in the clinic

Clostridium difficile Infection

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CME Objective: To review current evidence for the prevention, diagnosis, and treatment of Clostridium difficile infection.

The information contained herein should never be used as a substitute for clinical judgment.

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Antibiotic-associated diarrhea was described in the 1950s. By 1978, Clostridium difficile had been established as the most common cause of infection, accounting for 15% to 25% of cases (1). The reported incidence and severity as measured by total mortality and colectomy rates rose steadily from 1993 to 2003 (2). A national survey in 2008 of 648 U.S. hospitals reported an overall C. difficile prevalence of 13.1 per 1000 inpatients (3). In the past decade, a strain with increased virulence has been described in relation to outbreaks in Canada, the United States, and Europe. This strain, designated NAP1/BI/027, produces a binary toxin not previously associated with C. difficile and produces substantially (15- to 20-fold) more toxin A and B than other strains. This strain is associated with more severe disease and mortality rates of 7% or more. It also seems to be more readily transmissible, and has been associated with community-acquired disease in persons with no established risk factors, including peripartum women and children. It is very resistant to fluoroquinolones, and emergence is believed to have been fostered by extensive use of these drugs in health care settings and in the community (4-6). This emergence of a hypervirulent form of C. difficile should prompt increased caution in prescribing fluoroquinolones in addition to those agents previously identified as frequent triggers of C. difficile diarrhea.

How does a patient acquire C. difficile infection? Colonization with C. difficile occurs through the fecal–oral route, usually by person-to-person transmission. Contaminated fomites and the hands of health care workers are another source of transmission (7).

A prospective 11-month study of C. difficile transmission in hospitalized patients showed that 21% of patients who initially had negative test results acquired the organism during admission: C. difficile was cultured from environmental surfaces in 49% of hospital rooms of symptomatic patients and from the hands of 59% of the health care workers caring for these patients (8).

Although the risk for C. difficile infection is greatly increased for persons who are hospitalized compared with those in the community, the infection still causes an estimated 8 to 12 cases per 100 000 in the outpatient population (5). Isolation of the organism from hamburger and the gastrointestinal tracts of farm animals has been reported and may account for some acquisition in the community, although exposure to persons with health care–associated colonization or disease is assumed to be the usual source (9, 10). The organism forms hardy spores that survive the acid environment of the stomach. Asymptomatic colonization may occur in 20% or more of patients in acute care hospitals, and increasing length of stay correlates with a greater likelihood of acquisition. From 4% to 20% of long-term care residents carry the organism (11). Colonization rates in the community are estimated at about 2% to 8% (12). Once colonization is established, certain factors favor development of symptomatic disease. Antibiotic disruption of the microbial balance of the gut is the most common, and longer courses and use of multiple antibiotics increase the risk for disease. Clindamycin, cephalosporins, penicillins, and recently fluoroquinolones are frequently cited triggers, but almost all antibiotics carry some risk (13, 14).

Chemotherapeutic agents may have the same effect (15). Some data suggest that the use of proton-pump inhibitors or histamine-2 blockers may play a role in some...
patients, but reports are contradictory (16, 17). Other physical manipulations of the gastrointestinal tract, such as surgery, enemas, stool softeners, and even tube-feeding, have been identified in some studies as contributing factors (18-20). Specific immune defects, such as neutropenia or advanced HIV infection, may play a role in the development of disease. Finally, factors associated with general debility, such as advanced age or severe underlying disease, have been associated with increased risk, especially when multiple factors coexist (21).

What can clinicians do to reduce the likelihood of their patients developing C. difficile infection? The primary means of prevention are to limit the use and type of antibiotics and to adhere to infection-control measures. The latter includes the use of appropriate environmental cleaning methods and solutions, but because those measures generally are not within the purview of individual clinicians, they are not discussed here.

Physicians should participate in antibiotic stewardship programs (designed in conjunction with microbiologists, pharmacists, infection-control specialists, and hospital administrators) to limit unnecessary antibiotic administration, aid in the selection of agents that carry a lower risk of C. difficile disease whenever possible, and ensure that duration of antibiotic therapy is minimized to the extent appropriate for the infection being treated. Many strategies have been used, from restrictive and nonrestrictive protocols for the use of high-risk drugs to routine review of current cases with feedback to attending physicians.

Several large, prospective studies have confirmed that the introduction of such antibiotic use policies was associated with statistically significant reductions in C. difficile infection in both endemic and epidemic settings (22, 23).

A prospective controlled, interrupted time-series study of the geriatric service of a large teaching hospital evaluated the rates of C. difficile infection over 2 periods of 21 months, before and after institution of a feedback antibiotic prescription protocol to promote use of narrow-spectrum antibiotics when appropriate. During the study period, 6129 patients were admitted. After the institution of the antibiotic policy, C. difficile infection decreased significantly (incidence rate ratio, 0.33; P = 0.009) (22).

Because of the increasing frequency of community-acquired C. difficile in persons with no known risk factors, prescriptions for outpatients also should be carefully considered with regard to the antimicrobial spectrum and the relative frequency of association with C. difficile diarrhea.

