CME CREDIT

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Clostridium difficile diarrhea and colitis: A clinical overview

ABSTRACT

Infection with toxin-producing strains of *Clostridium difficile* is common and potentially life-threatening. It occurs mostly in patients in the hospital or nursing home who are taking or have recently taken antibiotics. Two toxins, A and B, damage the colonic mucosa, resulting in symptoms ranging from mild diarrhea to bloody diarrhea with fever and abdominal pain, colitis, or even pseudomembranous colitis. Severe cases may involve dehydration, toxic megacolon, or colonic perforation. This article reviews the microbiology, epidemiology, clinical manifestations, diagnosis, treatment, and prevention of this disease.

KEY POINTS

Hospitalization and antibiotic exposure are the most important risk factors for *C difficile* infection.

C difficile diarrhea and colitis are toxin-mediated inflammatory processes and are diagnosed by detecting the toxin in stool samples of patients at risk.

Oral metronidazole is the drug of choice for treating *C difficile* diarrhea. Relapses should be treated with a repeat course.

To prevent *C difficile* infection, limit antibiotic use to the shortest effective course of therapy. Wash hands before and after patient contact and wear gloves during contact with patients with *C difficile* diarrhea.

INFECTION with toxin-producing strains of *Clostridium difficile* is common and potentially life-threatening in patients in the hospital or nursing home who take antibiotics. The toxins damage the colonic mucosa, resulting in conditions ranging from mild diarrhea to colonic perforation.

This article briefly reviews the microbiology, epidemiology, clinical manifestations, diagnosis, treatment, and prevention of *C difficile* diarrhea.

A NOTE ON TERMINOLOGY

Clinicians use a variety of names to refer to *C difficile*-related diarrheal syndromes, including *C difficile*-associated diarrhea, *C difficile* diarrhea, *C difficile* colitis, antibiotic-associated *C difficile* colitis, and pseudomembranous colitis.[1] In this article the term "*C difficile* diarrhea" refers to the entire spectrum of syndromes, including the most severe colitis.

ILLUSTRATIVE CASE

A 40-year-old man was readmitted to the hospital 10 days after discharge. He had a history of recurrent alcohol-induced pancreatitis that resulted in pseudocysts and abscesses that required drainage. He had recently undergone closed drainage of a pseudocyst and had been receiving intravenous ceftriaxone therapy at home.

On readmission he complained of crampy abdominal discomfort and seven to 10 loose stools daily. He had a fever with a temperature ranging from 38 to 38.5°C, but no nausea or vomiting. His white blood cell count was 15.4 $\times 10^9$/L. The pseudocyst had drained complete-

ly. Blood cultures were negative. However, an assay for C *difficile* toxin was positive. The ceftriaxone was stopped, oral metronidazole was started, and his condition improved.

WHAT IS *CLOSTRIDIUM DIFFICILE*?

C *difficile*, so named because it is difficult to culture and isolate, is a noninvasive Gram-positive, spore-forming, obligate anaerobic bacillus, certain strains of which produce two toxins as they multiply. Toxin A is an enterotoxin, and toxin B is a cytopathic toxin.[2] Because not all strains of C *difficile* produce toxins, not all produce diarrheal disease. Generally, toxin-producing strains elaborate both toxins, although occasionally only toxin A or B is produced, a phenomenon that may be increasing in incidence[3] and that may make diagnosis more difficult, since most diagnostic assays measure only one of the toxins.

C *difficile* can be cultured from the stool in 5% of healthy adults[1] (range 2% to 15%), in 10% to 30% of asymptomatic hospital and nursing home patients[1] (especially if recently treated with antibiotics), and in 30% to 50% of healthy infants.[1,4] Therefore, the mere presence of C *difficile* does not necessarily indicate disease.

Antibiotic exposure may be as brief as a single dose

HOW IS *C DIFFICILE* TRANSMITTED?

C *difficile* is ubiquitous in the soil and water and on inanimate surfaces in the hospital. The spores are very hardy and can survive for weeks and even months. Spores or organisms are transmitted by the fecal-oral route, usually via the hands of hospital personnel, but also from patient to patient or from the environment to the patient.[2]

HOW COMMON IS *C DIFFICILE* DIARRHEA?

