

## Clinical Practice

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

## ANTIBIOTIC-ASSOCIATED DIARRHEA

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A 53-year-old woman reports severe watery diarrhea with cramps. She is in her 7th day of a 10-day course of cefixime, prescribed for bronchitis. How should she be evaluated and treated?

## THE CLINICAL PROBLEM

Antibiotic-associated diarrhea is defined as otherwise unexplained diarrhea that occurs in association with the administration of antibiotics. The frequency of this complication varies among antibacterial agents. Diarrhea occurs in approximately 5 to 10 percent of patients who are treated with ampicillin, 10 to 25 percent of those who are treated with amoxicillin-clavulanate, 15 to 20 percent of those who receive cefixime, and 2 to 5 percent of those who are treated with other cephalosporins, fluoroquinolones, azithromycin, clarithromycin, erythromycin, and tetracycline.<sup>1,2</sup> The rates of diarrhea associated with parenterally administered antibiotics, especially those with enterohepatic circulation, are similar to rates associated with orally administered agents.<sup>3</sup>

The spectrum of findings in antibiotic-associated diarrhea ranges from colitis, which is a potential source of serious progressive disease, to "nuisance diarrhea," which is defined as frequent loose and watery stools with no other complications. The clinical manifestations of antibiotic-associated colitis include abdominal cramping, fever, leukocytosis, fecal leukocytes, hypoalbuminemia, colonic thickening on computed tomography (CT), and characteristic changes apparent on endoscopic inspection or biopsy. Although infection with *Clostridium difficile* accounts for only 10 to 20 percent of the cases of antibiotic-associated diarrhea, it accounts for the majority of cases of colitis associated with antibiotic therapy.<sup>4-6</sup>

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## STRATEGIES AND EVIDENCE

The usual challenge to physicians is to identify cases of antibiotic-associated diarrhea that are due to *C. difficile* infection, since this is the most common identifiable and treatable pathogen. Clindamycin, cephalosporins, and penicillins are the antibiotics most frequently associated with *C. difficile* diarrhea, although they also cause diarrhea that is unrelated to superinfection with this organism.<sup>1</sup> Clinical features that can be used to distinguish between diarrhea associated with *C. difficile* infection and antibiotic-associated diarrhea that is due to other mechanisms are summarized in Table 1.

Mechanisms Other Than *C. difficile* Infection

Multiple laboratories report that only 10 to 20 percent of stool specimens submitted for testing for *C. difficile* toxin are positive.<sup>1,3-6</sup> Antibiotic-associated diarrhea may also be caused by other enteric pathogens, by the direct effects of antimicrobial agents on the intestinal mucosa, and by the metabolic consequences of reduced concentrations of fecal flora.

Other enteric pathogens that can cause diarrhea include salmonella, *C. perfringens* type A, *Staphylococcus aureus*, and possibly *Candida albicans*. *C. perfringens* type A produces an enterotoxin known to cause food poisoning; more recently, a different genotype has been implicated in antibiotic-associated diarrhea.<sup>7</sup> Infection with either subtype causes a self-limited diarrhea that generally resolves within 24 hours. There is no specific treatment, and few laboratories offer the diagnostic tests necessary to identify this pathogen.

*Staph. aureus* was implicated as the chief cause of antibiotic-associated pseudomembranous enterocolitis in the 1950s.<sup>8</sup> It is unclear whether this finding represented misdiagnosis of *C. difficile* infection or *Staph. aureus* caused a different disease — an enterocolitis instead of colitis. The distinction is important because metronidazole is effective for *C. difficile* infection but not for *Staph. aureus* infection. The finding of candida species in the stool at a concentration of more than 100,000 organisms per gram and in some patients whose condition has improved after nystatin therapy has suggested that candida species may cause antibiotic-associated diarrhea; however, many authorities question the validity of the evidence.<sup>9</sup> Multidrug-resistant *Salmonella newport* from contaminated beef was implicated in an outbreak of diarrhea among patients who had taken ampicillin.<sup>10</sup> Fluoroquinolone-resistant enteric disease caused by

**TABLE 1.** DIFFERENCES BETWEEN ANTIBIOTIC-ASSOCIATED DIARRHEA DUE TO *CLOSTRIDIUM DIFFICILE* AND CASES DUE TO OTHER CAUSES.

