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

JOHN G. BARTLETT, M.D.

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. The rates of diarrhea associated with parenterally administered antibiotics, especially those with enterohepatic circulation, are similar to rates associated with orally administered agents.

The spectrum of findings in antibiotic-associated diarrheal illness varies among antibacterial agents. Diarrhea is a common problem among patients who are treated with clindamycin, cefixime, or amoxicillin–clavulanate, whereas diarrhea is rare among patients who are treated with ampicillin or fluoroquinolones. The rates of diarrhea associated with oral cephalosporins, azithromycin, clarithromycin, erythromycin, and tetracycline are approximately 5 percent. The rates of diarrhea associated with oral amoxicillin–clavulanate, cefixime, and fluoroquinolones are approximately 10 percent. The rates of diarrhea associated with oral cephalosporins, azithromycin, clarithromycin, erythromycin, and tetracycline are approximately 2 percent.

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. Antibiotic-associated diarrhea may also be caused by other enteric pathogens, by the direct effects of antimicrobial agents on the intestinal flora, 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. 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.

Staphylococcus aureus was implicated as the chief cause of antibiotic-associated pseudomembranous enterocolitis in the 1950s. It is unclear whether this finding represented misdiagnosis of C. difficile infection or Staphylococcus aureus caused a different disease — enterocolitis instead of colitis. The distinction is important because metronidazole is effective for C. difficile infection but not for Staphylococcus 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. Multidrug-resistant Salmonella newport from contaminated beef was implicated in an outbreak of diarrhea among patients who had taken amoxicillin.

Fluoroquinolone-resistant enteric disease caused by...
Diarrhea Associated with C. difficile Infection

Infection with C. difficile causes a toxin-mediated enteric disease the characteristic clinical and pathological features of which have been reproduced in hamsters.\(^1\) 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.\(^1,16,17\) 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.\(^18\) The antibiotics most frequently implicated in diarrhea associated with C. difficile infection are clindamycin, expanded-spectrum penicillins, and cephalosporins.\(^1,4,6,19\) 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\(^20\) and against relapse.\(^21\)

**Diagnostic Tests**

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

---

**Table 1. Differences Between Antibiotic-Associated Diarrhea Due to Clostridium difficile and Cases Due to Other Causes.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Diarrhea Due to C. difficile Infection</th>
<th>Diarrhea from Other Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most commonly implicated antibiotics</td>
<td>Clindamycin, cephalosporins, penicillins</td>
<td>Clindamycin, cephalosporins, or amoxicillin–clavulanic acid</td>
</tr>
<tr>
<td>History</td>
<td>Usually no relevant history of antibiotic intolerance</td>
<td>History of diarrhea with antibiotic therapy common</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Findings on CT or endoscopy*</td>
<td>May be florid; evidence of colitis with cramps, fever, and fecal leukocytes common</td>
<td>Usually moderate in severity (i.e., &quot;nuisance diarrhea&quot;) without evidence of colitis</td>
</tr>
<tr>
<td>Complications</td>
<td>Evidence of colitis (not enteritis) common</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Results of assay for C. difficile toxin</td>
<td>Hypoalbuminemia, anasarca, toxic megacolon, relapses with treatment with metronidazole or vancomycin</td>
<td>Usually none except occasional cases of dehydration</td>
</tr>
<tr>
<td>Treatment</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Withdrawal of implicated antibiotic</td>
<td>May be epidemic or endemic in hospitals or long-term care facilities</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Antiperistaltic agents</td>
<td>May resolve but often persists or progresses</td>
<td>Usually resolves</td>
</tr>
<tr>
<td>Oral metronidazole or vancomycin</td>
<td>Prompt response</td>
<td>Often useful</td>
</tr>
</tbody>
</table>

