

## Review



## *Clostridium difficile*–Associated Diarrhea and Colitis

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*Clostridium difficile* is a spore-forming toxigenic bacterium that causes diarrhea and colitis, typically after the use of broad-spectrum antibiotics. The clinical presentation ranges from self-limited diarrhea to fulminant colitis and toxic megacolon. The incidence of this disease is increasing, resulting in major medical and economic consequences. Although most cases respond quickly to medical treatment, *C difficile* colitis may be serious, especially if diagnosis and treatment are delayed. Recurrent disease represents a particularly challenging problem. Prevention is best accomplished by limiting the

use of broad-spectrum antibiotics and following good hygienic techniques and universal precautions to limit the transmission of bacteria. A high index of suspicion results in early diagnosis and treatment and potentially reduces the incidence of complications.

*Mayo Clin Proc.* 2001;76:725-730

AAD = antibiotic-associated diarrhea; CDAD = *Clostridium difficile*-associated diarrhea; CT = computed tomography; ELISA = enzyme-linked immunosorbent assay; PMC = pseudomembranous colitis

During the past century, *Clostridium difficile* infection has changed from an often fatal postoperative event to primarily a nosocomial disease associated with antibiotic use. Because of widespread antibiotic use, *C difficile*-associated diarrhea (CDAD) has become a common problem with pronounced medical and economic effects. This is particularly important for surgeons because the most frequent indication for antibiotic use is perioperative prophylaxis and surgical patients comprise 55% to 75% of all patients with CDAD.<sup>1,2</sup> The overall incidence is increasing,<sup>1</sup> and *C difficile* now is one of the most frequently implicated enteric pathogens (second only to *Campylobacter jejuni*) and the fourth most common nosocomial disease reported to the Centers for Disease Control and Prevention.<sup>3</sup> This article summarizes the existing literature on *C difficile* disease.

We performed a MEDLINE search to identify articles with the key words *Clostridium difficile*, *pseudomembranous enterocolitis*, or *antibiotic-associated diarrhea* (as a text word). The resultant articles were initially limited to review articles of human studies in the English language between 1990 and 2001. The resultant citations were reviewed for appropriate articles. These references were then supplemented with original articles as identified in the bibliographies of the selected citations, including references before 1990.

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The first case of pseudomembranous colitis (PMC) was reported in 1893 as *diphtheritic colitis*,<sup>4</sup> and the *C difficile* organism was first described in 1935.<sup>5</sup> Early cases of PMC were thought to be due to *Staphylococcus aureus*, and it was not until the 1970s that *C difficile* was implicated as a causative factor.<sup>6,7</sup>

Although PMC was described before the antibiotic era, currently the vast majority of cases are associated with antibiotics, which alter the balance of normal gut flora and allow overgrowth of *C difficile*.<sup>3,8</sup> Clindamycin, lincomycin, ampicillin, or the cephalosporins have been implicated in most reported cases, but almost any antimicrobial agent (including antifungals, antivirals, vancomycin, and metronidazole) can incite the disease.<sup>9-11</sup> However, the aminoglycosides, erythromycin, trimethoprim-sulfamethoxazole, and the fluoroquinolones appear less likely to be causes.<sup>8,10</sup> Factors other than antimicrobial use that can predispose to CDAD include bowel ischemia, recent bowel surgery, uremia, malnutrition, chemotherapy, shock, and possibly Hirschsprung disease.<sup>8,12-14</sup>

The clinical spectrum of *C difficile* includes an asymptomatic carrier state, diarrhea without colitis, and variable degrees of colitis with or without pseudomembranes.