Infection with toxin-producing C *difficile* is responsible for 15% to 20% of cases of antibiotic-associated diarrhea[1,5] and is the most common cause of infectious nosocomial diarrhea. Furthermore, its incidence has been increasing in recent years.[2] More than 90% of cases of C *difficile* diarrhea are acquired in the hospital, whereas fewer than 5% are community-acquired.[3,6]

WHO IS AT RISK FOR *C DIFFICILE* DIARRHEA?

Recent or current exposure to antibiotics or, rarely, to antineoplastic agents[7] while in the hospital is almost always a prerequisite for C *difficile* diarrhea. Antibiotics alter the suppressive activity of the normal colonic flora, allowing overgrowth of C *difficile*, which results in toxin production and disease. Antibiotic exposure may be as brief as a preoperative prophylactic dose. The exposure may be current or within the previous 8 weeks.

The most commonly associated antibiotics are cephalosporins, clindamycin, and ampicillin, although almost all antibiotics have been implicated.[1–4,8,9] Rare cases have been reported without antibiotic exposure.[10]

Other risk factors for C *difficile* diarrhea are older age,[1,2] severe underlying illness, renal failure, enteral feedings, and use of rectal thermometers.[3,4,11] There is a linear relationship between length of hospital stay, colonization with C *difficile*, and development of C *difficile* diarrhea.[3]

WHAT ARE THE CLINICAL MANIFESTATIONS OF *C DIFFICILE* DIARRHEA?

C *difficile* can cause a spectrum of conditions ranging from asymptomatic carriage to severe disease with considerable morbidity and sometimes mortality. Patients may simply have diarrhea or may present with colitis without pseudomembranes, pseudomembranous colitis, fulminant colitis, or colonic perforation.

Diarrhea is often foul, watery, mucoid, and occasionally bloody. It can range from nonexistent (in the case of an ileus or toxic megacolon) to severe.

Abdominal pain may also be mild to severe.

Fever may vary from low to quite high, with temperatures as high as 40°C.

Leukocytosis may be mild or extreme, with white blood cell counts as high as 50×10^9/L.[1,4]

Colitis. Colonic edema visualized on abdominal radiographs appears as thickened bowel walls or as "thumbprinting."[4] Endoscopy reveals pseudomembranes in 50%

of cases (FIGURE 1). The colitis associated with C *difficile* diarrhea most often involves the entire colon, although left-sided colitis is more common than right-sided. Right-sided colitis is more often associated with ileus and therefore no diarrhea.[4]

Toxic megacolon is an especially severe form of the disease that can be difficult to diagnose because the ileus precludes diarrhea and therefore lowers the suspicion for this condition.

Rare extraintestinal manifestations of C *difficile* infection include intra-abdominal and perianal abscesses, bacteremia, and seeding of prosthetic joints.[12]

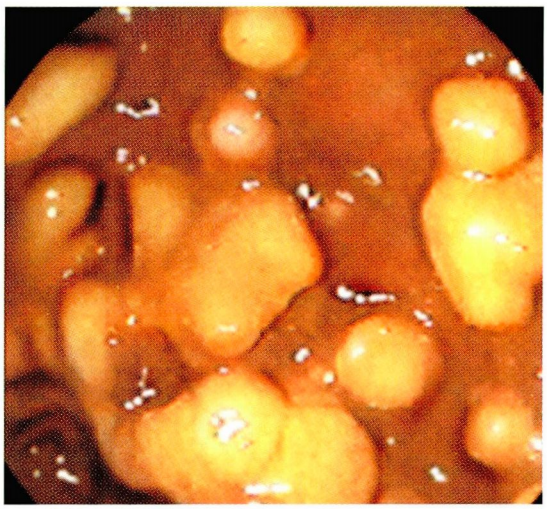

FIGURE 1. Colonoscopic view of pseudomembranous colitis secondary to *Clostridium difficile.*

HOW IS *C DIFFICILE* DIARRHEA DIAGNOSED?

C *difficile* diarrhea is defined by recent antibiotic use, evidence of toxin-producing strains of C *difficile* and, in select cases, by visualizing pseudomembranes on endoscopy or a pathologic specimen.[2] The presence of C *difficile* may be documented in the laboratory by a variety of methods.[13,14]

Tests for the bacterium

Although cultures are more sensitive than are tests for the toxin, they are also more expensive and time-consuming and are normally used only in epidemiologic studies. Furthermore, since not all isolates of C *difficile* produce toxins, a positive culture would require additional testing for the toxin to confirm the diagnosis. Moreover, not all laboratories are equipped to culture C *difficile*. Finally, C *difficile* diarrhea results from toxin-mediated inflammation. For all these reasons, testing stool samples for the toxin is the preferred approach, and cultures are usually reserved for epidemiologic studies and select clinical situations.