*CT denotes computed tomography.
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 spec-
imen for *C. difficile* toxin. Performing enzyme immu-
noassays on two or three specimens, rather than one, 
only increases the diagnostic yield by 5 to 10 per-
cent,23 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* tox-
in, with evidence of colitis (fever, leukocytosis, and 
characteristic findings on CT or endoscopy); severe 
diarrhea; persistent diarrhea despite the discontinu-
atation of the implicated agent; or the need to con-
tinue treating the original infection. Oral metronida-
zeole (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.22,23 The usual duration of ther-
apy is 10 days, although few studies have addressed 
the relative merits of longer or shorter courses. Ideal-
ly, all antibiotic treatment should be oral, since *C. dif-
fcile* is restricted to the lumen of the colon. If intrave-
nous 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.6 The anticipated response to treatment 
resolution of fever within one day and resolution 
of diarrhea in four to five days.6 Metronidazole is 
preferred because it is less expensive than vancomy-
cin and avoids the potential risk of promoting van-
comycin-resistant enterococci in nosocomial cases. 
Indications for oral vancomycin, as opposed to met-
ronidazole, are pregnancy, lactation, intolerance of 
metronidazole, or failure to respond to metronida-
zeole after three to five days of treatment.

Most *C. difficile* infections respond to either vanco-
mycin 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 pre-
vent the drug from reaching the target site. For pa-

tients with ileus, transport of the antibiotic to the 

colic 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 vanco-
mycin 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. 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. 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. 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). 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. Despite the logic, the cost is high, and published data are limited.

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, 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. Infection-control policies are well established but may fail. Restricting the use of antibiotics, particularly clindamycin, has been shown to control an epidemic. 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 unclear. 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 *Staphylococcus 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 and the Society for Hospital Epidemiology of America (SHEA) have devised guidelines for detecting *C. difficile* toxin (Table 2). The Infectious Diseases Society of America, SHEA, and the Centers for Disease Control and Prevention 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. Antiperistaltic agents should be avoided because they may promote retention of the toxin. SHEA guidelines for infection control in hospitals and long-term care facilities are summarized in Table 3. Outbreaks may require restricting the use of antibiotics, especially clindamycin.

**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 and B are the usual routine tests in most laboratories. However, the sensitivity of this test may be improved by the use of a heterologous antiserum. Because of occasional false-negative or inconclusive results, the use of a cytotoxicity assay is recommended as an alternative. Vancomycin assay is recommended only for the detection of relapse.

**Table 2. Guidelines for the Use of the Clostridium difficile Toxin Assay.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Diagnosis</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. difficile toxin assay</td>
<td>±</td>
<td>Only diarrhea 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 cytotoxic assay but is less sensitive. Diarrhea that develops after three days of hospitalization should be tested only for <em>C. difficile</em> toxin (the three-day rule).†</td>
</tr>
</tbody>
</table>

†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.
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 \textit{C. difficile} infection, and the need for further antibiotic therapy (Table 4). Many patients with enteric disease caused by \textit{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 \textit{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 \textit{C. difficile} toxin, she should be treated with metronidazole since she has severe diarrhea. Follow-up testing for \textit{C. difficile} toxin is not indicated, and the results could be misleading.

If the results of assays for \textit{C. difficile} toxin are negative in a patient with persistent symptoms who has probable \textit{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 \textit{C. difficile} toxin, it is reasonable to test for enteric pathogens, including \textit{Staph. aureus} and salmonella. The antibiotics used to treat infection with these microorganisms differ from those for \textit{C. difficile} infection.

### Table 3. Guidelines for Controlling \textit{Clostridium difficile} Infection in Hospitals and Long-Term Care Facilities. *

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

*Data are from the Society for Hospital Epidemiology of America.**

### Table 4. Management of Diarrhea and Colitis Associated with \textit{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.24 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.

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 \textit{C. difficile}–associated disease. The lack of a response to metronidazole and a negative result on assays for \textit{C. difficile} are strong evidence against this diagnosis.

### REFERENCES