Hospitalized patients with C. difficile infection should be assigned to private rooms or placed with other similarly infected patients until diarrhea has resolved. Routine infection-control procedures include strict hand hygiene between patient examinations and contact precautions, including use of gloves and gowns for any contact with patients who have C. difficile infection or with their bodily fluids. Conventional handwashing with soap and water should be strictly adhered to in outbreaks or after caring for a patient known or suspected to have C. difficile infection, rather than using alcohol-based hand rubs, which do not eliminate C. difficile spores.

No published trials have been designed specifically to study the protective effect of gowns, but C. difficile has been cultured from the uniforms of hospital workers. The use of disposable gowns is recommended on that basis (24, 25).

A prospective controlled trial examined the incidence of C. difficile infection on 3 similar hospital wards to evaluate the efficacy
of vinyl gloves in preventing nosocomial transmission of C. difficile on 1 of the 3 wards. The use of vinyl gloves was associated with a statistically significant reduction in symptomatic C. difficile infection and asymptomatic colonization (26).

The spores of C. difficile are highly resistant to alcohol, and at least 1 study has shown that conventional handwashing with soap and water is superior to the use of alcohol-based hand rubs for removing C. difficile (27). It has been postulated that use of alcohol-based rubs may actually promote nosocomial transmission of this organism. However, several studies have failed to show an increase in the rate of C. difficile associated with use of alcohol-based hand gels (28, 29). Although these studies were designed to investigate whether alcohol-based hand rubs were associated with an increase in C. difficile infection, no decrease was noted despite more frequent hand hygiene.

Prevention... Nosocomial transmission of C. difficile can be prevented by thorough hand hygiene, especially with soap and water, between all patient contacts and by careful adherence to contact precautions in the care of infected persons. Judicious use of antibiotics through stewardship protocols may prevent symptomatic disease in colonized patients.

**Clinical Bottom Line**

Diagnosis

What history, signs, and symptoms should raise suspicion of C. difficile infection?

Patients should be asked about the known risk factors for C. difficile diarrhea (Box).

Patients commonly develop antibiotic-related diarrhea with C. difficile during or shortly after receiving antibiotics (30), but the symptoms can occur up to several months after completing these drugs. In patients who have been hospitalized for at least 3 days, C. difficile is by far the most common enteric pathogen (31).

Consider C. difficile infection in patients who have diarrhea or abdominal pain, especially when they have a recognized risk factor. Nausea, vomiting, and fever are often but not always present. Physical findings are variable, depending on the length and severity of disease. Signs of dehydration may be present. The abdomen may be tender, and in severe cases, peritoneal signs may be present. Ileus or toxic megacolon may result in abdominal distention (Table 1).

What diagnostic tests should clinicians perform when they suspect C. difficile infection? Enzyme immunoassays designed to detect toxin in submitted stool specimens are the most widely used in clinical laboratories. They

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**Risk Factors for C. difficile Diarrhea**

- Antibiotic use: Clindamycin, cephalosporins, penicillins, and fluoroquinolones implicated most frequently, but all antibiotics have been associated. Risk increases with duration and number of antibiotics
- Antineoplastics agents
- Hospital or nursing home care: outpatient disease without previous hospital or nursing home exposure is becoming more common
- Advanced age
- Underlying disease: Malignant conditions, renal failure, generalized debility
- Gastrointestinal manipulation: Surgery, tube feeding, enemas, use of proton-pump inhibitors, and histamine-2 blockers may also be associated
provide results rapidly, with sensitivity and specificity of 65% to 85% and greater than 90%, respectively. Some commercially available kits test only for toxin A, and because some C. difficile strains produce only toxin B, such tests carry an increased likelihood of false-negative results.

Cytotoxin assay is the clinical reference standard for the diagnosis of C. difficile infection, with a sensitivity of 94% to 100% and specificity of 97%; however, it takes 24 to 48 hours and requires a tissue culture laboratory, which is not available in most hospitals. Culture is more sensitive than toxin assays but requires 48 hours or more for incubation, plus further testing to confirm that the isolate produces toxin. Culture and molecular typing of isolates are important in the epidemiologic study of outbreaks.

A report of 10,522 samples tested for C. difficile over 7 years showed that although 10% were positive by culture, only 4.4% were positive by cytotoxin tests (32).

Latex agglutination assays for glutamate dehydrogenase are not adequately sensitive. Enzyme-linked immunosorbent assays (ELISAs) for this enzyme have been developed and are very sensitive but not specific. Some authorities recommend their use for rapid screening as part of a 2-step test that includes confirmatory toxin testing (25).

Polymerase chain reaction (PCR) testing for C. difficile has been found in preliminary studies to be rapid and accurate and may emerge as the test of choice in routine diagnosis.

An observational validation study of PCR to diagnose C. difficile diarrhea reported these sensitivities; culture, 100%; PCR, 93%; cell culture cytotoxin assay, 76%; and ELISA for toxins A and B, 73% (33).

