected with *C difficile*.[17,42]

Age is also a significant risk factor for the development of CDAD. Patients older than 65 years have a 20-fold greater chance of developing a *C difficile* infection compared with younger patients.[33,39,43,44] Immunosuppressed patients are also at greater risk.[44] Weaker risk factors include the severity of the underlying disease and treatment with nonsurgical gastrointestinal procedures.[17,42] It has been suggested by some that antiulcer medications, by allowing increased survival of *C difficile* spores, play a role in the spread of this disease; however, this hypothesis has been questioned by others.[17,42]

CLINICAL PRESENTATION

Patients with a *C difficile* infection usually present with diarrhea several days after receiving an antibiotic, although symptoms may occur as long as 2 months after antibiotic treatment.[45] Symptomatic patients with mild to moderate disease usually have less than 10 watery bowel movements per day. Typically, stools have a characteristic odor, but stool characteristics can vary greatly. Clinically evident lower gastrointestinal bleeding is rare with CDAD.[45,46] More severe forms of the disease are associated with increased abdominal cramping and pain and signs of systemic inflammation, such as fever, leukocytosis, and hypoalbuminemia.[3,45]

Diarrhea may be absent in some patients with a *C difficile* infection. This may be caused by several factors, including a paralytic ileus secondary to a recent surgical procedure or the use of narcotics or other agents that impair bowel motility. Much more ominously, it may signal the progression of the infection to its most fulminant form.[3,45,47]

Patients with fulminant CDAD may initially present with nonspecific clinical symptoms and signs, such as nausea, vomiting, dehydration, lethargy, and tachycardia. These patients frequently go on to develop septic shock with concomitant organ dysfunction, such as renal failure.[3,45,47] The disease may also progress to toxic megacolon or, rarely, colonic perforation. Systemic symptoms are caused by toxin-induced inflammatory mediators and not bacteremia, which is reported extremely rarely in association with CDAD.[48] None of the features of *C difficile* infection are highly specific, and other infectious and noninfectious causes need to be considered in such patients. The possibility of CDAD should be considered, however, in critically ill patients with signs of septic shock and an obscure source of infection because the most fulminant form of CDAD may occur in the absence of diarrhea.[1]

DIAGNOSIS

Several laboratory tests are available to diagnose *C difficile* infections. When the patient has clinically evident disease, however, the physician should not wait for a positive test before instituting treatment.[22] Culture of the stool for *C difficile* is a sensitive test; however, not all *C difficile* strains produce toxin and the test may be positive for a nontoxigenic strain.[15,49–51] It may require 48 hours for a culture to become positive. This test is not used routinely in the United States except for epidemiologic studies and antibiotic susceptibility testing.[52]

Most other tests rely on identification of *C difficile* toxins in the stool. The cytotoxicity assay for *C difficile* toxins is considered the gold standard; it is sensitive to less than 10 pg of toxin. This test is very specific, but may be falsely negative if there has been toxin degradation because of improper stool sample storage. Because of the sensitivity of the test, it is not usually necessary to test multiple stool samples. The results of

this test are usually not available for several days, however, and even more time is needed when the test is performed in combination with stool culture.[1,15,49,50,53,54]

Many clinical laboratories use ELISA/enzyme immunoassays or immunochromatography to detect toxin A or toxin B. These tests are relatively specific but less sensitive; they have been reported to have false-negative rates up to 40%. These tests, however, allow for results to be available within hours.[49–51,55–58] Commercially available tests that test only for toxin A can miss small numbers of infections because of strains that produce only toxin B; these strains have been responsible for some epidemics.[59]

There are also tests for microbial proteins other than the *C difficile* toxins. An ELISA/enzyme immunoassay for glutamate dehydrogenase, an enzyme constitutively produced by *C difficile*, has been used. As with *C difficile* cultures, this test lacks specificity because it does not prove that a toxin-producing strain is present. In addition, other fecal microbes occasionally produce the enzyme. Nonetheless, it is a fairly sensitive, inexpensive, and rapid test that can be used as a screening tool for further *C difficile* testing.[52,60] A latex agglutination test is another rapid test that identifies a protein common to *C difficile* organisms. Similarly, this assay does not differentiate between toxigenic and nontoxigenic strains.[15,49,51] Both the ELISA/enzyme immunoassays and latex agglutination assays also have an elevated false-negative rate compared with other tests and may require analysis of repeated samples in a symptomatic patient.[49,61]