### EPIDEMIOLOGY

*C difficile* carriage is uncommon in healthy adults (1%-3%) but is common in debilitated patients and antibiotic-treated hospitalized adults (15%-25%), including those who received 1 dose of antibiotic before surgery.<sup>2,8,12,15-17</sup> Up to 50% of infants and children harbor the bacteria.<sup>18</sup> The incidence of CDAD in ambulatory adults has been estimated at 7 to 12 cases per 100,000 person-years.<sup>19,20</sup>

The incidence of antibiotic-associated diarrhea (AAD) varies from 5% to 39% depending on the antibiotic used,<sup>8</sup> and most cases in outpatients are due to the antibiotic and not *C difficile*.<sup>21</sup> However, most hospital-based outbreaks of AAD are likely due to *C difficile*.<sup>8</sup> Pseudomembranous colitis occurs in only 10% of patients with AAD.<sup>8,22</sup> Pseudomembranous colitis is rare in infants and young children, perhaps because of a higher prevalence of antibodies to *C difficile* in younger compared to older subjects<sup>18,22</sup> or to immature toxin receptors on colonocytes in infants.<sup>23</sup>

Populations at high risk for CDAD include elderly persons; patients with uremia, burns, or abdominal surgery or cesarean section; and cancer patients or those in the intensive care unit. Whether these groups have more exposure to nosocomial infections or are more susceptible to CDAD as a result of their illness is unknown.<sup>16</sup>

### CLINICAL FEATURES

Typically, CDAD presents within 1 to 2 weeks after an antibiotic has been instituted, although presentation varies from 1 day to 6 weeks.<sup>24</sup> The disease usually presents with profuse watery or mucoid diarrhea that may contain blood, abdominal pain, and low-grade fever, although symptoms range from only loose stools in the mildest cases to toxic megacolon or perforation in the most severe cases.<sup>24,25</sup> Extraintestinal manifestations such as arthritis are rare.<sup>8,24,26</sup>

Dehydration, electrolyte depletion, and hypoproteinemia (from a protein-losing colonopathy) may occur with prolonged or severe disease.<sup>24</sup> Other complications include hemorrhage, sepsis, and pneumatosis coli. Mortality is low (2%-5%), although it is higher in elderly or debilitated patients (10%-20%) or in those with fulminant colitis or toxic megacolon (30%-80%).<sup>27-30</sup> In 1 study, the only factor associated with death was delay in the diagnosis of CDAD.<sup>27</sup>

In some patients (5%-19%), disease will be localized to the proximal colon. These patients may present with an acute abdomen, localized rebound tenderness, no diarrhea, and normal findings on sigmoidoscopy. Considering this diagnosis in such a patient with subsequent confirmation based on stool studies and computed tomography (CT) may help avoid unnecessary surgery.<sup>25</sup>

After recovery, patients may become asymptomatic carriers of *C difficile*, but most never have a relapse.<sup>31</sup> However, 10% to 20% of patients will experience relapse regardless of the therapeutic agent used to treat CDAD. Such patients usually respond well to re-treatment with metronidazole or vancomycin,<sup>8,31,32</sup> but the risk of further recurrences may be as high as 65%.<sup>33</sup>

### DIFFERENTIAL DIAGNOSIS

Staphylococcal enterocolitis is an uncommon cause of AAD and is suspected when gram-positive cocci are seen

on a stool smear with negative results on *C difficile* tests.<sup>34</sup> Neutropenic enterocolitis (typhlitis) is suspected when a patient receiving chemotherapy develops diarrhea and abdominal pain in the setting of neutropenia.<sup>35</sup> Crohn disease and ulcerative colitis can mimic CDAD,<sup>36</sup> and *C difficile* infection can cause a flare in such patients.<sup>36,37</sup>

Other diseases in the differential diagnosis include chemical colitis (chemotherapy, gold), ischemic colitis, and other infections (*Campylobacter*, *Salmonella*, *Shigella*, *Escherichia coli*, *Listeria*, and cytomegalovirus).<sup>38</sup>

### PATHOPHYSIOLOGY

In general, *C difficile* is noninvasive. Rare cases of intestinal tissue invasion have been reported in children with malignancy or a compromised immune system.<sup>39</sup> The development of CDAD requires an alteration in normal gut flora or mucosal immunity, acquisition and germination of spores, overgrowth of *C difficile*, and toxin production.<sup>40,41</sup> The most important toxins are toxin A (enterotoxin and cytotoxin) and toxin B (cytotoxin).<sup>3,40</sup>