Because the tests designed to detect toxin carry a measurable risk for false-negative results, repeated testing on different stool specimens may be necessary. But clinical decisions about treatment should be based on the patient’s risk factors and other clinical and laboratory data (25). In their overview of the performance and role of various tests for C. difficile, Peterson and Robicsek recommended using tests with higher sensitivity, avoiding testing for C. difficile for a single episode of diarrhea, and paying greater attention to key aspects of the patient’s history (34) (Table 2).

Another test with diagnostic value is direct inspection via

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Table 1. Clinical Features and Complications of C. difficile Infection

<table>
<thead>
<tr>
<th>Spectrum of Disease</th>
<th>Diarrhea</th>
<th>Other Symptoms</th>
<th>Physical Examination</th>
<th>Colonicoscopic and Other Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic carrier</td>
<td>None</td>
<td>None</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Simple antibiotic-associated diarrhea</td>
<td>Mild</td>
<td>Systemic symptoms usually absent</td>
<td>Normally normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Early colitis</td>
<td>Profuse</td>
<td>Nausea, anorexia</td>
<td>Low-grade fever, with or without mild abdominal tenderness</td>
<td>Nonspecific patchy erythema</td>
</tr>
<tr>
<td>Pseudomembranous colitis</td>
<td>Profuse</td>
<td>Nausea, malaise, abdominal discomfort</td>
<td>Fever (sometimes high), abdominal tenderness, distention</td>
<td>Pseudomembranes (raised yellow plaques), leukocytosis (may be &gt;10^9 cells/L, with left shift)</td>
</tr>
<tr>
<td>Fulminant colitis</td>
<td>Usually profuse and severe, may be absent in ileus or toxic megacolon</td>
<td>Nausea, abdominal discomfort or pain</td>
<td>Toxic appearance, fever (often high), abdominal tenderness, distention, and peritoneal signs</td>
<td>Endoscopy contraindicated in severely ill patients; leukocytosis reaction common; radiographic studies may show colonic dilatation, mucosal thickening, perforation</td>
</tr>
</tbody>
</table>

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sigmoidoscopy or colonoscopy. Characteristic raised yellow mucosal plaques, or “pseudomembranes,” are highly suggestive of C. difficile-associated diarrhea. Unprepared flexible sigmoidoscopy is often adequate and has been shown to be an effective means of establishing the diagnosis in many cases in which toxin tests were negative (35). However, sigmoidoscopy may miss cases that could be detected by colonoscopy, because of more proximal disease, as reported in at least 2 small prospective studies using flexible sigmoidoscopy for diagnosis (36, 37). Conversely, many cases diagnosed by toxin testing or other methods do not have pseudomembranes, which may be a marker of severe disease.

Other tests that may provide supporting evidence for the diagnosis and are of value in assessing severity of disease and complications include complete blood count, creatinine, lactate level, and computed tomography of the abdomen (Table 3).

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete blood count, $\times 10^9$ cells/L</td>
<td></td>
<td></td>
<td>Patients with severe C. difficile infection may have leukocytosis $&gt;50$ x $10^9$ cells/L.</td>
</tr>
<tr>
<td>Blood urea nitrogen and creatinine</td>
<td></td>
<td></td>
<td>Severe disease may cause dehydration, end-organ dysfunction.</td>
</tr>
<tr>
<td>Cytotoxin assay</td>
<td>94 to 100</td>
<td>97</td>
<td>Uses tissue culture; not readily available in hospital laboratories; takes 24-48 h.</td>
</tr>
<tr>
<td>Enzyme-linked immunosorbent assay</td>
<td>65 to 85</td>
<td>95 to 100</td>
<td>Widely available, rapid turnaround.</td>
</tr>
<tr>
<td>Plain abdominal films</td>
<td>100</td>
<td>100*</td>
<td>Culture requires several days. May show thickened mucosa; dilated colon, which suggests toxic megacolon; or perforation (free air).</td>
</tr>
<tr>
<td>Computed tomography</td>
<td></td>
<td></td>
<td>May show thickened mucosa; dilated colon, which suggests toxic megacolon; or perforation (free air). May reveal pseudomembranes; highly suspicious for C. difficile.</td>
</tr>
<tr>
<td>Lower endoscopy for C. difficile</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*If toxin production is verified by separate testing.
A high leukocyte count (>20 x 10^9 cells/L) or elevated creatinine (176.8 μmol/L (>2.0 mg/dL) were associated with a 30-day mortality of 25.5% in a retrospective study of 1721 patients with documented C. difficile infection at 1 hospital over 12 years (38).

Indeed, a high leukocyte count may be a diagnostic clue to the presence of C. difficile infection.

A retrospective review of 70 patients with diarrhea, 35 of whom had positive stool test results for C. difficile, revealed a mean leukocyte count in those patients of 15.8 x 10^9 cells/L versus 7.7 x 10^9 cells/L in those who had negative C. difficile test results (P < 0.01), and a prospective study of 60 patients with unexplained leukocytosis (>15 x 10^9 cells/L) showed positive results on C. difficile ELISA tests in 58% compared with 12% in a control group of hospitalized patients with normal leukocyte counts (39, 40). A retrospective observational cohort study of patients who required intensive care for C. difficile infection showed a lactate level of 5 mmol/L or more to be an independent predictor of 30-day mortality (41).