Polymerase chain reaction analyses have been developed to detect *C difficile* and its toxins. These are exquisitely sensitive, because they are capable of detecting very small amounts of genetic material. Technical difficulties related to sample preparation and to performance of the assay prevent their widespread clinical use.[62]

Overall, no laboratory test is ideal. The use of a cell cytotoxicity assay or ELISA with stool culture can allow for sensitive and specific detection of a toxigenic organism, but requires prolonged time and is labor intensive.[63] In the United States, most laboratories currently use the ELISA/enzyme immunoassays tests because they are rapid, inexpensive, and technically simple. However, this may result in a higher false-negative rate compared with the use of stool culture as a screen followed by a toxin assay to determine pathogenicity.[64]

Direct endoscopic visualization of the colonic mucosa can be useful in making the diagnosis of CDAD. Greater than 95% of patients identified with pseudomembranes have a *C difficile* infection.[14] Many patients with *C difficile* colitis, however, do not have pseudomembranes; nonspecific colitis may be the only endoscopic finding in such patients. In addition, 20% to 33% of patients with pseudomembranes only have lesions proximal to the sigmoid colon; the diagnosis would be missed using flexible sigmoidoscopy as compared with full colonoscopy.[15,19,49,51,65,66] Overall, endoscopy for the diagnosis of a *C difficile* infection can have a 10% false-negative rate.[6] Because of concern for colonic perforation, this technique has generally been reserved for patients with severe disease and negative laboratory results in whom there is a need for rapid diagnosis.[15,19,49,51,65,66]

Although they are rarely required, radiographic studies can be useful for differentiating *C difficile* infection from other causes of colitis. CT can help determine the extent of the disease and the presence of pneumatosis or colonic perforation.[49,67,68] Intravenous or oral contrast is usually not required to make the diagnosis.[22] Typically, the scan demonstrates the nonspecific finding of a thickened colonic wall. Other signs may be found with CDAD, however, including pericolonic stranding; an "accordion sign" (high-attenuation oral contrast in the colonic lumen alternating with low-attention inflamed mucosa); a "double-halo sign target sign" (intravenous contrast displaying

varying degrees of attenuation caused by submucosal inflammation and hyperemia); and ascites (caused by hypoalbuminenia).[49,67,68] Except for an ileus, small bowel findings are usually absent, although *C difficile* enteritis has been occasionally reported.[1,68,69]

MEDICAL THERAPY

The first step in treating any *C difficile* infection is to discontinue the causative antibiotic if at all possible (**Fig. 1**). If not, changing to antibiotics with less association with CDAD, such as macrolides, aminoglycosides, sulfamethoxazole, tetracyclines, or vancomycin, might be attempted. There are no controlled studies that demonstrate the benefit of this approach, however, and there remains disagreement about which antibiotics, if any, are safest for use in patients with *C difficile* infections.[24,25] Antiperistaltic agents should not be used in patients with CDAD. Opiates should be avoided or minimized to the extent possible.[70] Reduction of peristaltic activity by those agents allows toxins to accumulate in the gastrointestinal lumen and exacerbate the disease.[37]

Antimicrobial Treatment with Metronidazole and Vancomycin

Although other antimicrobial regimens are potentially available for the treatment of *C difficile* infection, the two most commonly used antibiotics are metronidazole and intraluminal vancomycin. Only intraluminal vancomycin has been approved by the Food and Drug Administration as a medical therapy for *C difficile*.[71] Both medications are highly active against *C difficile*. Significant resistance to either drug has not been demonstrated.[71–74] Metronidazole, however, is much less expensive than oral vancomycin.[71]