CHARACTERISTIC	DIARRHEA DUE TO <i>C. DIFFICILE</i> INFECTION	DIARRHEA FROM OTHER CAUSES
Most commonly implicated antibiotics	Clindamycin, cephalosporins, penicillins	Clindamycin, cephalosporins, or amoxicillin–clavulanate
History	Usually no relevant history of antibiotic intolerance	History of diarrhea with antibiotic therapy common
Clinical features		
Diarrhea	May be florid; evidence of colitis with cramps, fever, and fecal leukocytes common	Usually moderate in severity (i.e., “nuisance diarrhea”) without evidence of colitis
Findings on CT or endoscopy*	Evidence of colitis (not enteritis) common	Usually normal
Complications	Hypoalbuminemia, anasarca, toxic megacolon, relapses with treatment with metronidazole or vancomycin	Usually none except occasional cases of dehydration
Results of assay for <i>C. difficile</i> toxin	Positive	Negative
Epidemiologic pattern	May be epidemic or endemic in hospitals or long-term care facilities	Sporadic
Treatment		
Withdrawal of implicated antibiotic	May resolve but often persists or progresses	Usually resolves
Antiperistaltic agents	Contraindicated	Often useful
Oral metronidazole or vancomycin	Prompt response	Not indicated

\*CT denotes computed tomography.

salmonella has also been reported; most of the affected patients had previously taken fluoroquinolones.<sup>11</sup> Salmonella may also cause pseudomembranous colitis.<sup>12</sup>

Drugs have multiple effects on the gastrointestinal tract,<sup>13</sup> including some that are independent of antimicrobial activity. Erythromycin acts as a motilin-receptor agonist and accelerates the rate of gastric emptying. The clavulanate in amoxicillin–clavulanate appears to stimulate small-bowel motility, and in rare instances, penicillins may cause segmental colitis.<sup>14</sup>

Antibiotics may substantially reduce the concentration of fecal anaerobes that are normally present. As a consequence, the metabolism of carbohydrates may decrease, which causes osmotic diarrhea, and the rate of breakdown of primary bile acids, which are potent colonic secretory agents, may be reduced. Neither mechanism is clearly established as a cause of antibiotic-associated diarrhea, but the efficacy of enemas with fecal flora in treating this problem suggests that changes in fecal flora are a contributing factor.<sup>15</sup>

In many suspected cases, nonantibiotic drugs are the cause of diarrhea attributed to antibiotics; these include laxatives, antacids, contrast agents, products containing lactose or sorbitol, nonsteroidal antiinflammatory drugs, antiarrhythmic drugs, and cholinergic agents.<sup>13</sup>

#### Diarrhea Associated with *C. difficile* Infection

Infection with *C. difficile* causes a toxin-mediated enteric disease the characteristic clinical and patho-

logical features of which have been reproduced in hamsters.<sup>1</sup> It has a characteristic endoscopic appearance in people (Fig. 1).

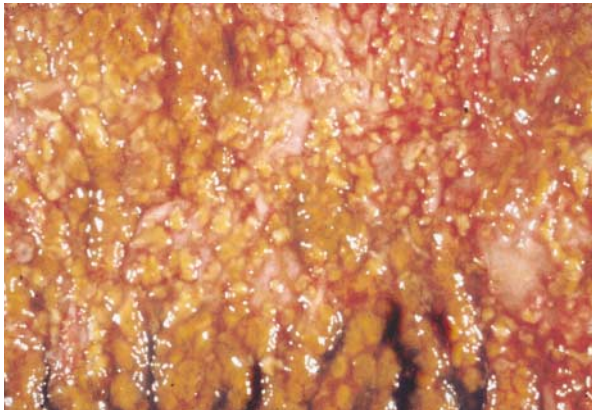
#### Risk Factors

Major risk factors for *C. difficile* infection include advanced age, hospitalization, and exposure to antibiotics. Hospitalized adults have rates of colonization of 20 to 30 percent, as compared with a rate of 3 percent in outpatients.<sup>1,16,17</sup> A population-based study in Sweden showed that, in people who were older than 60 years of age, the incidence of positive assays for *C. difficile* toxin was 20 to 100 times as high as the incidence in people who were 10 to 20 years of age.<sup>18</sup> The antibiotics most frequently implicated in diarrhea associated with *C. difficile* infection are clindamycin, expanded-spectrum penicillins, and cephalosporins.<sup>1,4-6,19</sup> However, virtually any antibiotic may be implicated, including brief courses of antibiotics that are given prophylactically before surgery (with the exception of parenteral vancomycin). Occasional cases follow treatment with methotrexate or paclitaxel for cancer chemotherapy.