Patients with C. difficile infection may have findings suggestive of colitis, such as mucosal thickening, on abdominal imaging (42). Complications, such as toxic megacolon or perforation, may be detected.

What other diseases should clinicians consider when they suspect C. difficile infection?

Other infectious and noninfectious causes should be considered in patients with diarrhea and a work-up that is negative for C. difficile.

Other infectious causes include Salmonella, Shigella, Campylobacter, Shiga-toxin-producing strains of Escherichia coli, and in immunocompromised persons, cytomegalovirus, Cryptosporidium, or other opportunistic organisms. These are unusual in patients who develop diarrhea in the hospital. Intestinal obstruction, ischemic bowel, inflammatory bowel disease, gastrointestinal malignant conditions, and noninfectious forms of drug-associated diarrhea should also be considered in the differential diagnosis.

When should clinicians refer patients with suspected C. difficile infection to subspecialists?

Referral or consultation for further evaluation should be sought when the diagnosis is uncertain. Lower endoscopy by a gastroenterologist may provide a diagnosis when stool studies are negative or when a diagnosis is needed more rapidly than available laboratory support can provide.

Diagnosis. A variety of tests are available to detect C. difficile in the stool; endoscopy can also be used to make the diagnosis in many cases. Other laboratory and imaging studies are useful in supporting the diagnosis and in determining the presence of complications or indicators of poor outcome that require hospitalization and aggressive treatment.

CLINICAL BOTTOM LINE

When is discontinuation of antibiotics alone sufficient to treat C. difficile infection?

Discontinuing antibiotic therapy should be considered in all patients with C. difficile infection if doing so will not jeopardize recovery from the condition for which the antibiotics were prescribed. Patients with mild diarrhea who have normal or nearly normal leukocyte counts and normal creatinine levels, and are not otherwise at risk for severe disease or complications, may be observed for a few days to determine whether they respond to that measure alone.
In a 10-year prospective study of 908 patients with documented *C. difficile* diarrhea, 135 patients (15%) responded to cessation of antibiotics alone (43).

Which supportive measures should be used to treat *C. difficile* infection?

When antibiotics cannot be discontinued, substitution with alternative agents that are less likely to exacerbate *C. difficile* should be considered (Table 4). Fluid and electrolyte imbalances should be corrected. Antiperistaltic agents should be avoided, because they prevent both distribution of the therapeutic antibiotic within the gut and expulsion of the toxin.

Which drugs should be used to treat *C. difficile* infection?

Metronidazole and vancomycin are the mainstays of therapy in the United States (Table 5). Oral metronidazole is usually recommended for treatment of mild to moderate disease; the usual dose for adults is 500 mg 3 times daily for 10 to 14 days. For patients who cannot tolerate metronidazole or for those with severe disease, vancomycin is the drug of choice. Severe disease has been variously defined, but minimum criteria cited in 1 guideline are a leukocyte count of 15,000/mm³ or more or a creatinine level 1.5 times baseline or higher; preexisting renal failure is also widely considered to be a risk factor (24, 45). Another definition, which rests on a point system, is shown in the Box.

In cases of severe disease, the dose and route of administration are adjusted on the basis of severity and factors that alter drug delivery. For those with moderately severe disease, the recommended dose of vancomycin is 125 mg given orally or by nasogastric tube 4 times daily for 10 to 14 days. In patients with immediately life-threatening conditions or in whom ileus or other factors may prevent adequate distribution through the gut lumen, expert consensus advocates a higher dose of vancomycin—500 mg 4 times daily. Doses may be given by rectal instillation instead of or in addition to the oral doses. Intravenous metronidazole, 500 mg every 8 hours, is often added as well (25).

The choice and duration of antibiotic is also influenced by whether

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**Severe *Clostridium difficile* Infection**

Two or more points based on the following:

- Temperature >38.3°C (1 point)
- Age >60 y (1 point)
- Albumin <0.25 g/L (1 point)
- Leukocyte count >15 × 10⁹ cells/L (1 point)
- Pseudomembranous colitis (2 points)
- Intensive care unit (2 points)

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**Table 4. Antibiotics Associated With *Clostridium difficile* Infection***

