The Spectrum of Pseudomembranous Enterocolitis and Antibiotic-Associated Diarrhea

Brian W. Hurley, MD; Cuong C. Nguyen, MD

Pseudomembranous (entero)colitis is primarily caused by *Clostridium difficile* infection. The most common predisposing factor is prior use of antibiotics, including vancomycin and metronidazole, which themselves are therapy for *C difficile* colitis. Other risk factors have also been described. The presence of *C difficile* in the gastrointestinal tract leads to a spectrum of manifestations from the asymptomatic carrier state to fulminant colitis. Successful treatment of *C difficile* colitis requires prompt treatment with appropriate antibiotics, withdrawal of the suspected predisposing antibiotics, and, in rare cases, total colectomy. Preventive measures of adequate infection control and judicious use of antibiotics are necessary means in attempting to control the spread of *C difficile* infection. Attempts at making an effective human vaccine are currently under way.

**HISTORICAL PERSPECTIVE**

**Preantibiotic Era**

The first reported case of pseudomembranous enterocolitis (PMC) was reported by J. M. Finney in association with William Osler in 1893. They described a 22-year-old woman who underwent resection of gastric tumors and developed postoperative diarrhea. She died on the 15th postoperative day, and at autopsy, the small bowel revealed diphtheritic membranes. In the preantibiotic era, PMC was rare. Only about 4 cases were recognized annually at the Mayo Clinic (Rochester, Minn). It was feared as a catastrophic complication of surgery because the diagnosis was only made at autopsy.

The most common clinical setting in those cases not associated with antibiotic therapy was colonic, pelvic, or gastric surgery. Other risk factors include spinal fracture, intestinal obstruction, colon carcinoma, leukemia, severe burns, shock, uremia, heavy metal poisoning, hemolytic-uremic syndrome, ischemic cardiovascular disease, Crohn disease, shigellosis, severe infection, ischemic colitis, and Hirschsprung disease. There is no definitive explanation for how these conditions lead to PMC, but it may be related to alterations in host defense mechanisms and enteric flora. Several postoperative cases were related to hypotension and shock, suggesting an ischemic origin.

**Early Antibiotic Era (1950-1969)**

During the dawn of the antibiotic era, PMC became a common complication of antibiotic use. *Staphylococcus aureus*, the principal nosocomial pathogen at that time, was implicated as the agent responsible for this condition by Gram stains and cultures of stools. Thus, vancomycin became the standard treatment.

**Established Antibiotic Era (1970s)**

Because vancomycin therapy worked, the causative agent was not questioned until the middle to late 1970s. The use of clindamycin had become widespread during this period. A landmark study by Tedesco et al at the Barnes-Jewish Hospital...
in St Louis, Mo, implicated clindamycin as a cause of PMC. It was the first study to prospectively use endoscopy to establish the diagnosis of PMC in the setting of antibiotic-associated diarrhea. Among 200 patients treated with clindamycin, 21% developed diarrhea and 10% developed PMC. Furthermore, S aureus could not be isolated from these patients. Subsequent studies of 8 stool specimens collected and tested 5 years later in Tedesco’s laboratory showed that all contained C difficile and its cytopathic toxins.1 Meanwhile, animal studies and subsequent human studies isolated C difficile and its toxins in almost all patients with endoscopic evidence of PMC.

### PSEUDOMEMBRANOUS ENTEROCOLITIS

Pseudomembranous enterocolitis occurred in the preantibiotic era. There were risk factors other than antimicrobial therapy that were important in the development of PMC. Staphylococcus aureus was implicated in the early antibiotic era as the causative pathogen; however, later studies shifted the focus to C difficile. Reports of possible S aureus-related PMC in patients testing negative for C difficile serve as reminders that this entity may indeed occur, albeit rarely.4 One theory for this etiologic shift is that, with the advent of newer antibiotics, more effective antistaphylococcal activity favored emergence of C difficile.4 Pseudomembranous enterocolitis primarily affects the large bowel, but it can rarely affect the small bowel. Since the 1970s, C difficile has been recognized as the most common cause of PMC. Other causes of pseudomembrane formation in the large and small bowel include early ischemia, verotoxin-producing organisms such as Escherichia coli, and drug therapy with chlorpropamide, gold, and nonsteroidal anti-inflammatory agents.