Toxin A binds to mucosal receptors and causes cytotoxicity by disrupting cytoplasmic microfilaments. Toxin B then enters the damaged mucosa and causes further toxicity, resulting in hemorrhage, inflammation, and necrosis. The toxins interfere with protein synthesis, attract granulocytes, and increase capillary permeability and peristalsis.<sup>3,24,41</sup> In patients with severe disease, inflammation may involve deep layers, resulting in toxic dilatation or perforation.<sup>27</sup>

### DIAGNOSTIC TESTING

The diagnosis of CDAD is based on a combination of clinical findings, laboratory tests, and sometimes endoscopy. Sudden occurrence of an otherwise unexplained leukocytosis in a hospitalized patient might suggest underlying CDAD and should prompt investigation.<sup>42</sup> Fecal leukocytes can be seen, but their absence does not exclude colitis. Culture for *C difficile* is demanding and has a low predictive value because of the rate of asymptomatic carriers in antibiotic-treated patients and the prevalence of nonpathogenic isolates.<sup>3,15</sup>

Stool cytotoxicity assays are considered positive when cultured cells undergo cytopathic changes after exposure to stool filtrates. The result is confirmed by neutralizing these effects with specific antitoxins. This is considered the gold standard diagnostic method because of its high sensitivity and specificity.<sup>3,43</sup> Of note, however, 5% to 10% of patients with PMC have negative tests by cytotoxin assay.<sup>43,44</sup> Furthermore, cytotoxicity assays are expensive and time consuming.

The enzyme-linked immunosorbent assay (ELISA) for detection of toxin A or B is less expensive and faster than

the cytotoxicity assay<sup>43</sup> and thus is preferred at many institutions. Sensitivity is lower (75%-85%),<sup>43</sup> but performing the test on 2 to 3 separate stool specimens should increase the sensitivity to the 90% range. A newer ELISA to detect the presence of either toxin has excellent specificity (about 100%) and overall agreement (>98%) compared with the cytotoxicity assay.<sup>45,46</sup> By detecting strains that only produce toxin B, this assay (TOX A/B test) improves sensitivity compared with ELISAs that detect only toxin A.<sup>45,46</sup> The latex agglutination test has poor sensitivity and specificity and does not distinguish toxigenic from nontoxigenic strains.<sup>47</sup>

Abdominal radiographs may show mucosal edema or ileus and are useful for ruling out megacolon or perforation.<sup>7</sup> A barium enema examination has a risk of perforation and precipitating megacolon and therefore is not recommended.<sup>7</sup> Abdominal CT may show colonic distention, thickening, pericolonic inflammation, or free air and is most valuable in severe cases and those localized to the proximal colon.<sup>25,48</sup>

The diagnosis of CDAD is difficult to establish in infants because they commonly carry the organism and toxins. A therapeutic trial with vancomycin may be the only noninvasive method to confirm the clinical importance of toxins in the stool.

Although findings on endoscopy may be normal in patients with mild CDAD, most patients have abnormal mucosa, ranging from minimal erythema or edema to ulcerated mucosa, often with nodular exudates, which may coalesce to form yellowish "pseudomembranes"<sup>49</sup> consisting of mucus and fibrin filled with dead leukocytes and mucosal cells.<sup>50</sup> Flexible sigmoidoscopy will be diagnostic in most patients, but colonoscopy may be necessary when the disease is localized above the splenic flexure. Endoscopy can suggest CDAD quickly<sup>44,49</sup> and should be safe in a patient with a nondistended abdomen, but it may be dangerous in patients with severe disease with colonic dilatation. In experienced hands, however, gentle flexible sigmoidoscopy with minimal air insufflation may provide the diagnosis and allow initiation of therapy before stool test results are available.

### TREATMENT OF PRIMARY INFECTION

In patients with mild CDAD, supportive care alone may be sufficient, including discontinuing or changing the offending antibiotic, rehydration, and enteric isolation of hospitalized patients. Diarrhea will resolve with conservative therapy (ie, no antibiotics) in 15% to 23% of patients.<sup>18,51,52</sup> Antidiarrheal agents and narcotics should be avoided because they may result in severe colitis.<sup>53</sup>

Specific antibiotic therapy should be given when supportive therapy fails after a few days, when the offend-

ing antibiotic cannot be discontinued, and when symptoms are severe. In patients with severe CDAD, hospitalization for antibiotics and intravenous hydration may be necessary. Empiric antibiotic treatment should be initiated when the diagnosis is suspected in elderly and severely ill patients before the results of diagnostic tests are known.<sup>43</sup>