Empiric treatment is often instituted before the availability of *C difficile* laboratory results to avoid undue delay in therapy.[48] Typically, patients are treated for 10 to 14 days after discontinuation of an offending antimicrobial.[25] A response to medical treatment, such as improvement in the patient's leukocytosis, fever, abdominal pain, or diarrhea, should be apparent within 1 to 2 of days of therapy. Complete resolution of diarrhea may take up to a week. Anecdotal reports indicate that patients infected with the BI/NAP1/027 strain may require longer periods of time to show improvement in their clinical symptoms and signs.[25] Patients who do not demonstrate some improvement after several days or whose condition worsens should have their treatment escalated.[25] It is not recommended that stool be tested in patients who have completed their medical therapy and have resolution of their symptoms because patients may shed the organism or one of its toxins for several weeks after completion of treatment.[75–77]

Oral metronidazole is completely absorbed by the small intestine. After absorption, secretion of the drug into the colon can produce therapeutic fecal concentrations of the drug. Because of this secretion into the colon, fecal metronidazole levels can also be attained with parental administration.[78] Metronidazole reaches the colonic wall in about 1 to 2 hours, but it is not known how long it takes to be secreted out of the colon into the stool.[26] This process is apparently somewhat variable. Fecal metronidazole levels decrease significantly with resolution of diarrhea and are undetectable in the stool of asymptomatic patients colonized with *C difficile*.[78,79] Colonic inflammation with severe *C difficile* infections may also interfere with the delivery of metronidazole to the colonic lumen.[80]

Side effects of metronidazole include gastrointestinal intolerance and, with prolonged courses of therapy, polyneuropathy. This latter side effect should be taken