**Figure 1** demonstrates the histologic changes associated with PMC. **Figure 2** illustrates the gross pathologic appearance of PMC. **Figure 3** illustrates the appearance of PMC on endoscopy.

### ANTIBIOTIC-ASSOCIATED DIARRHEA

Most cases of antibiotic-associated diarrhea are categorized as nonspe-
specific diarrhea (Figure 4). These are mild diarrhea episodes without a definitive cause. They usually resolve with simple discontinuation of antibiotic therapy. Alteration of colonic flora leading to impaired colonic carbohydrate metabolism may be the cause in some cases. Approximately 20% of cases of antibiotic-associated diarrhea are due to C difficile. Two percent to 3% of cases are due to other pathogens such as E. coli, S. aureus, and Candida albicans. Also, a few cases are categorized as antibiotic specific. One example of this type would be the promotility adverse effect of erythromycin causing diarrhea. Another example is the malabsorption caused by large doses of neomycin.

**CLOSTRIDIUM DIFFICILE–RELATED SPECTRUM OF DISEASE**

**Description of Organism and Epidemiology**

Clostridium difficile is a spore-forming, gram-positive bacillus. It was given its name because it was difficult to grow in culture and isolate. It forms spores and thus can survive under harsh environmental conditions and withstand antibiotic therapy. In his doctoral thesis in 1974, Hafitz noted that C difficile survives well in nature and is widely distributed in the environment. The organism is frequently transmitted by person-to-person contact. Therefore, strict hand washing and contact and enteric precautions are imperative measures in preventing the spread of the organism. It has been cultured from many items including toilets, bedpans, floors, telephones, call buttons, scales, shoes of hospital personnel, fingernails, finger tips, and the underside of rings. Clostridium difficile can be cultured in rooms of infected individuals up to 40 days after discharge. Clostridium difficile infection is primarily a nosocomial infection. It causes approximately 3 million cases of diarrhea and colitis annually in the United States. Only about 20000 cases are diagnosed in the outpatient setting. Community-acquired disease does occur, but the epidemiologic factors in this setting are not fully understood. In a recent study, Riley et al suggested that the incidence in the community may be underestimated: this may be owing to a lack of awareness and investigation by physicians of this organism as a cause of community-acquired diarrhea. Table 1 demonstrates the distribution of C difficile from the stools of various patient populations. Clostridium difficile can be isolated from up to 3% of healthy adults in the general population and up to 80% of healthy newborns and infants. Infants are exposed from nosocomial infection and not from maternal transmission. A review by Johnson and Gerding revealed that the rate of colonization was approximately 20% in patients who were hospitalized for more than 1 week. A minority of these patients were colonized on admission. However, of those who were initially negative for C difficile on admission, the risk of acquiring the organism increased in direct proportion to the duration of the hospital stay. Another study by Clabots et al showed that the rate of acquisition was 13% up to 2 weeks and 50% for those hospitalized for more than 4 weeks (Figure 5).

**Pathogenesis**

Development of C difficile–associated diarrhea (CDAD) requires several factors (Figure 6). The first 2 factors are treatment with antimicrobials and colonization or acquisition of C difficile. However, most patients subsequently develop asymptomatic colonization rather than frank CDAD. Therefore, other additional factors likely play a role in the development of CDAD. These may be related to host susceptibility or immunity, the virulence of the particular C difficile strain, or the type and timing of antimicrobial exposure. However, it is clear from molecular typing studies that even the most virulent of C difficile strains produces asymptomatic colonization more often than CDAD, and this finding suggests that factors in addition to virulence are necessary for CDAD to occur. In the article by Shim et al, 4 longitudinal studies revealed that once asymptomatic colonization is established, these patients are at decreased risk for subsequent development of CDAD. Virtually every antibiotic has the potential to cause CDAD or colitis, including the antibiotics used to treat the disorder itself (Table 2). Ampicillin, cephalosporins, and clindamycin are the most frequently implicated antibiotics. Ampicillin and cephalosporins are prescribed more frequently than clindamycin and...
Therefore cause a greater number of cases of CDAD. However, clindamycin causes a greater percentage of cases relative to its frequency of use. Symptoms can occur at any time during antibiotic therapy and even up to 8 weeks after discontinuation of the antibiotic. However, most episodes of CDAD occur from days 4 through 9 of antibiotic treatment.8