<table>
<thead>
<tr>
<th>Frequent</th>
<th>Infrequent</th>
<th>Rarely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin plus clavulanic acid, amoxicillin</td>
<td>Ampicillin</td>
<td>Vancomycin</td>
</tr>
<tr>
<td>Second- or third-generation cephalosporins</td>
<td>Sulfonamides with or without trimethoprim, erythromycin</td>
<td>Penicillin or antistaphylococcal penicillin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Aminoglycosides</td>
<td>First-generation cephalosporin</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Metronidazole</td>
<td>Tetracycline</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Side Effects</th>
<th>Benefits and Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>500 mg PO; 3 times daily for 10 to 14 d</td>
<td>Rarely causes CDAD. CNS side effects of seizures and peripheral neuropathy, most worrisome. Possible disulfiram-like reaction with alcohol. Dysgusia.</td>
<td>Preferred first-line therapy for mild or moderate initial episode or first recurrence. Cost-effective, efficacious. Reserve IV form for patients who cannot tolerate PO.</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>250 mg PO 4 times daily for 10 to 14 d</td>
<td>Rarely causes CDAD. May lead to vancomycin-resistant enterococcus, renal toxicity, and ototoxicity.</td>
<td>Preferred for severe initial episode, such as fulminant colitis, or in immunocompromised patients or for multiple recurrences, in a tapered or pulsed regimen. Complicated severe initial episode, such as hypotension or shock with ileus or megacolon.</td>
</tr>
<tr>
<td>Vancomycin with metronidazole</td>
<td>Vancomycin, 500 mg IV every 8 h; for ileus, consider adding vancomycin by rectal instillation</td>
<td>Same as vancomycin or metronidazole alone.</td>
<td>Inferior to metronidazole and vancomycin. Has been granted orphan drug status for treatment of CDAD. Limited clinical evidence. Adjuvant therapy in multiple relapses. Not used as monotherapy. Can bind vancomycin, so give several hours after Limited evidence.</td>
</tr>
<tr>
<td>Bacitracin</td>
<td>25,000 IU PO 4 times daily for 7-14 d</td>
<td>Rarely causes CDAD. May cause nephrotoxicity and CNS toxicity. GI upset, and malabsorption.</td>
<td>Adjuvant therapy in multiple relapses. Not used as monotherapy. Can bind vancomycin, so give several hours after Limited evidence.</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>4 g PO 3-4 times daily</td>
<td>Constipation.</td>
<td>Adjuvant therapy in multiple relapses. Not used as monotherapy. May restore natural defense mechanisms. Limited evidence.</td>
</tr>
<tr>
<td>Colestipol</td>
<td>5 g PO every 12 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probiotics</td>
<td>&gt;10^10 organisms per day for 4 wk</td>
<td>Rare Blood stream infection in immuno-compromised patients.</td>
<td></td>
</tr>
</tbody>
</table>

CDAD = Clostridium difficile-associated diarrhea; CNS = central nervous system; GI = gastrointestinal; IV = intravenous; PO = orally.


the patient is being treated for the initial episode or for a recurrence (see below and Figure).

Vancomycin is more expensive than metronidazole, and its use in some settings has been discouraged because of the widespread emergence of vancomycin-resistant enterococci. However, its pharmacokinetic properties make it superior to metronidazole in severe C. difficile disease. Orally administered vancomycin is not well absorbed from the gastrointestinal tract, and therefore luminal drug levels are very high—well above the susceptibility breakpoint for all strains of C. difficile tested so far. Metronidazole, on the other hand, is well absorbed from the gastrointestinal tract, and luminal concentrations tend to decrease as mucosal inflammation improves, possibly permitting relapse before cure is complete (25, 46).
Figure. Treatment strategies for *Clostridium difficile* diarrhea. GI = gastrointestinal; ID = infectious disease; IV = intravenous; PO = oral; QID = four times daily; TID = three times daily.

*Leukocyte count ≥ 15 x 10⁹ cells/L or creatinine level ≥ 1.5 times baseline.

*Associated with significant ileus, toxic megacolon, hypertension, or shock.
A systematic review of RCTs of antibiotics for use in *C. difficile* infection also noted no differences between metronidazole and vancomycin, among others (49). However, recent observational reports and some studies have raised the possibility that, at least in severe disease, metronidazole may not be as effective as often or as promptly as vancomycin (50–52).

A prospective RCT compared vancomycin with metronidazole for the treatment of *C. difficile*-associated diarrhea in patients with either mild or severe disease. The 2 drugs were found to be equivalent in mild disease, but in severe disease, vancomycin was superior, resulting in a cure rate of 97% versus 76% with metronidazole (P = 0.02) (44).

When data from a large study comparing metronidazole, vancomycin, and tolevaran (an anionic polymer resin) were stratified according to disease severity, vancomycin was associated with significantly better clinical outcomes in patients with severe disease, with similar but nonsignificant trends in mild and moderate disease (53, 54).

Most of the work comparing vancomycin with metronidazole was done before the emergence of the hypervirulent NAP1/BI/027 strain, although at present there is no indication that the in vitro antibiotic susceptibility pattern of this strain differs from others (25).

Teicoplanin, a glycopeptide similar to vancomycin, has been found to be equivalent or perhaps superior to vancomycin, but it is not available in the United States (49). Nitazoxanide, beicitrin, fusidic acid, rifampin, and rifaximin are some of the other antibiotics that have been studied, but data on these agents are limited. Toxin-binding anion-exchange resins, such as cholestyramine, colestipol, and tollevaran, have not been consistently shown to be effective, but again, data are limited. If these agents are used, administration must be timed to minimize inactivation of vancomycin.