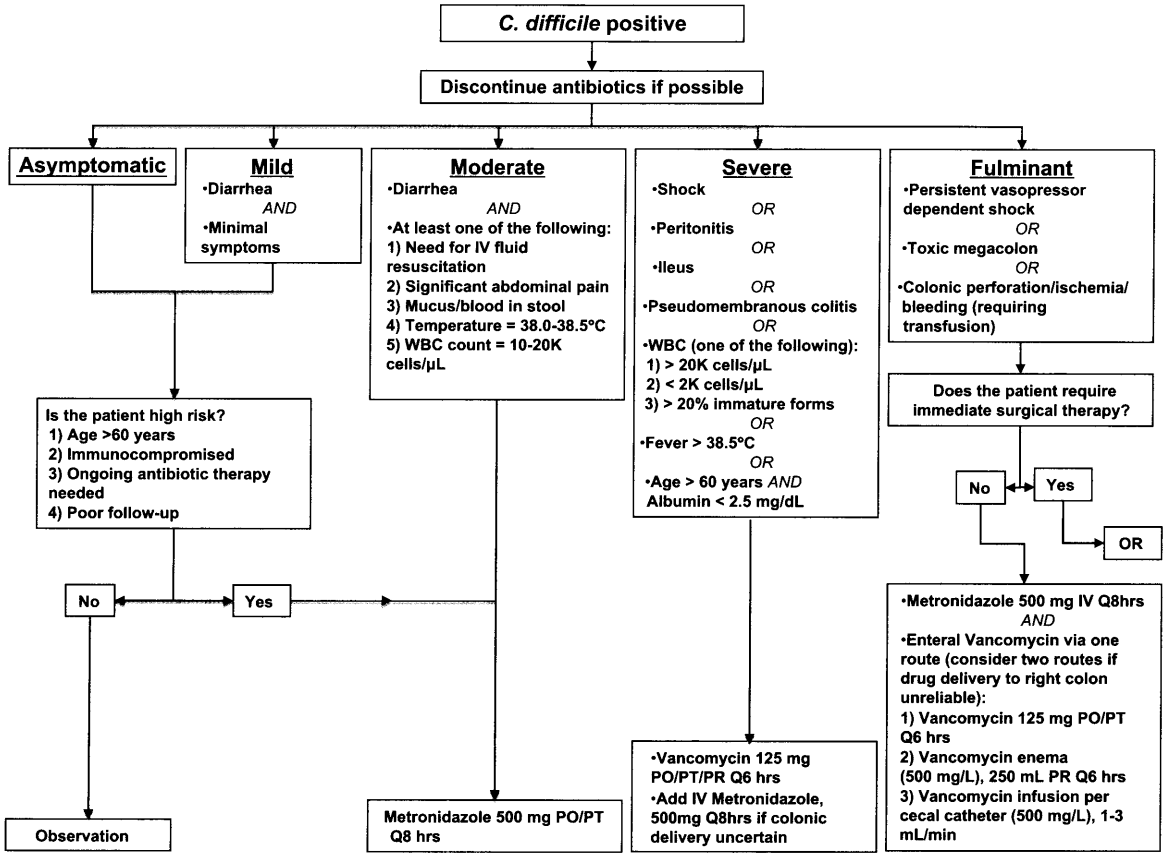


Fig. 1. Algorithm for the medical treatment of primary or initial *C difficile* infections. This algorithm assumes that other possible causes of the patient's signs and symptoms have been excluded. Treatment should be for 10–14 days, with consideration given to continuing treatment for 7 days after discontinuation of potentially causative antibiotics. Metronidazole therapy should be used with caution in pregnant patients.

into account if an antibiotic course greater than 14 days is anticipated.[26] Metronidazole probably does not have teratogenic properties, but should nonetheless be used with caution in pregnant or lactating women and in children younger than 10 years of age.[12,22] Allergic reactions to metronidazole are rare. Oral dosing is typically 250 mg four times per day or 500 mg three times per day.[25]

The use of supplemental agents along with metronidazole has not been shown to be beneficial. Combination therapy of metronidazole and oral rifampin demonstrated no advantage over metronidazole alone in the treatment of *C difficile* infections.[81]

Oral vancomycin is not absorbed from the gastrointestinal tract and can achieve very high colonic concentrations that do not vary with the degree of the patient's diarrhea.[78,79] In patients without an ileus, it takes less than 6 hours for the ingested drug to reach the ileocecal valve.[26] Oral vancomycin has relatively few side effects or allergic reactions.[26] Because of the expense of the oral formulation, it is a common practice to administer the intravenous form of vancomycin enterally in the hospital setting, especially in patients who receive medications through a gastric or intestinal tube.[71] This formulation has a noxious taste, however, and may not be well tolerated with oral administration.[71] Further, this option may not be available for outpatient treatment because many community pharmacies do not carry parenteral vancomycin. Typical dosing of oral vancomycin is 125 mg 4 times per day.[25,26]

Delivery of vancomycin to the colon may be an issue in patients with a nonfunctioning gastrointestinal tract. Under such circumstances, vancomycin can be instilled directly into the colon by an enema or through a catheter placed during colonoscopy. Carefully done trials of this type of treatment, however, are lacking; most of the supportive evidence comes from small series of patients. There is also the potential risk of iatrogenic perforation in patients with a friable colon caused by fulminant colitis.[48]

The available clinical data do not indicate any preference for one agent over the other. Earlier prospective studies demonstrated equivalency of metronidazole and oral vancomycin in the treatment of *C difficile* infection, with neither drug being superior in preventing relapse.[72,74,80,82–87] The numbers of subjects in these clinical trials were relatively small, however, making a type II error possible. In addition, the studies were typically not blinded and the patients were not stratified according to severity of disease.[26,71,80]

More recent prospective trials have suggested that cure rates are higher in patients with severe *C difficile* infections treated with oral vancomycin compared with oral metronidazole.[71,80,88] In one study, patients with severe *C difficile* infections were identified as those having pseudomembranous colitis or meeting two of the following criteria: age greater than 60 years, serum albumin less than 2.5 mg/mL, peripheral leukocyte count greater than 15,000 cells/mL, or a temperature greater than 38.3°C.[80] In a second study, patients with severe colitis were defined as those having 10 or more bowel movements per day, a peripheral leukocyte count greater than or equal to 20,000 cells/mL, or severe abdominal pain.[71,88] Two criticisms of these trials are that the scoring systems used for defining severe *C difficile* infection had not been previously validated, and that they reported intermediate end points, such as cessation of diarrhea or a negative toxin assay, as their end points.[26]

