Clostridium difficile–Associated Diarrhea

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***Clostridium difficile* infection is responsible for approximately 3 million cases of diarrhea and colitis annually in the United States. The mortality rate is 1 to 2.5 percent. Early diagnosis and prompt aggressive treatment are critical in managing *C. difficile*–associated diarrhea. Major predisposing factors for symptomatic *C. difficile* colitis include antibiotic therapy; advanced age; multiple, severe underlying diseases; and a faulty immune response to *C. difficile* toxins. The most common confirmatory study is an enzyme immunoassay for *C. difficile* toxins A and B. The test is easy to perform, and results are available in two to four hours. Specificity of the assay is high (93 to 100 percent), but sensitivity ranges from 63 to 99 percent. In severe cases, flexible sigmoidoscopy can provide an immediate diagnosis. Treatment of *C. difficile*–associated diarrhea includes discontinuation of the precipitating antibiotic (if possible) and the administration of metronidazole or vancomycin. Preventive measures include the judicious use of antibiotics, thorough hand washing between patient contacts, use of precautions when handling an infected patient or items in the patient's immediate environment, proper disinfection of objects, education of staff members, and isolation of the patient. (Am Fam Physician 2005;71:921-28. Copyright© 2005 American Academy of Family Physicians.)**

See page 835 for strength-of-recommendation labels.

Clostridium difficile is a gram-positive, spore-forming rod that is responsible for 15 to 20 percent of antibiotic-related cases of diarrhea and nearly all cases of pseudomembranous colitis.[1] The species was named "difficile" because initially it was hard to culture.[2] Early studies showed that *C. difficile* could be isolated from the gastrointestinal tracts of most neonates; thus, it was believed to be a commensal organism. In the late 1970s, however, *C. difficile* was found to be the primary cause of pseudomembranous colitis.[3] Because of the frequent use of broad-spectrum antibiotics, the incidence of *C. difficile* diarrhea has risen dramatically in recent decades.[4,5]

C. difficile–associated diarrhea often is perceived to be an occasional and easily treated side effect of antibiotic therapy. Research has shown, however, that *C. difficile* infection accounts for considerable increases in the length of hospital stays and more than $1.1 billion in health care costs each year in the United States.[5] The condition is a common cause of significant morbidity and even death in elderly or debilitated patients.

Family physicians should stress preventive measures for *C. difficile*–associated diarrhea (especially the judicious use of antibiotics) and should maintain a high index of suspicion for *C. difficile* infection in their patients.

Illustrative Case

An 87-year-old white woman was readmitted to the hospital because of recurrent pneumonia. Ten days earlier, she had been treated for right lower lobe pneumonia at another institution. She was discharged on moxifloxacin (Avelox) and doxycycline (Vibramycin). She returned home, where she was recovering, but then she became weak, short of breath, and constipated.

On readmission, chest radiography revealed right lower lobe pneumonia. The patient's white blood cell (WBC) count was 16,300 per mm^3 (16.3×10^9 per L), compared with 7,500 per mm^3 (7.5×10^9 per L) during her previous hospitalization.

At the time of readmission, the patient was afebrile, and her vital signs were stable. Moxifloxacin and doxycycline were continued. Overnight, however, the patient became febrile, and her WBC count rose to 36,000 per mm^3 (36×10^9 per L). She also passed several loose stools. In light of the patient's recent history of antibiotic use, the sudden leukocytosis, her age and frail condition, and her recent hospital admission, *C. difficile*–associated diarrhea was considered, and a stool sample was obtained for analysis.

Empiric treatment with oral metronidazole (Flagyl) and famotidine (Pepcid) was initiated. Shortly thereafter, the patient developed marked hypotension. Fluid boluses produced

Strength of Recommendations

Key clinical recommendation	*Label*	*References*
Test for *Clostridium difficile* toxin in patients with community-acquired or traveler's diarrhea who have had antibiotics or chemotherapy in recent weeks.	B	20
Test for *C. difficile* toxin in patients with nosocomial diarrhea beginning three or more days after admission to the hospital.	B	20
If necessary, rapid diagnosis of *C. difficile*–associated diarrhea can be made by flexible sigmoidoscopy or abdominal computed tomography.	C	4
In patients with confirmed *C. difficile* infection, the offending antibiotic should be withdrawn.	B	20
The recommended antibiotic is metronidazole (Flagyl) in a dosage of 250 mg orally four times per day or 500 mg orally three times per day for 10 to 14 days.	A	20

A = consistent, good-quality, patient-oriented evidence; B = inconsistent or limited-quality, patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. See page 835 for more information.

no improvement, and a dopamine (Intropin) drip was started. Moxifloxacin and doxycycline were discontinued, and treatment with oral vancomycin (Vancocin), intravenous metronidazole, and intravenous ceftizoxime (Cefizox); (anti–*C. difficile*–associated diarrhea therapy) was started.