Tests for the toxin

Two tests for the toxin are available.

The cytotoxin assay uses a tissue culture. It is the gold standard but is not practical for general clinical use.[1]

The enzyme immunoassay is more common and practical for clinical use. It has a sensitivity of 70% to 95% and a specificity of 99% to 100%.[1] Sending more than one stool sample for enzyme immunoassay testing during the same day is not likely to be cost-effective.

Other tests use latex agglutination to detect glutamate dehydrogenase, a clostridial enzyme, and a polymerase chain reaction (under development) to detect the toxin.[2]

Whom to test

Since 80% of cases of diarrhea in hospitalized patients are *not* due to C *difficile*, not every case of nosocomial diarrhea needs to be evaluated for C *difficile*. Antibiotic therapy, prolonged hospitalization, presence of leukocytes in the stool, and abdominal pain are factors that increase the likelihood of a positive C *difficile* assay.[15,16]

Look for: diarrhea, antibiotic use, a long hospital stay, abdominal pain, and WBCs in the stool

HOW IS *C DIFFICILE* DIARRHEA TREATED?

To treat C *difficile* diarrhea, the physician should:

Stop the offending antibiotic if possible, which may lead to improvement in up to 20% of cases, obviating the need for additional therapy.[2,3]

Replace fluids and electrolytes.

Give a 10-day course of either metronidazole or vancomycin. The metronidazole dosage is 250 mg by mouth four times a day; the vancomycin dosage is 125 mg by mouth four times a day. The success rate is greater than 95% for either agent. Relapse rates are similar for both medications.[2,4,17] However, of