Clostridium difficile produces 2 toxins that are responsible for its pathogenesis. Toxin A is a 308-kd protein and toxin B is a 250-kd protein. Both toxins are high-molecular-weight proteins and are heat labile. They are separated by only a small area on the C difficile chromosome. Both toxins play a role in the pathogenesis of CDAD and colitis and share common intracellular mechanisms of action as a result of their homology. Nontoxicigenic strains lack toxins A and B.1

Toxin A is primarily an enterotoxin that causes excretion of fluid from bowel. This fluid is profoundly inflammatory, containing neutrophils, lymphocytes, serum proteins, erythrocytes, and mucus. Toxin B is primarily cytotoxic, causing the disintegration of filamentous actin and leading to the collapse of the microfilament cytoskeleton and cell rounding. Clostridium difficile toxins also stimulate leukocyte chemotaxis in vitro and up-regulate the production of cytokines and other inflammatory mediators. These stimulatory effects may underlie the ability of C difficile toxins to elicit a profound colonic inflammatory response, culminating in PMC.6 Clostridium difficile also produces tissue degradative enzymes, which may play a minor role in the pathogenesis. These include chondroitin 4-sulfatase, collagenase, and hyaluronidase.17

Clinical Features and Complications of C difficile Infection

Clostridium difficile infection leads to a spectrum of disease. This spectrum includes the asymptomatic carrier state, simple antibiotic-associated diarrhea, PMC, and fulminant colitis. The basis for the variable expression of disease may be related to host immune factors and virulence factors of the organism.8

The asymptomatic carrier state is the end result for most patients infected with C difficile. These patients act as a silent reservoir of infection and probably perpetuate contamination of the hospital environment. Treatment of asymptomatic carriers with antibiotics does not eradicate the carrier state and is not recommended.8

Simple antibiotic-associated diarrhea is mild. As previously stated, C difficile accounts for only 20% of all cases of antibiotic-associated diarrhea. Obvious colitis and systemic symptoms are absent.

Colitis without pseudomembrane formation is a more serious illness than simple antibiotic-associated diarrhea. Patients may present with malaise, abdominal pain, nausea, anorexia, watery diarrhea, low-grade fever, and a peripheral leukocytosis. Endoscopy reveals a nonspecific diffuse or patchy erythematous colitis without pseudomembranes.8

Pseudomembranous enterocolitis is the characteristic manifestation of full-blown C difficile colitis. Sigmoidoscopic examination reveals the classic pseudomembranes—raised yellow plaques from 2 to 10 mm in diameter scattered over the colorectal mucosa.8 Patients with PMC have a more serious illness than patients who have colitis without pseudomembrane formation. Approximately 20% of patients have more proximal disease not detected on routine flexible sigmoidoscopy. Pseudomembranous enterocolitis may rarely affect the small bowel.

Fulminant colitis occurs in only 3% of patients with C difficile infection. Patients may exhibit severe abdominal pain and diarrhea, high fevers, and a marked peripheral leukocytosis. Diarrhea may be absent if ileus develops, and these patients are at greatest risk to develop toxic megacolon. A protein-losing enteropathy may lead to hypoalbuminemia, which in turn can cause ascites. Complications may include colonic perforation, toxic megacolon, prolonged ileus, ascites, and

<table>
<thead>
<tr>
<th>Antimicrobial Agents That Predispose to C difficile Diarrhea and Colitis</th>
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<tbody>
<tr>
<td><strong>Frequently</strong></td>
</tr>
<tr>
<td>Ampicillin and amoxicillin</td>
</tr>
<tr>
<td>Cephalosporins</td>
</tr>
<tr>
<td>Clindamycin</td>
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*Reprinted from Kelly and LaMont8 with permission from the Annual Review of Medicine.
even death. Endoscopy is usually not prudent owing to the risk of perforation, and exploratory laparotomy and total colectomy may become necessary interventions. Figure 7 is an upright abdominal plain film that demonstrates the complication of toxic megacolon.

