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.\(^1,2\) The rates of diarrhea associated with parenterally administered antibiotics, especially those with enterohepatic circulation, are similar to rates associated with orally administered agents.\(^3\)

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.\(^4,5\)

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.\(^1\) 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.\(^1,3,6\) 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.\(^7\) 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.\(^8\) 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.\(^9\) Multidrug-resistant Salmonella newport from contaminated beef was implicated in an outbreak of diarrhea among patients who had taken ampicillin.\(^10\) Fluoroquinolone-resistant enteric disease caused by

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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. 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. 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. The antibiotics most frequently implicated in diarrhea associated with C. difficile infection are clindamycin, expanded-spectrum penicillins, and cephalosporins. 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 and against relapse.

Diagnostic Tests

Findings that are considered nonspecific for but suggestive of C. difficile infection include leukocytopenia and C. difficile-associated leukocytosis. The therapeutic implications of these findings are not well established, and no study has shown that they are a useful screening test for C. difficile infection. However, if leukocytosis is present, treatment with metronidazole, vancomycin, or ciprofloxacin is appropriate. Occasional cases that fail to respond to these agents, or that have a complicated course, may require more definitive diagnostic assays.

**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–clavulanate</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>May be florid; evidence of colitis with cramps, fever, and fecal leukocytes common</td>
<td>Usually moderate in severity (i.e., “nuisance diarrhea”) without evidence of colitis</td>
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<tr>
<td>Findings on CT or endoscopy*</td>
<td>Evidence of colitis (not enteritis) common</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Complications</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>Results of assay for C. difficile toxin</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Epidemiologic pattern</td>
<td>May be epidemic or endemic in hospitals or long-term care facilities</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Treatment</td>
<td>May resolve but often persists or progresses</td>
<td>Usually resolves</td>
</tr>
<tr>
<td>Withdrawal of implicated antibiotic</td>
<td>Contraindicated</td>
<td>Often useful</td>
</tr>
<tr>
<td>Antiperistaltic agents</td>
<td>Prompt response</td>
<td>Not indicated</td>
</tr>
<tr>
<td>Oral metronidazole or vancomycin</td>
<td></td>
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*CT denotes computed tomography.
supplanted by assays for ten expensive, and they have been almost completely methods are nonspecific, relatively insensitive, and of-

uncommon but specific, since nearly all cases are at-

membranous colitis. Pseudomembranous colitis is

findings in the colon range from normal to pseudo-

enteropathy), and fecal leukocytes.

if it is done correctly, is the high degree of sensitiv-

genic strains.

say, with broth cultures of isolates to identify toxi-

in one day.

C. difficile

been the gold standard for diagnosis. It is the most

dominant rate of 10 to 20 percent. Commercially avail-

zyme immunoassays are now offered by most labo-

B. However, most laboratories do not offer tissue-cul-

rature assays, and the results of the assay are not avail-

oramidazole (500 mg three times daily or 250 mg four times daily) and oral vancomycin (125 mg four times dai-

have similar rates of efficacy, with response rates of 90 to 97 percent.22,33 The usual duration of ther-

apy is 10 days, although few studies have addressed the relative merits of longer or shorter courses. Ideal-

all antibiotic treatment should be oral, since C. dif-

dicate 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.6 The anticipated response to treatment is 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 vancomycin-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-

tol 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 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 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 aesthetic 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 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 and the Society for Hospital Epidemiology of America 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 recommended, but response rates 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 aesthetic appeal, is mechanically unwieldy, and carries a potential risk of transmission of retroviruses or other agents.

Table 2. Guidelines for the Use of the Clostridium difficile toxin assay.*

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<tr>
<td>Only diarrheal stools should be tested unless there is ileus.</td>
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<tr>
<td>“A test of cure” should not be performed except as part of an epidemiologic investigation.</td>
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<tr>
<td>Only specimens from patients who are older than one year of age should be tested.</td>
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<tr>
<td>Enzyme immunoassay is an acceptable alternative to the cytotoxin assay but is less sensitive.</td>
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<tr>
<td>Diarrhea that develops after three days of hospitalization should be tested only for C. difficile toxin (the three-day rule).†</td>
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*Data are based on recommendations from the Infectious Diseases Society of America and the Society for Hospital Epidemiology of America.† 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.
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**


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