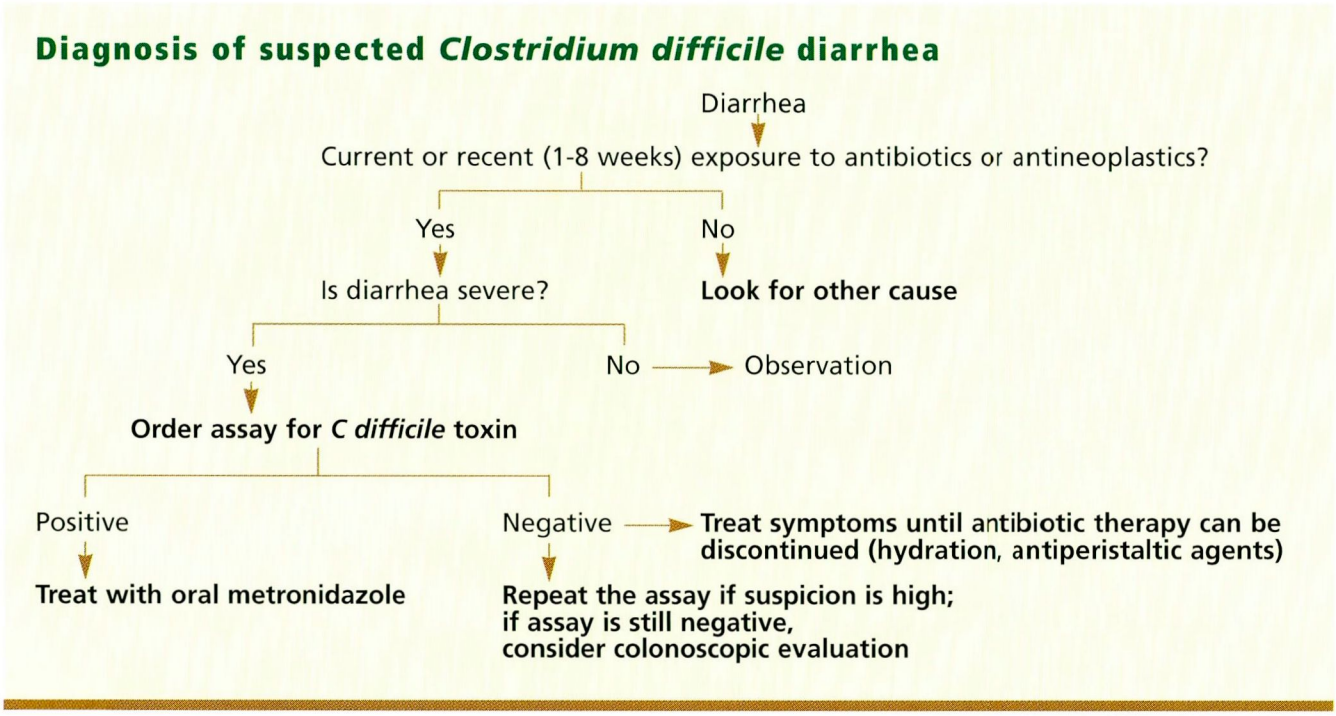

FIGURE 2

Avoid antiperistaltic agents in proven *C difficile* infection

the two, metronidazole is preferred for several reasons:

- Lower cost: A 10-day course of vancomycin costs $230, while the same course of metronidazole costs $9
- Concern about the emergence of vancomycin-resistant enterococcus
- Lack of evidence demonstrating superiority of either vancomycin or metronidazole,[18] although some experts recommend vancomycin for more severe cases.[19]

Antiperistaltic agents should be avoided during the treatment of proven C *difficile* infection, as they may worsen the condition.[1–4]

Treatment side effects

Side effects of oral metronidazole treatment include nausea, a metallic dysgeusia, peripheral neuropathy, and a disulfiram-type reaction to alcohol. Oral vancomycin is relatively devoid of side effects.

Oral vs intravenous therapy

The oral route is preferred, as C *difficile* diarrhea is a luminal disease. In the event of an ileus, oral agents may still be given through a nasogastric tube while the patient also receives intravenous metronidazole (which undergoes hepatobiliary secretion) and, in some instances, vancomycin by retention enema. Intravenous vancomycin is not effective against C *difficile* diarrhea.

When is surgery needed?

Patients with toxic megacolon or colonic perforation require surgical consultation.[1–3] Total abdominal colectomy and diversion appear to be more effective than diversion alone when surgical intervention is needed.[20]

Suggested approach to treatment

FIGURE 2 illustrates one possible approach for suspected C *difficile* diarrhea. Once the diagnosis is suspected and evaluation is started, some experts start metronidazole empirically, particularly in severe cases. If the diarrhea is mild and the offending antibiotic can safely be discontinued, clinical observation without treatment may be appropriate pending laboratory confirmation.

HOW ARE RELAPSES OF *C DIFFICILE* DIARRHEA TREATED?

C *difficile* diarrhea recurs in up to 20% of cases. Subsequent relapses may occur in approxi-

mately 8% of cases after treatment of the initial relapse. Relapses tend to occur within 1 to 2 weeks of treatment but have been reported as late as 8 weeks after treatment. Current guidelines recommend retreatment with the same agent for 10 days.[1–4]

Approaches used for subsequent relapses include repeated courses of metronidazole alternating with vancomycin, the addition of rifampin to vancomycin, or a course of treatment slowly tapered over several weeks.[2,3] Oral *Saccharomyces boulardii* combined with the antibiotic may protect against subsequent relapses.[21] *Lactobacillus* supplements or enemas may help restore normal intestinal flora. Resin-binding agents such as cholestyramine are thought to bind the toxin. The effectiveness of these measures is unclear since no controlled trials have been performed for most of these approaches.

Children with immunoglobulin deficiencies may be at risk for recurrent C *difficile* diarrhea. Therapy with intravenous immunoglobulin may be effective in preventing relapses in this select group of patients.[1]

HOW CAN *C DIFFICILE* DIARRHEA BE PREVENTED?

Some institutions have decreased the incidence of C *difficile* diarrhea by restricting the use of specific antibiotics such as clindamycin.[2,22] Moreover, it is prudent to limit antibiotic use to the shortest effective course of therapy for each patient. Other effective measures are to:

- Wash hands before and after each patient contact
- Wear gloves during contact with patients with C *difficile* diarrhea[3]
- Use isolation precautions for handling the stool of patients with C *difficile* diarrhea[1]
- Disinfect objects or surfaces contaminated with C *difficile*.

Some experts recommend isolation of patients, but this has not proven conclusively to be of benefit.[2,3]

Limit antibiotic use to the shortest effective course

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