**Diagnosis**

There are various methods and assays available for the detection of *Clostridium difficile* infection. Table 3 compares and contrasts various methods used to diagnose *C. difficile* infection. The cytotoxin assay is considered the standard for the diagnosis of *C. difficile* infection (Figure 8). It detects toxin B, which is the primary cytoxin. It has a sensitivity of 94% to 100% and a specificity of 97%. However, it requires a tissue culture facility, which is not widely available in most hospitals. It also takes 24 to 48 hours to perform.

The method used most widely in the clinical setting to diagnose *C. difficile* infection is the enzyme-linked immunosorbent assay (ELISA). It only takes 2 to 6 hours to perform. Characteristics of this assay include a sensitivity of 85% with a specificity of 100%. The sensitivity of ELISA may be improved by serial testing.

Another diagnostic assay is the latex agglutination assay. It does not detect any of the toxins produced by *C. difficile*, but rather it detects a bacterial enzyme, glutamate dehydrogenase. This enzyme is found in many other bacteria. Therefore, this assay has poor specificity. It also has poor sensitivity.

*Clostridium difficile* can be cultured. The culture detects both toxigenic and nontoxigenic strains. It is highly sensitive and allows for strain typing during epidemics. Its major disadvantage is that it takes 2 to 5 days to perform. It is also not specific for toxin-producing bacteria. Table 4 compares the culture method with the cytotoxin assay in patients with various manifestations of *C. difficile* infection.

Polymerase chain reaction can be used to diagnose *C. difficile* infection. Its sensitivity and specificity closely resemble those of ELISA. It is not widely available in most hospitals and clinical settings, likely be-

**Table 3. Stool Test for Diagnosis of Clostridium difficile Infection**

<table>
<thead>
<tr>
<th>Test</th>
<th>Detects</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxin assay</td>
<td>Toxin B</td>
<td>Standard highly sensitive and specific</td>
<td>Requires tissue culture facility, takes 24-48 h</td>
</tr>
<tr>
<td>Enzyme immunoassay</td>
<td>Toxin A or B</td>
<td>Fast (2-6 h), easy to perform, high specificity</td>
<td>Not as sensitive as the cytotoxin assay</td>
</tr>
<tr>
<td>Latex agglutination assay</td>
<td>Bacterial enzyme (glutamate dehydrogenase)</td>
<td>Fast, inexpensive, easy to perform</td>
<td>Poor sensitivity and specificity</td>
</tr>
<tr>
<td>Culture</td>
<td>Toxigenic and nontoxigenic <em>C. difficile</em></td>
<td>Sensitive, allows strain typing in epidemics</td>
<td>Requires aerobic culture, not specific for toxin-producing bacteria, takes 2-5 d</td>
</tr>
</tbody>
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**Table 4. Clostridium difficile and Its Cytotoxin in Patients With Various Manifestations of C difficile Infection**

<table>
<thead>
<tr>
<th>Condition</th>
<th><em>C. difficile</em> Culture, % Positive</th>
<th><em>C. difficile</em> Cytotoxin, % Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudomembranous colitis</td>
<td>95-100</td>
<td>95-100</td>
</tr>
<tr>
<td>Colitis without pseudomembranes</td>
<td>75-90</td>
<td>60-75</td>
</tr>
<tr>
<td>Antibiotic-associated diarrhea</td>
<td>20-40</td>
<td>15-30</td>
</tr>
<tr>
<td>Hospitalized adults, asymptomatic</td>
<td>10-15</td>
<td>2</td>
</tr>
<tr>
<td>Healthy adults</td>
<td>0-3</td>
<td>0</td>
</tr>
<tr>
<td>Healthy neonates and infants</td>
<td>30-80</td>
<td>25-50</td>
</tr>
</tbody>
</table>

*Reprinted from Bartlett with permission from WB Saunders Co.*
cause of increased costs compared with ELISA. Its use today is primarily as a research tool. However, a group of investigators from Spain recently developed a rapid detection method for toxigenic *Clostridium difficile* from stool samples by a nested polymerase chain reaction of the tox gene. It takes only a few hours to perform and has a sensitivity and specificity of 96% and 100%, respectively. Thus, the clinical use of polymerase chain reaction may soon become more widespread.