How should clinicians monitor patients who have *C. difficile* infection?

Patients should be followed for clinical evidence of improvement, including, where applicable, resolution of fever, reduction in stool frequency and improved consistency, normalization of abdominal examination, rehydration as indicated by physical examination and laboratory variables, and resolution of leucocytosis. Repeated stool testing is not needed in patients whose symptoms have resolved and is discouraged because treatment of asymptomatic carriers is not indicated (25). On the other hand, patients who do not respond or who relapse should be retested and, under some circumstances, may require work-up for alternative or concurrent diagnosis.

Should probiotics be used to treat *C. difficile* infection?

Numerous formulations of probiotics have been proposed to treat *C. difficile* colitis on the premise that these normally nonpathogenic yeasts and bacteria may repopulate the gastrointestinal tract and limit growth of *C. difficile*, but data are inconclusive.

A systematic review found only 4 studies of acceptable size and quality, and of those, 1 showed a statistically significant reduction in the rate of relapse in patients treated with Saccharomyces boulardii in addition to vancomycin. The authors concluded that evidence is insufficient to recommend the use of probiotics, and guidelines written by a panel of experts warn of S. boulardii fungemia in immunocompromised patients (25, 55).
Should fecal transplants be used to treat *C. difficile* infection?

Fecal transplantation has been proposed as a way of recolonizing the gastrointestinal tract with normal flora to restore a microbial milieu unfavorable to *C. difficile* toxin production.

Successful treatment of refractory infection by instillation of stool from normal donors has been reported in individual cases and small case series by several investigators (56–58).

Such measures carry obvious concerns about the possibility of introducing other unrecognized pathogens.

What should be done when the patient does not respond to initial treatment?

Patients who do not improve or who relapse after initial improvement should be reevaluated clinically to assess whether *C. difficile* is still the correct diagnosis or whether an alternate explanation for lack of improvement should be sought (for example, in hospitalized patients, persistent fever and leukocytosis may be due to a superimposed nosocomial infection, persistent diarrhea may be due to supplemental enteral feedings). In patients who do not improve on medication, it is also important to ensure that the medication is being delivered effectively to the site of infection (for example, severe ileus may prevent orally administered vancomycin from getting to the colon). In patients who do not improve after 48 to 72 hours while receiving metronidazole alone, a switch to vancomycin should be considered; in patients already receiving vancomycin, the dose and delivery should be maximized, and addition of intravenous metronidazole should be considered.

What are the indications for obtaining a consultation for a patient with *C. difficile* infection?

Consultation with a gastroenterologist or infectious disease specialist (or both) should be considered for patients who respond slowly or relapse. Management changes may be guided by endoscopy and may include manipulation of current antibiotic therapy. Surgical consultation is essential if there is evidence of perforation and should be strongly considered in patients with toxic megacolon. It may also be of value in other patients with severe illness in whom medical therapy has failed.

When should patients with suspected *C. difficile* infection be hospitalized?

Patients should be hospitalized for severe disease, complications, or in other circumstances in which outpatient treatment is inadequate to meet the patient's treatment or monitoring needs. Dehydration and inability to tolerate oral medication are indications for admission. Any patient with signs of peritonitis, toxic megacolon, the sepsis syndrome, or other complications should be hospitalized.

Consideration should be given to admitting patients with other indicators of severe disease (elevated creatinine, leukemoid reaction, advanced age).

When should patients with *C. difficile* infection be admitted to an intensive care unit?

Admission to intensive care is necessary for patients with severe disease and an unstable clinical condition, such as septic shock, toxic megacolon, peritonitis, or severe dehydration with hypotension or end-organ dysfunction.

When should total colectomy be considered in a patient with *C. difficile* infection?

Colectomy is required in patients with colonic perforation. It may also be of benefit in patients with toxic megacolon or septic shock due to *C. difficile* disease, especially those with an elevated lactate level. In addition, colectomy may be useful in a patient without toxic megacolon in whom all medical therapies have failed.
Two recent retrospective studies analyzed the effect of colectomy in patients with severe infection due to C. difficile. The first study of 14 patients included 10 patients with systemic toxicity and perforation, 3 patients with progressive dilatation of the colon, and 1 patient with toxic megacolon and perforation. Overall mortality was 35.7%, but total colectomy was associated with a mortality rate of 11.1% (1 of 9 patients) (59). The other larger study of 165 patients with C. difficile colitis requiring intensive care (leucocytosis of ≥50 x 10^9 cells/l; lactate ≥5 mmol/l; age ≥75 y; immunosuppression; or shock requiring vasopressors) showed a significant survival advantage to colectomy (adjusted odds ratios, 0.22 [95% CI, 0.07 to 0.67]; P = 0.008) (41).