Nonetheless, these data suggest that oral vancomycin may be preferable for the treatment of patients with more severe disease even though neither drug has been proved superior for the treatment of infections caused by the BI/NAP1/027 strain.[26] In addition to the severity of the infection, the presence of an ileus, which limits delivery of oral agents to the colon, may influence the choice of therapy.[25] For patients with mild or moderate *C difficile* infections, there does not seem to be any advantage of oral vancomycin over oral metronidazole. It is still unclear whether patients with

mild *C difficile* infections require any treatment other than discontinuation of the inciting antibiotic.[89]

Other Therapies

Other antimicrobial regimens may be of potential use for *C difficile* infection, although they have been little used in this regard. Antibiotics that have been studied include bacitracin, teicoplanin, and fusidic acid.[22] In some studies, bacitracin demonstrated efficacy equivalent to that of metronidazole and vancomycin for relief of symptoms secondary to *C difficile* infection.[90,91] Bacitracin was less effective, however, at eliminating *C difficile* from the stool. Teicoplanin and fusidic acid, neither of which are available in the United States, display efficacies similar to bacitracin.[90,91] Nitazoxanide, a thiazolide antiparasitic agent that blocks anaerobic metabolism, is a relatively new agent that has demonstrated potential for the treatment of *C difficile* infection.[34,92] Nitazoxanide and its metabolite, tizoxanide, inhibit growth of *C difficile* in vitro. Approximately two thirds of an oral dose is recovered in the stool.[92,93] Dosed orally at 500 mg twice a day, nitazoxanide seemed similar to oral metronidazole for the treatment of *C difficile* infections. It was also used successfully in an uncontrolled study to treat patients who had failed previous therapy with metronidazole.[92,93] Nitazoxanide is much more expensive, however, than oral metronidazole.

Agents other than antibiotics have also been studied with regard to their potential for treating *C difficile* infections.[34,92] Tolevamer is an anionic polymer binding agent. When used at a high dose (6 g per day) to treat mild to moderate *C difficile* infections, this agent demonstrated noninferiority to oral vancomycin.[94]

There has also been considerable interest in the use of probiotics as complements to antimicrobial therapy for CDAD, particularly with regard to their role in restoring a more normal colonic flora. Two randomized trials demonstrated increased efficacy with addition of *Saccharomyces boulardii* to specific antibiotic therapies.[95,96] Other probiotics seem to be less effective in this regard. A recent meta-analysis concluded that only *S boulardii* was an effective therapy for *C difficile* infection.[97] Even this evidence is disputed by some; Dendukuri and colleagues[98] believed that current data did not support the use of any probiotics for *C difficile* infection. Although usually considered harmless, both *S boulardii* and *Lactobacillus* therapy are capable of inducing fungemia and bacteremia, respectively.[99–102]

Experimental treatments being developed to treat *C difficile* infections include tinidazole; tiacumicin B complex (OPT-80); ramoplanin; rifalazil; and rifaximin.[103–108] The use of passive immunity for patients with CDAD is being studied, and efforts to develop a vaccine effective against *C difficile* are proceeding.[25]

Treatment of Recurrent C difficile Infections

Recurrent *C difficile* infections are most likely to develop in the first or second week after completion of therapy. Overall, 15% to 35% of patients infected with *C difficile* develop a recurrence. Recurrences, which occur even more commonly after a second episode of CDAD, are found in 33% to 65% of patients with two or more episodes of *C difficile* infections.[76,87,109–112] The early onset of recurrence may indicate that these are relapses rather than reinfections; the recurrence may result from re-establishment of the infection because of endogenous spores that remain in the patient's gastrointestinal tract after an initial course of therapy.[84,113] Recurrence may also be caused by a new infection following ingestion of spores from an exogenous source, particularly if the patient remains in an environment where such contamination is prevalent. Antimicrobial resistance has not been shown to play a role in recurrence. Rather, recurrence likely reflects inadequate host defenses against the infection.[114,115] The

advanced age and pre-existing comorbidities characteristic of the patients who develop CDAD, and the frequent need for continuation of systemic antibiotics, are factors that may make a *C difficile* infection refractory to treatment.[114–116]