Recent studies suggest that immunologic susceptibility has a role in *C. difficile* infection. The presence of IgG antibody against toxin A protects against the clinical expression of *C. difficile* infection<sup>20</sup> and against relapse.<sup>21</sup>

#### Diagnostic Tests

Findings that are considered nonspecific for but suggestive of *C. difficile* infection include leukocyto-



**Figure 1.** Typical Endoscopic Findings in a Patient with Diarrhea Associated with *Clostridium difficile* Infection.

Widely disseminated, punctate yellow plaques are present, which are characteristic of pseudomembranes.

sis,<sup>22</sup> hypoalbuminemia (reflecting a protein-losing enteropathy), and fecal leukocytes.<sup>23,24</sup> Histologic findings in the colon range from normal to pseudomembranous colitis. Pseudomembranous colitis is uncommon but specific, since nearly all cases are attributed to *C. difficile* infection.<sup>1,4-6,16</sup> Although abdominal radiography, CT, and endoscopy may facilitate the detection of *C. difficile* infection, these methods are nonspecific, relatively insensitive, and often expensive, and they have been almost completely supplanted by assays for *C. difficile* toxin.

The cytotoxin assay that uses tissue culture has been the gold standard for diagnosis. It is the most sensitive test,<sup>25,26</sup> detecting as little as 10 pg of toxin B. However, most laboratories do not offer tissue-culture assays, and the results of the assay are not available for 24 to 48 hours. Alternatives include enzyme immunoassays and "toxin-culture assays."<sup>1,4-6,25-31</sup> Enzyme immunoassays are now offered by most laboratories and have good specificity, but 100 to 1000 pg of either toxin A or toxin B must be present for the test to be positive. Therefore, there is a false negative rate of 10 to 20 percent. Commercially available reagents will detect toxin A or toxins A and B. Those that detect both toxin A and toxin B are preferred, since 1 to 2 percent of cases involve strains of *C. difficile* that produce only toxin B.<sup>31</sup> The results of this test should be available within hours or within one day.

The diagnosis can also be made by culturing stool on selective medium, including the toxin-culture assay, with broth cultures of isolates to identify toxigenic strains.<sup>27,29,30</sup> The advantage of this approach, if it is done correctly, is the high degree of sensitiv-

ity. Limitations are the lack of specificity, the delay of three to four days before results are available, and the small number of laboratories that offer this test.

It may be useful to test more than one stool specimen for *C. difficile* toxin. Performing enzyme immunoassays on two or three specimens, rather than one, not only increases the diagnostic yield by 5 to 10 percent,<sup>23</sup> but also increases the cost, since each assay costs approximately \$40.

#### Treatment

Indications for treatment with metronidazole or vancomycin include positive assays for *C. difficile* toxin, with evidence of colitis (fever, leukocytosis, and characteristic findings on CT or endoscopy); severe diarrhea; persistent diarrhea despite the discontinuation of the implicated agent; or the need to continue treating the original infection. Oral metronidazole (500 mg three times daily or 250 mg four times daily) and oral vancomycin (125 mg four times daily) have similar rates of efficacy, with response rates of 90 to 97 percent.<sup>32,33</sup> The usual duration of therapy is 10 days, although few studies have addressed the relative merits of longer or shorter courses. Ideally, all antibiotic treatment should be oral, since *C. difficile* is restricted to the lumen of the colon. If intravenous treatment is required, only metronidazole (and not vancomycin) is effective, since this approach will still result in moderate concentrations of the drug in the colon.<sup>6</sup> The anticipated response to treatment is resolution of fever within one day and resolution of diarrhea in four to five days.<sup>6</sup> Metronidazole is preferred because it is less expensive than vancomycin and avoids the potential risk of promoting vancomycin-resistant enterococci in nosocomial cases. Indications for oral vancomycin, as opposed to metronidazole, are pregnancy, lactation, intolerance of metronidazole, or failure to respond to metronidazole after three to five days of treatment.

Most *C. difficile* infections respond to either vancomycin or metronidazole, and the lack of a response should prompt an evaluation of compliance, a search for an alternative diagnosis, or an assessment for ileus or toxic megacolon, since these conditions may prevent the drug from reaching the target site. For patients with ileus, transport of the antibiotic to the colonic lumen may be increased by using high doses of oral vancomycin (500 mg four times daily) or by instilling vancomycin or metronidazole through long tubes inserted orally or anally. Severely ill patients who have no response to metronidazole or vancomycin may, in rare instances, require colectomy.