What should be done for patients with recurrent disease? Patients who develop recurrent symptoms after apparent response to initial treatment may have relapsed or developed infection due to a different strain; for practical purposes, the difference cannot be readily determined with the clinical tools available. Therefore, for the first recurrence, expert guidelines recommend retreatment with the same course of therapy used for the initial presentation if that course is consistent with the patient's current presentation (25). On the other hand, if a patient with mild disease treated initially with metronidazole develops recurrent disease associated with indicators of severity (for example, a leukemoid reaction and dehydration), treatment should be adjusted accordingly (Figure).

Recurrences after a second course of metronidazole should not be treated again with that drug because of the possibility of cumulative neurotoxicity (25). Patients who have had more than 1 relapse or recurrence can be treated with a prolonged course of vancomycin tapered at intervals or by a regimen of intermittent or "pulse" doses. This recommendation is based on a small observational study and a consensus based on the clinical experience of experts (25).

A case series of 22 patients with several relapses of pseudomembranous colitis reported 2 to 12 months (mean, 6 months) free of disease after a tapering dose of oral vancomycin for 21 days followed by pulse doses for 21 days (60).

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**Treatment...** Use either metronidazole or vancomycin for mild disease; use vancomycin for more severe conditions. Patients with ileus or with very severe disease may benefit from rectal instillation of vancomycin and intravenous metronidazole in addition to oral vancomycin. Multiple recurrences may require longer treatment with a tapered dose regimen.

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**Clinical Bottom Line**

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**Practice Improvement**

What do professional organizations recommend for preventing, diagnosing, and treating C. difficile infection?
The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) have published Clinical Practice Guidelines for C. difficile Infection in Adults (25). The Healthcare Infection Control Practices Advisory Committee of the CDC publishes periodic guidelines on infection control (61).

What other tools are available to help clinicians manage C. difficile infection?
The Centers for Disease Control and Prevention Web site has information on C. difficile for clinicians and patients (www.cdc.gov/ncidod/dhqp/id_CdiffFAQ).
Clostridium difficile Infection

PIER Modules
www.pier.umn.org
Access the PIER modules on *Clostridium difficile* infection. PIER modules provide evidence-based, updated information on current diagnosis and treatment in an electronic format designed for rapid access at the point of care.

Patient Information
www.annals.org/10010127/2007/0305077v1/Articles/4066418
Access the Patient Information material that appears on the following page for duplication and distribution to patients.

www.cdc.gov/ncidod/diseases/id_cdiff/FAQ_general.html
www.cdc.gov/ncidod/diseases/id_cdiff/guidelines/Cdiff_taged.pdf
Access general information and a FAQ handout on *C. difficile* from the U.S. Centers for Disease Control and Prevention.

www.mayo.edu/patient_information/leaflets/clostridium_difficile
Access patient information on *C. difficile* from the British National Health Service.

www.mayoclinic.com/health/c-difficile/DS00736
Information about *C. difficile* colitis from the Mayo Clinic.

Clinical Guidelines
www.journals.uchicago.edu/doi/abs/10.1086/651276?user_csr
=Z38.88-2003&gr_interlinking=org&gr_article_pub
ed=duchic.mim.msh.harvard.edu
The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) updated clinical practice guidelines for *C. difficile* infection in adults in 2010.


www.mayoclinic.org/physicians/guidelines/CdifficleDiarrhea.pdf
The American College of Gastroenterology, Practice Parameters Committee published guidelines for the diagnosis and management of *C. difficile*-associated diarrhea and colitis in 1997.

Diagnostic Tests and Criteria
www.annals.org/content/151/3/176.full
Access the Improving Patient Care article published in 2005 in *Annals of Internal Medicine: Does My Patient Have Clostridium difficile Infection?*

Quality Measures
Strategies to prevent *C. difficile* infections in acute-care hospitals from the Infectious Diseases Society of America—Medical Specialty Society and the Society for Healthcare Epidemiology of America—Professional Association.
THINGS YOU SHOULD KNOW ABOUT *C. DIFFICILE* INFECTION

What is *Clostridium difficile* infection and how is it spread?
- *C. difficile* (often called *C. diff.*) is a bacterium that can cause mild to severe diarrhea and other symptoms.
- The bacteria are typically spread when people touch surfaces or other persons contaminated with trace amounts of stool and then touch their mouth or nose.
- Workers in health care settings can accidentally spread the bacteria directly to patients or contaminate surfaces that patients touch.

What are symptoms of *C. difficile* infection?
- The main symptom is having at least 3 watery bowel movements daily for 2 days or more.
- Other symptoms include fever, nausea, and abdominal pain.
- *C. difficile* infection can lead to colitis, severe intestinal problems, and sepsis. In rare cases, it can be fatal.

Who gets *C. difficile* infection?
- The infection usually occurs in people who are hospitalized or in nursing homes, and a long length of stay increases the risk.
- Taking antibiotics changes the normal balance of bacteria in the gut, allowing *C. difficile* to multiply and produce toxins. The diarrhea usually occurs during or just after taking antibiotics but can occur up to 3 months later.
- Other risk factors include gastrointestinal surgery or a serious underlying illness.
- Elderly people and people who have a weakened immune system, such as those who are receiving chemotherapy or who have HIV, are also at increased risk.