Oral administration is preferred because it is superior to parenteral administration.<sup>54,55</sup> Metronidazole is an inexpensive and effective treatment. When used orally (250-500 mg 4 times daily or 500-750 mg 3 times daily for 7-10 days), metronidazole has response and relapse rates comparable to those of vancomycin.<sup>51,56,57</sup> Because of the cost of vancomycin and concerns about the development of vancomycin resistance in other organisms such as enterococci, metronidazole is the preferred first line of treatment.<sup>58</sup> However, metronidazole has more adverse effects and is not recommended for children or pregnant women. Patients whose condition does not improve promptly (within 48-72 hours) should be reassessed to make sure that no other diagnosis has been overlooked. If other pathologic conditions have been ruled out, metronidazole should be switched to vancomycin because some *C difficile* organisms are resistant to metronidazole.<sup>43</sup>

Vancomycin is a reliable but more expensive treatment, with response rates of 90% to 100%, and is the preferred treatment for severely ill patients.<sup>31,57-59</sup> Because oral vancomycin is poorly absorbed, high concentration in the stool can be achieved without systemic adverse effects. The recommended dosage is 125 mg every 6 hours for 7 to 14 days. A higher dose (250-500 mg 4 times daily) can be used for severely ill patients. For infants, 500 mg per 1.73 m<sup>2</sup> every 6 hours is recommended. Patients whose condition does not improve promptly should be reassessed because failure with vancomycin therapy is unusual. If other pathologic conditions have been ruled out and the patient is not severely ill, vancomycin can be switched to metronidazole.<sup>60</sup> However, most patients in whom vancomycin fails are severely ill, and surgery may be indicated (as discussed subsequently).

Parenteral therapy is less effective than oral, but when it is necessary (eg, paralytic ileus), intravenous metronidazole, 500 to 750 mg 3 to 4 times daily, is recommended, perhaps supplemented by vancomycin, 500 mg 4 times daily, via a nasogastric tube or enema.<sup>43,54,55</sup>

Bacitracin is less effective than vancomycin and metronidazole.<sup>59</sup> Teicoplanin has been used successfully in Europe but is not available in the United States. Teicoplanin compares favorably with vancomycin and has a longer half-life.<sup>61</sup>

Anion exchange resins work by binding toxin. Cholestyramine (4 g 4 times daily) can help decrease symptoms associated with mild disease, but when used alone, results

have been discouraging with variable and generally low cure rates.<sup>62</sup> Obstipation is the most common adverse effect. Cholestyramine binds vancomycin, and therefore they should not be used simultaneously.<sup>62</sup>

### TREATMENT OF RECURRENT INFECTION

A major problem with CDAD is recurrence in 10% to 30% of patients.<sup>8,22,33,43</sup> Recurrent disease usually responds well symptomatically to re-treatment with metronidazole or vancomycin at standard doses. With multiple recurrences, several therapeutic options are available. One is to administer prolonged courses of vancomycin, followed by gradual tapering<sup>63</sup> (eg, 125 mg 4 times daily for 4-6 weeks, 125 mg twice daily for 1 week, 125 mg daily for 1 week, or 125 mg every other day for 1 week, followed by 125 mg every 72 hours for 2 weeks). A similar prolonged tapering course of metronidazole can be considered, although adverse effects may increase with longer treatment. Another regimen is "pulse therapy," intermittent treatment periods for 5 to 7 days with antibiotic and anion exchange resin, alternating with periods of no antibiotics.<sup>64</sup> Treatment with a combination of vancomycin and rifampin has also been successful.<sup>65</sup> Other treatments have aimed to alter the colonic flora to suppress growth of *C difficile*; results have been encouraging. These regimens use oral *Lactobacillus* GG,<sup>66</sup> enemas with feces from healthy subjects,<sup>67</sup> and oral nonpathogenic yeast (*Saccharomyces boulardii*).<sup>32,66</sup> None of these regimens have been proved superior, and the choice is based on the individual patient.