#### Relapsing Infection

The chief complication of antibiotic treatment is relapse, which occurs in about 20 to 25 percent of

cases.<sup>4-6,25,34,35</sup> Relapse is suggested by the recurrence of symptoms, usually 3 to 21 days (average, 6) after metronidazole or vancomycin is discontinued. Assays for *C. difficile* toxin are usually unnecessary immediately after the completion of treatment, and the results may be misleading, since about one third of patients for whom therapy is successful have positive assays. Most relapses respond to another course of antibiotics in standard doses for 10 days, but 3 to 5 percent of patients have more than six relapses.<sup>1,25,34-37</sup> Factors that do not appear to influence the frequency of relapses are switching from one antibiotic to another for treatment and prolonged courses of these drugs.

Management is controversial, and the course may involve complications and considerable expense, with a mean cost of \$10,970 in one report.<sup>36</sup> For repeated relapses, treatment for four to six weeks has been proposed to control *C. difficile* infection while the normal flora becomes reestablished. Approaches to this more prolonged treatment include the use of pulsed doses of vancomycin (125 mg every other day to keep *C. difficile* in the spore state with minimal effects on the fecal flora), the administration of anion-exchange resins to absorb *C. difficile* toxin (such as 4 g of cholestyramine three times daily), or the use of agents to antagonize *C. difficile* (such as *Saccharomyces boulardii* or lactobacillus strain GG).<sup>35,37</sup> Others have proposed the use of intravenous immune globulin, on the basis of recent data showing that patients with relapses have reduced plasma concentrations of IgG antibodies against toxin A.<sup>21</sup> Despite the logic, the cost is high, and published data are limited.<sup>38</sup>

Enemas with human stool or stool flora obtained from broth cultures have also been suggested as a means of reconstituting normal flora. Response rates are good,<sup>39</sup> but this solution is usually unnecessary, lacks esthetic appeal, is mechanically unwieldy, and carries a potential risk of transmission of retroviruses or other agents.

#### Epidemics

*C. difficile* is an important nosocomial pathogen, and some hospitals and long-term care facilities have reported epidemics of diarrhea caused by this agent.<sup>40-42</sup> Infection-control policies are well established but may fail. Restricting the use of antibiotics, particularly clindamycin, has been shown to control an epidemic.<sup>40,43</sup> Strain typing has been suggested as a method to evaluate epidemics, but most laboratories do not offer this test, and there are no clearly effective strain-specific interventions.

#### AREAS OF UNCERTAINTY

The optimal approach to managing a relapse of diarrhea associated with *C. difficile* infection is un-

clear. More effective interventions are needed to limit epidemics in hospitals and long-term care facilities. Better understanding is needed of the causes of antibiotic-associated diarrhea that is not due to *C. difficile* infection. There is no diagnostic test specific for antibiotic-associated diarrhea, and effective treatment is generally limited to discontinuation of the implicated agent, with or without therapy with antiperistaltic agents. Infections with *Staph. aureus* and candida are treatable, but methods for their detection are not well standardized, and their role as enteric pathogens is debated.

#### GUIDELINES

The Infectious Diseases Society of America<sup>24</sup> and the Society for Hospital Epidemiology of America<sup>40</sup> (SHEA) have devised guidelines for detecting *C. difficile* toxin (Table 2). The Infectious Diseases Society of America, SHEA,<sup>40</sup> and the Centers for Disease Control and Prevention<sup>45</sup> have all issued guidelines for treatment. All advocate metronidazole as the preferred therapy, at a dose of 500 mg orally three times daily or 250 mg orally four times daily for 10 days.<sup>24</sup> Antiperistaltic agents should be avoided because they may promote retention of the toxin.<sup>24</sup> SHEA guidelines for infection control in hospitals and long-term care facilities are summarized in Table 3.<sup>40</sup> Outbreaks may require restricting the use of antibiotics, especially clindamycin.<sup>5,40-43</sup>

#### CONCLUSIONS AND RECOMMENDATIONS

The possibility of *C. difficile* infection should be considered in all patients with unexplained diarrhea who are receiving or who have recently received antibiotics. The tests used for diagnosis will depend on the kinds of laboratory tests that are available. Enzyme immunoassays to detect toxin A or toxins A

**TABLE 2.** GUIDELINES FOR THE USE OF THE *CLOSTRIDIUM DIFFICILE* TOXIN ASSAY.\*

Only diarrheal stools should be tested unless there is ileus.
"A test of cure" should not be performed except as part of an epidemiologic investigation.
Only specimens from patients who are older than one year of age should be tested.
Enzyme immunoassay is an acceptable alternative to the cytotoxin assay but is less sensitive.
Diarrhea that develops after three days of hospitalization should be tested only for <i>C. difficile</i> toxin (the three-day rule).†