The development of a recurrent *C difficile* infection after successful treatment of a first episode does not necessitate any change in therapy. Secondary response rates are similar with use of either metronidazole or vancomycin. Although complications are more likely to develop with a second or subsequent episode of CDAD, the risk of such complications is also similar with use of either antibiotic.[75,84] High-quality data, however, regarding the optimal treatment of recurrent *C difficile* infections are lacking.[25] Combination therapy of vancomycin and rifampin has been shown to be somewhat efficacious, but this method is limited because of patient intolerance of high-dose rifampin, the numerous interactions of rifampin with other drugs, and emerging resistance to rifampin.[25,117] Cholestyramine, an anion-exchange binding resin that can bind the toxins, has not been demonstrated to be an effective treatment for recurrent *C difficile* infection. In addition, cholestryramine can bind to drugs used to treat *C difficile* infection, such as vancomycin.[25,118] Intravenous immunoglobulin has been used when no other therapeutic options are available. This therapy, however, seems to be of marginal efficacy, optimal dosing has not been determined, and these preparations are very expensive and in short supply.[25] The use of rifaximin following initial vancomycin therapy seemed promising at first, but resistance to rifaximin after treatment has now been documented.[119] The efficacy of probiotic therapy for recurrent *C difficile* infections, as with primary infections, continues to be debated, as are attempts to re-establish normal colonic therapy using stool infusion therapy.[25,95–102]

FULMINANT *C DIFFICILE* COLITIS

Fulminant colitis develops in approximately 3% to 8% of patients with *C difficile* infections, but accounts for most of the serious complications caused by this disease.[22,48] Mortality for fulminant *C difficile* infection ranges from 30% to 90%.[22] Predictors of mortality with fulminant *C difficile* colitis include a patient's American Society of Anesthesiology classification, a need for vasopressor therapy, and a low serum albumin level.[48] Fulminant *C difficile* colitis is associated with a prolonged hospital course in 40% of patients, and with relapse in 20% of patients following adequate medical therapy.[22]

Fulminant CDAD is more likely to develop in patients who have undergone recent surgery, chemotherapy, transplantation, immunosuppression, and those who have autoimmune diseases or HIV-AIDS. Antimicrobial exposure within 2 weeks of the onset of symptoms is also a risk factor for fulminant disease.[48] The emergence of the BI/NAP1/027 strain of *C difficile* has been associated with the development of more severe disease.

Hallmarks of fulminant disease include hypotension, hypoalbuminemia, and a pronounced leukocytosis.[22] Often, patients with fulminant colitis present with an acute surgical abdomen or unexplained shock.[48] Typically, patients with fulminant colitis have a marked leukocytosis. This leukocytosis usually precedes the development of hypotension and the need for vasopressor therapy; the diagnosis of CDAD should be considered in a patient with a marked elevation in the white blood cell count in an appropriate clinical setting.[22,48]

Diagnosis may be problematic in many patients with fulminant disease. About 20% of these patients do not have diarrhea because of an ileus or colonic atony. The clinical findings may be attributed to routine postoperative sequelae of patients who have undergone recent abdominal operations.[48] In the absence of diarrhea, patients may

have negative assays for *C difficile* toxin in the stool, further complicating the diagnosis.[22,48] CT of the abdomen can suggest the diagnosis of fulminant *C difficile* infection in patients with otherwise obscure clinical findings. Colonoscopic findings of pseudomembranes or severe inflammation also suggest the disease and the need for aggressive therapy.[48,49,68] The results of these tests may trigger earlier surgical intervention, which may decrease the morbidity and mortality of a fulminant *C difficile* infection.[48]

Optimal treatment of fulminant *C difficile* has yet to be determined. No drug has been demonstrated to be superior to intraluminal vancomycin as a medical treatment for severe *C difficile* infections. Because gastrointestinal motility is compromised in many of these patients, however, delivery of the antibiotic to the colonic lumen cannot be guaranteed. To obtain significant colonic concentrations of the drug in the setting of an adynamic ileus, vancomycin can be delivered directly into the intestine through a tube positioned beyond the ligament of Treitz, or it can be administered rectally by an enema. Neither of these approaches, however, ensures that the drug reaches significant concentrations in the right colon. Direct instillation of vancomycin into the colon through a tube introduced colonscopically into the right colon has been used successfully to treat fulminant *C difficile* colitis.[120,121] Nonetheless, a controlled trial of this approach is lacking. Intravenous metronidazole is frequently used in the treatment of fulminant *C difficile* colitis, although there are no carefully designed trials of its use in this setting. A typical approach for the treatment of patients with fulminant disease is to administer intravenous metronidazole along with intraluminal vancomycin by the oral, enteral, or rectal route. A failure of such medical therapy in patients with fulminant disease is usually an indication for colectomy.[25,122]