**Treatment**

The treatment of symptomatic *C. difficile* infection should begin with nonspecific measures. The most important of these is the discontinuation of the offending antibiotic, whenever possible. Discontinuation of antibiotic therapy may not be realistic for patients who are receiving therapy for a life-threatening illness. However, consideration of a change to another agent that is less frequently associated with CDAD should be made. Other nonspecific measures include supportive measures, such as correction of fluid losses and electrolyte abnormalities. One should avoid anti-peristaltic agents and place infected patients on enteric isolation precautions.³

Oral agents used for first-line therapy include vancomycin, metronidazole, and bacitracin. Table 5 outlines the various first-line treatment regimens. Metronidazole given intravenously can be used to treat patients who cannot tolerate an oral agent. Intravenous administration of vancomycin is not efficacious in the treatment of *C. difficile* infection.

A first or initial relapse should be treated with a second course of the initial antibiotic regimen used for first-line therapy. Of patients treated for a first episode of CDAD, 15% to 20% will have a relapse.⁸ There are many different regimens used with varying degrees of success to treat multiple relapses (Table 6).¹⁹ A new agent, Synsorb Cd (SYNSORB Biotech Inc, Calgary, Alberta), is currently in phase 3 clinical trials for the treatment of recurrent *C. difficile* infection when given for 25 days in combination therapy with metronidazole. Synsorb Cd is a synthetic oligosaccharide with bioadsorbent properties that selectively binds toxin A.

There has been considerable controversy regarding whether metronidazole or vancomycin should be used for initial therapy. Prospective randomized studies reveal no difference in initial response rates to metronidazole and vancomycin.²⁰ Previous exposure to vancomycin given orally and intravenously has been proven to be a risk for the development of vancomycin-resistant *Enterococcus*.⁵ The cost of vancomycin and metronidazole at Mayo Clinic Scottsdale’s pharmacy (as of January 2002) for a 10-day course is $215.33 and $15.97, respectively. For these reasons, metronidazole is recommended as the drug of choice for CDAD. Oral vancomycin treatment should be reserved for patients with metronidazole intolerance, for patients who do not respond to metronidazole, for patients with severe or fulminating colitis, and, perhaps, for patients who are immunocompromised.⁶ However, there is little clinical evidence, even in these circumstances, that oral vancomycin is superior.

**Immunology**

Are there natural protective antibodies against *C. difficile*? Kelly²¹ found higher levels of serum IgG antibody against *C. difficile* toxins in patients with mild, self-limiting diarrhea than in patients with more severe diarrhea requiring specific therapy. Moreover, the appearance of neutralizing serum antibodies correlated with resolution of the diarrhea. Two further studies have reported low serum IgG antibody levels against toxin A in patients with prolonged, relapsing CDAD, and one also showed that fecal IgA antitoxin levels were reduced in this patient population.²¹ Thus, there is considerable, albeit inconclusive, evidence that an inadequate humoral response to *C. difficile* infection predisposes to severe or prolonged CDAD.²¹

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**Table 5. Treatment of *Clostridium difficile*–Induced Diarrhea and Colitis**

<table>
<thead>
<tr>
<th>Antimicrobial agents (only if symptoms are severe or persistent)</th>
<th>Oral agent (preferred)</th>
<th>Parenteral agent (to be used only until oral agents are tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole: 250 mg, 3 times daily, 7-14 d</td>
<td>Bacitracin: 25,000 U, 4 times daily, 7-14 d</td>
<td>Metronidazole: 500 mg, given intravenously every 6 h</td>
</tr>
</tbody>
</table>

*Modified from Bartlett¹ with permission from WB Saunders Co.