### SURGICAL TREATMENT

Surgery is usually unnecessary in patients with CDAD, being required in 0.4% to 5%.<sup>1,28,68,69</sup> The need for surgery is higher in ill patients with more severe disease (eg, 20% of patients in the intensive care unit in 1 report<sup>29</sup>). Development of severe disease is associated with advanced age, malignancy, renal failure, chronic lung disease, immunosuppression, use of antiperistaltic drugs, and the development of hypoalbuminemia (albumin level <3 g/L), hemoglobin concentration (hemoglobin increase >5%), and extremes of white blood cell counts (>25 × 10<sup>9</sup>/L or <15 × 10<sup>9</sup>/L).<sup>30</sup> Indications for surgery include an acute abdomen (which may precede the diagnosis of CDAD<sup>25,69</sup>), sepsis, multi-organ failure, hemorrhage, toxic dilatation, perforation, and deterioration despite medical therapy.<sup>28,29,68,69</sup>

Patients who present with an acute abdomen may not have diarrhea.<sup>25</sup> In such patients, sigmoidoscopy (after dilatation and free air have been ruled out) or abdominal CT may help identify colitis,<sup>25,48</sup> and in the absence of perforation or abscess, surgery may be avoided if the patient's condition responds to medical therapy.<sup>27</sup> Similarly, the presence of pneumatosis coli does not nec-

essarily indicate surgery if the patient's condition is stable and responds promptly to medical therapy.<sup>70,71</sup>

At laparotomy, many patients have ascites, and the colon is often edematous and distended.<sup>28</sup> The serosa can appear surprisingly normal despite severe mucosal disease.<sup>28,68,69</sup> Segmental resections and diverting ileostomy or colostomy have been described; however, these operations often fail, and further surgery is necessary.<sup>25,27,29,68,69</sup> Moreover, these "partial" operations are associated with increased mortality. Therefore, total abdominal colectomy with Brooke ileostomy is the procedure of choice for severe CDAD.<sup>29,68,69,72,73</sup> As mentioned previously, the serosal appearance can be misleading and should not influence the choice of operation.<sup>68,69</sup>

Depending on the integrity of the tissues, the rectum may be stapled and left as a "stump," or a distal mucous fistula may be created to allow antibiotic irrigation of the remaining colorectum.<sup>28</sup> The former option leaves a shorter segment of disease; however, a rectal tube should be placed, or digital examinations of the anus should be performed daily to keep the rectal stump decompressed.

Patients undergoing surgery can have high mortality that may be partly due to a delay in performing the operation.<sup>28</sup> In addition, the risk of complications such as perforation increases substantially in patients with fulminant colitis that does not respond to medical therapy. Therefore, all patients with severe CDAD should have early surgical consultation, and some experts advocate surgery for patients whose condition does not respond within 2 to 3 days.<sup>1,68</sup> Cecostomy or ileostomy has been described in patients with paralytic ileus to instill antibiotic into the lumen, but neither has apparent benefits and should not be performed.

### PREVENTION

*C difficile* spores can survive up to 5 months in the environment, and a primary mode of infection is via the hands of hospital personnel or contaminated objects.<sup>16,74-76</sup> Therefore, prevention has a crucial role in disease management and can be facilitated by prudent use of antibiotics, routine hand washing, disinfection of potentially contaminated objects, and isolation of infected patients, including the use of gloves for patient contact.

Treatment of asymptomatic carriers is not recommended because treatment may prolong the carrier state, which usually resolves spontaneously.<sup>77</sup> Finally, restricting the use of antibiotics, such as clindamycin<sup>78</sup> or the cephalosporins,<sup>79</sup> has decreased the rate of CDAD at some institutions.

### FUTURE CONSIDERATIONS

Monoclonal antibodies and immunoglobulin concentrates are available with activity against *C difficile* toxins. These

agents have been successful in vitro and in animal studies<sup>80-82</sup> and may be useful in protecting patients at risk of acquiring the disease or experiencing relapse. A synthetic oligosaccharide (SYNSORB) may be useful in the treatment of CDAD because it can bind and neutralize toxin.<sup>83,84</sup> The results of clinical trials using these new agents are awaited.

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