\*Data are based on recommendations from the Infectious Diseases Society of America<sup>24</sup> and the Society for Hospital Epidemiology of America.<sup>40</sup>

†Exceptions to the three-day rule may be made in the case of patients who are at least 65 years of age, those with coexisting conditions, those infected with human immunodeficiency virus, and those with neutropenia.<sup>44</sup>

**TABLE 3.** GUIDELINES FOR CONTROLLING *CLOSTRIDIUM DIFFICILE* INFECTION IN HOSPITALS AND LONG-TERM CARE FACILITIES.\*

Personnel should wash their hands frequently with soap.  
 Clinicians should use vinyl gloves when they are caring for patients.  
 Environmental surfaces should be cleaned with sporicidal agents.  
 Symptomatic patients should be placed in private rooms, especially if they are incontinent of stool.  
 The use of rectal thermometers should be avoided.  
 Outbreaks may require restriction of the use of antibiotics.

\*Data are from the Society for Hospital Epidemiology of America.<sup>40</sup>

and B are usually available. An enzyme immunoassay that detects both toxins A and B is preferable to prevent false negative results in cases caused by strains that produce only toxin B.

The decision to continue, change, or discontinue antibiotics in a patient with antibiotic-associated diarrhea depends on the severity of symptoms, the probability of *C. difficile* infection, and the need for further antibiotic therapy (Table 4). Many patients with enteric disease caused by *C. difficile* infection have a response to withdrawal of the inducing agent. This approach has the advantage of averting relapses. In a case such as that described in the vignette, I would discontinue treatment with the antibiotic, which precipitated *C. difficile* infection.

If there is evidence of colitis or severe diarrhea or if discontinuation of the implicated antibiotic is not possible or does not result in resolution of diarrhea, a 10-day course of therapy with metronidazole or vancomycin is indicated. The oral route should be used whenever possible, although metronidazole can be given intravenously if necessary. The majority of patients will have a response, although relapse may occur. If the patient in the vignette has a positive assay for *C. difficile* toxin, she should be treated with metronidazole since she has severe diarrhea. Follow-up testing for *C. difficile* toxin is not indicated, and the results could be misleading.

If the results of assays for *C. difficile* toxin are negative in a patient with persistent symptoms who has probable *C. difficile*-induced enteric disease, the alternatives are to repeat the test, use alternative tests, expand the diagnostic evaluation to include other causes, or treat empirically. Repeating the test slightly increases the diagnostic yield. In patients who have severe cases and negative results on assays for *C. difficile* toxin, it is reasonable to test for enteric pathogens, including *Staph. aureus* and salmonella. The antibiotics used to treat infection with these microorganisms differ from those for *C. difficile* infection.

**TABLE 4.** MANAGEMENT OF DIARRHEA AND COLITIS ASSOCIATED WITH *CLOSTRIDIUM DIFFICILE* INFECTION.

Discontinue treatment with the implicated antibiotic.  
 If it is necessary to treat the original infection, use an antibiotic that is infrequently implicated in antibiotic-associated diarrhea: aminoglycosides, sulfonamides, macrolides, vancomycin, tetracycline, or possibly fluoroquinolones.  
 Avoid the use of clindamycin, cephalosporins, extended-spectrum penicillins, and agents implicated in the current case.  
 Use supportive measures.  
 Correct fluid losses and electrolyte imbalances.  
 Give additional oral fluids to patients with moderately severe diarrhea.  
 In patients with severe or dehydrating diarrhea, provide intravenous or oral fluids (or both) that contain electrolyte concentrations similar to those recommended by the World Health Organization.<sup>24</sup>  
 Avoid the use of antiperistaltic agents (e.g., loperamide and opiates).  
 Observe infection-control policies for hospitalized patients.\*  
 Provide antibiotic therapy if diarrhea is severe, there is evidence of colitis, diarrhea persists despite the discontinuation of implicated agent, or there is a need to continue treatment of the original infection.  
 The usual treatment consists of 500 mg of metronidazole orally three times daily or 250 mg of metronidazole orally four times daily for 10 days.  
 If the patient is pregnant, cannot tolerate metronidazole, or has no response to metronidazole therapy, treatment with vancomycin (125 mg orally four times daily for 10 days) should be initiated.  
 Teach patients to recognize the symptoms of relapse.

\*The policies are outlined in Table 3.<sup>40</sup>

In cases in which the validity of a negative result on the toxin assay is seriously questioned, the recommendation is to treat it as a case of *C. difficile*-associated disease. The lack of a response to metronidazole and a negative result on assays for *C. difficile* are strong evidence against this diagnosis.

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