SURGICAL THERAPY

Approximately 0.4% to 3.5% of patients with a *C difficile* infection undergo colectomy. Indications for surgical therapy include the rare colonic perforation caused by CDAD, toxic megacolon, and refractory disease associated with ongoing sepsis.[91] Risk factors for surgical therapy parallel risk factors for fulminant colitis, and include advanced age, malignancy, immunosuppression, renal failure, and the use of antiperistaltic agents.[22,91] Patients who have undergone a surgical procedure within the previous 8 weeks, particularly a cardiothoracic, vascular, or transplantation procedure, represent a significant proportion of the patients undergoing colectomy for *C difficile* infections.[6]

The primary surgical strategy is to resect the involved bowel and to create proximal fecal diversion.[48] Nonresectional therapy with only an ileostomy or cecostomy has been used for fulminant disease; however, this is associated with a higher mortality than is colectomy and fecal diversion.[48] Successful outcomes have been reported for patients undergoing only segmental colonic resections for fulminant *C difficile* infection.[6,48] Regardless multiple patient series indicate that survival is higher with subtotal colectomy than with segmental colectomy or colostomy with catheter placement.[123–129] The current recommendation is to perform subtotal colectomy in patients undergoing surgical treatment of fulminant *C difficile* infection, because the disease is likely to be pancolonic in most patients.

Although emergent colectomy can salvage patients with fulminant *C difficile* colitis, patients undergoing a surgical procedure still have about a 50% overall mortality.[6,48,122] The outcome is worse in patients who have colonic perforation or who have refractory shock requiring vasopressor therapy for blood pressure maintenance at the time of the surgical procedure. It is desirable to intervene before the development of these complications.[22,48,122] Unfortunately, it is not possible to predict which

patients are likely to develop these problems. Ultimately, the need for and the timing of operative intervention for fulminant *C difficile* colitis is best determined by having an experienced surgeon carefully follow these patients and their response to medical therapy.

PREVENTION

Prevention of *C difficile* infections requires appropriate infection control practices and avoidance of unnecessary antibiotics.[37] Once a patient is infected with *C difficile*, strict isolation measures should be implemented to prevent further spread of the disease, because health care workers and patients can transmit the disease throughout an institution and to other institutions. Patients should optimally be housed in a single room or, if necessary, in a room shared with another patient with CDAD.[33,130] Health care workers should wear gowns and gloves when entering the room. Equipment used on the patient (ie, blood pressure cuffs and stethoscopes) should be used only for that particular patient or cleaned before use on another patient.[33,131] Rectal thermometers should be avoided.[37] Environmental cleaning should be performed with a sporacidal agent, such as bleach.[132] Alcohol is ineffective at eliminating *C difficile* spores; health care workers should wash their hands with soap or chlorhexidine and water when caring for these patients.[133] Implementation of these and other infection control measures, along with careful use of antibiotics, are the most important means of limiting the spread of *C difficile* infection within the hospital setting.[33]

SUMMARY

Clostridium difficile is a common cause of diarrhea and an occasional cause of colitis in the surgical population. The emergence of a new strain of this bacterium, the highly toxigenic BI/NAP1/027 strain, has not only increased outbreaks of *C difficile* infections but has also led to an increase in the morbidity and mortality of CDAD. Most patients with mild to moderate or severe *C difficile* infections can be treated medically; however, fulminant *C difficile*, which is frequently lethal, often requires early surgical intervention for optimal management. Containment of this nosocomial infection can only be achieved through careful infection control measures and appropriate antimicrobial-prescribing practices by physicians. It is vital that antibiotics have a clear indication for use, and that unnecessarily prolonged therapy be avoided.

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