Sigmoidoscopy revealed diffuse pseudomembranes throughout the patient's distal colon, confirming *C. difficile* infection *(Figure 1)*. An abdominal computed tomographic (CT) scan was consistent with this diagnosis. Ceftizoxime was discontinued, and total parenteral nutrition was initiated.

Over the next eight days, the patient's condition continued to decline as she became more acidotic, her urine output diminished, her mental status fluctuated, and her abdomen became grossly distended and tympanic. Subtotal colectomy and ileostomy were considered, but were refused by the patient and her husband.

After more than a week of severe illness, the patient began to improve. Eventually, she was transferred to a skilled nursing facility for rehabilitation.

Epidemiology

Each year, *C. difficile* infection results in approximately 3 million cases of diarrhea and colitis in the United States. The case mortality rate is approximately 1 to 2.5 percent. Until recently, *C. difficile* infection was thought to result from an overgrowth of commensal organisms in the colon; however, studies have shown that fewer than 3 percent of adults carry this pathogen.[1]

Acquisition of *C. difficile* occurs primarily in the hospital setting, where the organism has been cultured from bed rails, floors,

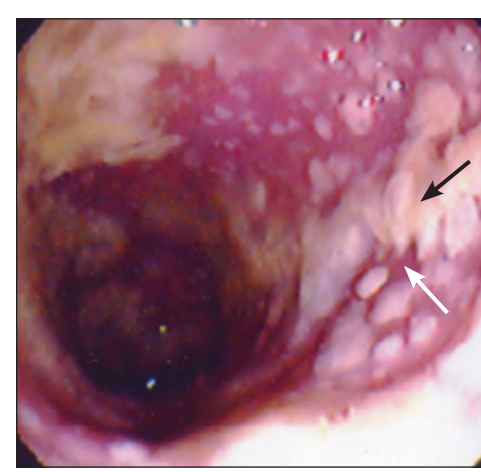

Figure 1. Irregular yellow plaques of necrotic debris *(black arrow)* with intervening edematous bowel mucosa *(white arrow)* in an 87-year-old woman. These findings are consistent with pseudomembranes caused by *Clostridium difficile* infection.

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TABLE 1
Risk Factors for *Clostridium difficile*–Associated Diarrhea

Admission to intensive care unit
Advanced age
Antibiotic therapy
Immunosuppressive therapy
Multiple and severe underlying diseases
Placement of a nasogastric tube
Prolonged hospital stay
Recent surgical procedure
Residing in a nursing home
Sharing a hospital room with a *C. difficile*–infected patient
Use of antacids

Information from references 4 and 6.

windowsills, and toilets, as well as the hands of hospital workers who provide care for patients with *C. difficile* infection *(Table 1)*.[4,6] The organism can persist in hospital rooms for up to 40 days after infected patients have been discharged.[1]

The rate of *C. difficile* acquisition is estimated to be 13 percent in patients with hospital stays of up to two weeks and 50 percent in those with hospital stays longer than four weeks.[7] Patients who share a room with a *C. difficile*–positive patient acquire the organism after an estimated hospital stay of 3.2 days, compared with a hospital stay of 18.9 days for other patients.[2]

Pathophysiology

The precipitating event for *C. difficile* colitis is disruption of the normal colonic microflora. This disruption usually is caused by broad-spectrum antibiotics *(Figure 2)*,[1,5,8-11] with clindamycin (Cleocin) and broad-spectrum penicillins and cephalosporins most commonly implicated.[8] Antibiotics with a reduced propensity to induce infection include aminoglycosides, metronidazole, antipseudomonals, and vancomycin.[8] The risk of developing antibiotic-associated diarrhea more than doubles with longer than three days of antibiotic therapy (risk ratio: 2.28).[12]

After disruption of the colonic microflora, colonization of *C. difficile* generally occurs through the ingestion of heat-resistant spores, which convert to vegetative forms in the colon.[9] Depending on host factors, an asymptomatic carrier state or clinical manifestations of *C. difficile* colitis develop.[9] Manifestations of the disease range from mild diarrhea to life-threatening *C. difficile* colitis. *C. difficile*–associated diarrhea can occur up to eight weeks after the discontinuation of antibiotics.[1] Most cases of *C. difficile* infection occur on days 4 through 9 of antibiotic therapy.[9]

The rate of *Clostridium difficile* acquisition is estimated to be 13 percent in patients with hospital stays of up to two weeks and 50 percent in those with hospital stays longer than four weeks.