**Table 6. Approach to Management of Recurrent *Clostridium difficile* Colitis**

<table>
<thead>
<tr>
<th>First relapse</th>
<th>Second relapse</th>
<th>Further relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm diagnosis</td>
<td>Confirm diagnosis</td>
<td><em>Saccharomyces boulardii</em> in combination with metronidazole or vancomycin, or</td>
</tr>
<tr>
<td>Symptomatic treatment if symptoms are mild</td>
<td>Vancomycin taper</td>
<td>Vancomycin in tapering dose (as specified above) plus cholestyramine, 4 g twice daily, or Vancomycin, 125 mg 4 times daily, and rifampin, 600 mg twice daily for 7 days, or Intravenous immunoglobulin, or Therapy with microorganisms</td>
</tr>
<tr>
<td>10- to 14-d course of metronidazole or vancomycin</td>
<td>125 mg every 6 h for 7 d</td>
<td>125 mg every 6 h for 7 d</td>
</tr>
<tr>
<td>125 mg every 12 h for 7 d</td>
<td>125 mg/d for 7 d</td>
<td>125 mg every other day for 7 d</td>
</tr>
<tr>
<td>125 mg every 3 d for 7 d</td>
<td>125 mg every 12 h for 7 d</td>
<td>125 mg every 3 d for 7 d</td>
</tr>
</tbody>
</table>

*Modified from Linevsky and Kelly¹⁰ with permission from Marcel Dekker.
Kyne et al,22 found no evidence of immune protection against colonization by C difficile. However, after colonization, there was an association between a systemic immune response to toxin A, as evidenced by increased serum concentrations of IgG antibody against toxin A, and the asymptomatic carrier state.

Passive Vaccination

Kelly21 gave 5 children with recurrent CDAD, who had low serum values of IgG antitoxin A, pooled intravenous human gamma globulin. Their gastrointestinal tract symptoms resolved after treatment, and there was clearance of C difficile toxin from their stools. A case report by Kelly22 noted successful treatment of 2 patients with the use of gamma globulin as an adjunct to vancomycin and metronidazole for fulminant colitis. The patients were able to avoid surgical intervention.

Animal studies demonstrated efficacy of oral anti–C difficile bovine immunoglobulin concentrate. Previous studies demonstrated protection from other bacteria with oral administration of hyperimmune globulin.23,24 An anti-clostridium immune concentrate has been successfully produced from cows immunized against C difficile. Clinical studies are under way to determine whether anti–C difficile bovine immunoglobulin concentrate is effective in the prevention and treatment of C difficile infection.21,25

Active Vaccination

Several animal studies demonstrated efficacy of parenteral immunization.26–28 Oral or mucosal immunization, as used for cholera toxin, is an alternative approach currently under investigation.21,29 A study in hamsters indicated that a combination of parenteral and mucosal (intranasal) immunization appears to provide the best protection against C difficile disease.21,30 Formalin-inactivated culture filtrate from toxigenic C difficile as well as purified and inactivated toxins have been used to immunize animals with good effect.21,25,28,31 These studies may provide the impetus for further human investigation using similar preparations. Although immunization against C difficile toxins may reduce symptomatic disease, there is no evidence indicating that it will directly influence intestinal colonization rates.

Prevention

Because there is no effective commercially available human vaccine, adequate infection control measures are absolutely necessary in controlling the spread of C difficile infection. Table 7 outlines an effective practice guideline for the prevention of C difficile infection.

**SUMMARY**

Pseudomembranous enterocolitis is primarily caused by C difficile infection. There are risk factors other than antibiotics and C difficile, which have historically been associated with the development of PMC. Most cases of antibiotic-associated diarrhea do not have a definitive cause. Clostridium difficile accounts for only about 20% of all cases of antibiotic-associated diarrhea. Infection with C difficile leads to a spectrum of disease, from the asymptomatic carrier state to fulminant colitis. Vaccination is not yet available. Therefore, strict hand washing, enteric precautions, and judicious use of antibiotics are imperative and remain the most effective means of preventing the spread of the organism and disease.

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**REFERENCES**


Table 7. Practice Guidelines for Prevention of Clostridium difficile Diarrhea*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limit the use of antimicrobial drugs.</td>
<td>Wash hands between contact with all patients. Use enteric (stool) isolation precautions for patients with C difficile diarrhea. Wear gloves when handling patients with C difficile diarrhea or their environment. Disinfect objects contaminated with C difficile with sodium hypochlorite, alkaline glutaraldehyde, or ethylene oxide. Educate the medical, nursing, and other appropriate staff members about the disease and its epidemiology.</td>
</tr>
</tbody>
</table>