How do you know if it is *C. difficile*?
- When diarrhea and nausea are severe or persistent along with fever or abdominal pain, it suggests *C. difficile* infection.
- When doctors think a person might have *C. difficile*, they will order stool tests that see if it is the cause.

How is it treated?
- If you are taking an antibiotic, your doctor may tell you to stop taking it. Some patients may need no other treatment.
- Patients often require a different antibiotic to treat *C. difficile*.
- In the most severe cases, surgery may be needed to remove the infected part of the intestines.

For More Information

http://digestive.niddk.nih.gov/ddiseases/pubs/diarrhea/
National Institute of Diabetes and Digestive and Kidney Diseases information on what causes diarrhea.

www.nlm.nih.gov/medlineplus/clostridiumdifficileinfections.html#cat69
Information from the National Library of Medicine’s MEDLINE Plus on *C. difficile* and on what to expect if you need tested for it.
CME Questions

1. A 68-year-old man is diagnosed with *Clostridium difficile* infection 5 days after elective hip replacement surgery. This hospital has recently reported a higher incidence of *C. difficile* infections. The patient was in a 2-bed hospital room. In addition to bleach for enhanced room cleaning, which of the following "bundled" measures would be most effective in preventing the spread of *C. difficile* in this hospital setting?
   A. Airborne precautions and alcohol hand sanitizer
   B. Airborne precautions and soap and water for hand hygiene
   C. Barrier precautions and alcohol hand sanitizer
   D. Barrier precautions and soap and water for hand hygiene
   E. Droplet precautions and soap and water for hand hygiene

2. An 80-year-old woman is evaluated for diarrhea characterized by 6 to 8 bowel movements per day with abdominal pain. She was hospitalized 2 months ago for pneumonia complicated by *C. difficile* infection (CDI) treated with a course of metronidazole. One month after discharge, she developed a urinary tract infection and was given ciprofloxacin; CDI was again diagnosed 5 days later and treated with a course of metronidazole.

On physical examination, the patient is afebrile, blood pressure is 130/78 mm Hg, and pulse rate is 90/min. Abdominal examination reveals hyperactive bowel sounds with mild diffuse tenderness.

The leukocyte count is $18.9 \times 10^3$ cells/L. The results of *C. difficile* toxin assay are positive.

A course of which of the following is the most appropriate treatment?

A. Intravenous vancomycin
B. Oral metronidazole followed by tapering doses of metronidazole
C. Oral vancomycin followed by tapering doses of metronidazole
D. Oral vancomycin followed by tapering doses of vancomycin

3. A 74-year-old woman is evaluated in the emergency department with a 2-day history of diarrhea characterized by 10 bowel movements daily, with worsening abdominal pain and fever. Today, she has had no bowel movements but does have an increasingly distended abdomen. Five weeks ago, the patient was hospitalized with necrotizing fasciitis of the right thigh, for which she had debridement, received nafcillin and clindamycin therapy, and was discharged after 2 weeks. On discharge, she was prescribed a 2-week course of nafcillin, which she completed 1 week ago.

On physical examination, the patient is awake but disoriented. Temperature is 38.5°C (101.5°F), blood pressure is 90/55 mm Hg, pulse rate is 122/min, and respiratory rate is 24/min. The abdomen is distended and tender to palpation, and bowel sounds are absent.

Laboratory studies indicate a leukocyte count of $32.5 \times 10^3$ cells/L, serum albumin level of 25 g/L (2.5 g/dL), and a serum creatinine level of 221 μmol/L (2.5 mg/dL). Stool, blood, and urine samples are obtained for culture, and she is admitted to the intensive care unit.

Which is the most appropriate treatment?

A. Intravenous metronidazole and oral vancomycin
B. Intravenous vancomycin
C. Oral metronidazole
D. Oral metronidazole and oral vancomycin
E. Oral vancomycin

4. A 32-year-old man is evaluated in the emergency department for a 5-day history of worsening crampy abdominal pain and 8 to 10 loose bowel movements a day. The patient has a 5-year history of ulcerative colitis treated with azathioprine and topical mesalamine; before this episode, he had 1 or 2 bowel movements of well-formed stool a day. The patient had sinusitis recently, which resolved with antibiotic therapy. He has otherwise been healthy and has not traveled recently, had contact with sick persons, or been noncompliant with medication.

On physical examination, the temperature is 38.3°C (101°F), the blood pressure is 130/76 mm Hg sitting and 105/50 mm Hg standing, the pulse rate is 90/min sitting and 120/min standing, and the respiration rate is 18/min. The abdomen is diffusely tender without rebound or guarding. Laboratory studies reveal hemoglobin levels of 12.3 g/L, leukocyte count of $28 \times 10^3$ cells/L with 15% band forms, and platelet count of $234 \times 10^3$ cells/L. Intravenous fluids are started, and stool studies are obtained.

Which is the most appropriate treatment for presumed *C. difficile* infection?

A. Increase dose of azathioprine
B. Start oral vancomycin
C. Start oral mesalamine
D. Small-bowel radiographic series