The major host factors predisposing patients to the development of symptomatic *C. difficile*–associated diarrhea include antibiotic therapy, advanced age, number and severity of underlying diseases, and faulty immune response to *C. difficile* toxins *(Table 1)*.[4,6] Patients at highest risk for fulminant disease include those who recently received immunosuppressive therapy or recently under-

Pathogenesis of *Clostridium difficile* Infection

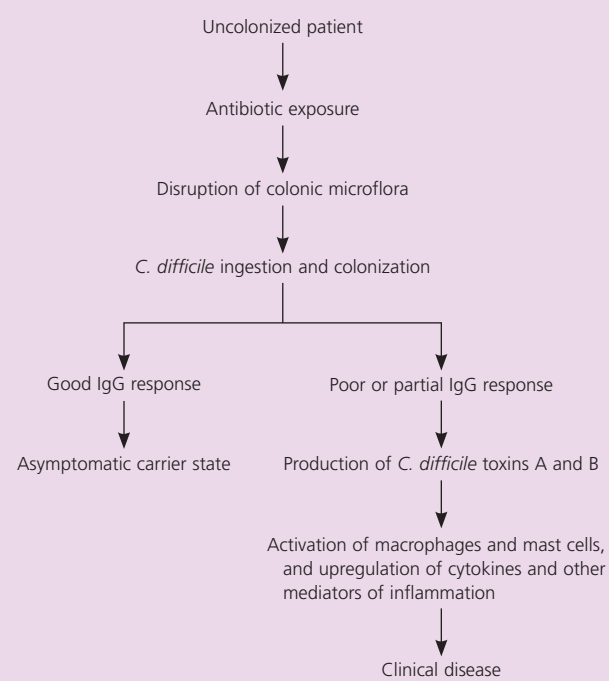

Figure 2. Pathogenesis of *Clostridium difficile* infection.

Information from references 1, 5, and 8 through 11.

TABLE 2
Selected Differential Diagnosis of *Clostridium difficile*–Associated Diarrhea

Disorder	*Typical presentation*
C. difficile–associated diarrhea	Recent history of antibiotic use, evidence of colitis, fecal leukocytes, fever; may not resolve with discontinuation of antibiotics; diarrhea typically watery, may be florid
Antibiotic intolerance	History of antibiotic intolerance, no evidence of colitis; resolves with antibiotic withdrawal
Infectious enteritis or colitis (diarrhea not associated with *C. difficile*): bacterial gastroenteritis, viral gastroenteritis, amebic dysentery	History of travel, camping, infectious contacts, or day care attendance; associated with nausea and vomiting
Inflammatory bowel disease: Crohn's disease, ulcerative colitis	Bloody diarrhea, abdominal pain, nausea, vomiting, loss of appetite, family history
Ischemic colitis	History of vascular disease; pain associated with eating

Information in part from reference 6.

went surgical procedures, and those with a history of *C. difficile*–associated diarrhea.[4] The increased risk may be due partly to the debilitated patient's inability to mount an IgG antibody immune response against *C. difficile* toxin A.[5] The ability to mount an immune response is not protective against *C. difficile* colonization, but it is associated with decreased morbidity, mortality, and recurrence of *C. difficile*–associated diarrhea.[10,13]

C. difficile causes toxin-mediated colitis. Pathogenic strains of *C. difficile* produce two protein exotoxins: toxin A and toxin B.[1] Toxin A activates macrophages and mast cells. Activation of these cells causes the production of inflammatory mediators, which leads to fluid secretion and increased mucosal permeability.[1] Toxin B has little enterotoxic activity but is extremely cytotoxic in vitro. *C. difficile* toxins also cause leukocyte chemotaxis and the upregulation of cytokines and other inflammatory mediators. Consequently, there is a profound colonic inflammatory response, which is evidenced clinically by a high WBC count.[1] As colitis worsens, focal ulcerations occur, and the accumulation of purulent and necrotic debris forms the typical pseudomembrane.[9]

An important indicator of impending fulminant colitis is a sudden rise in the peripheral white blood cell count.

Diagnosis

The diagnosis of *C. difficile*–associated diarrhea requires a careful history, with particular emphasis on antibiotic use during the preceding three months *(Figure 3)*.[18] The clinical presentation ranges from no symptoms to fulminant pseudomembranous colitis. A detailed description of the patient's diarrhea, including color, consistency, and frequency, is important in differentiating other causes of diarrhea from *C. difficile*–associated diarrhea. Other important factors include a history of fever, immunosuppression, a recent surgical procedure, previous infection with *C. difficile,* recent change in bowel habits, and the presence of abdominal symptoms *(Table 1)*.[4,6] A selected differential diagnosis is provided in *Table 2*.[6]

The most common laboratory test for diagnosing *C. difficile*–mediated disease is an enzyme immunoassay that detects toxins A and B. This test provides results within two to six hours and has a specificity of 93 to 100 percent. The sensitivity is 63 to 99 percent, which means that false-negative results can occur.[13-16] However, the majority of combination enzyme immunoassays have a sensitivity of 85 to 95 percent.[8] The immunoassay should not be used as an indicator of response to therapy because results remain positive for extended peri-

Diagnosis and Treatment of *Clostridium difficile*–Associated Diarrhea

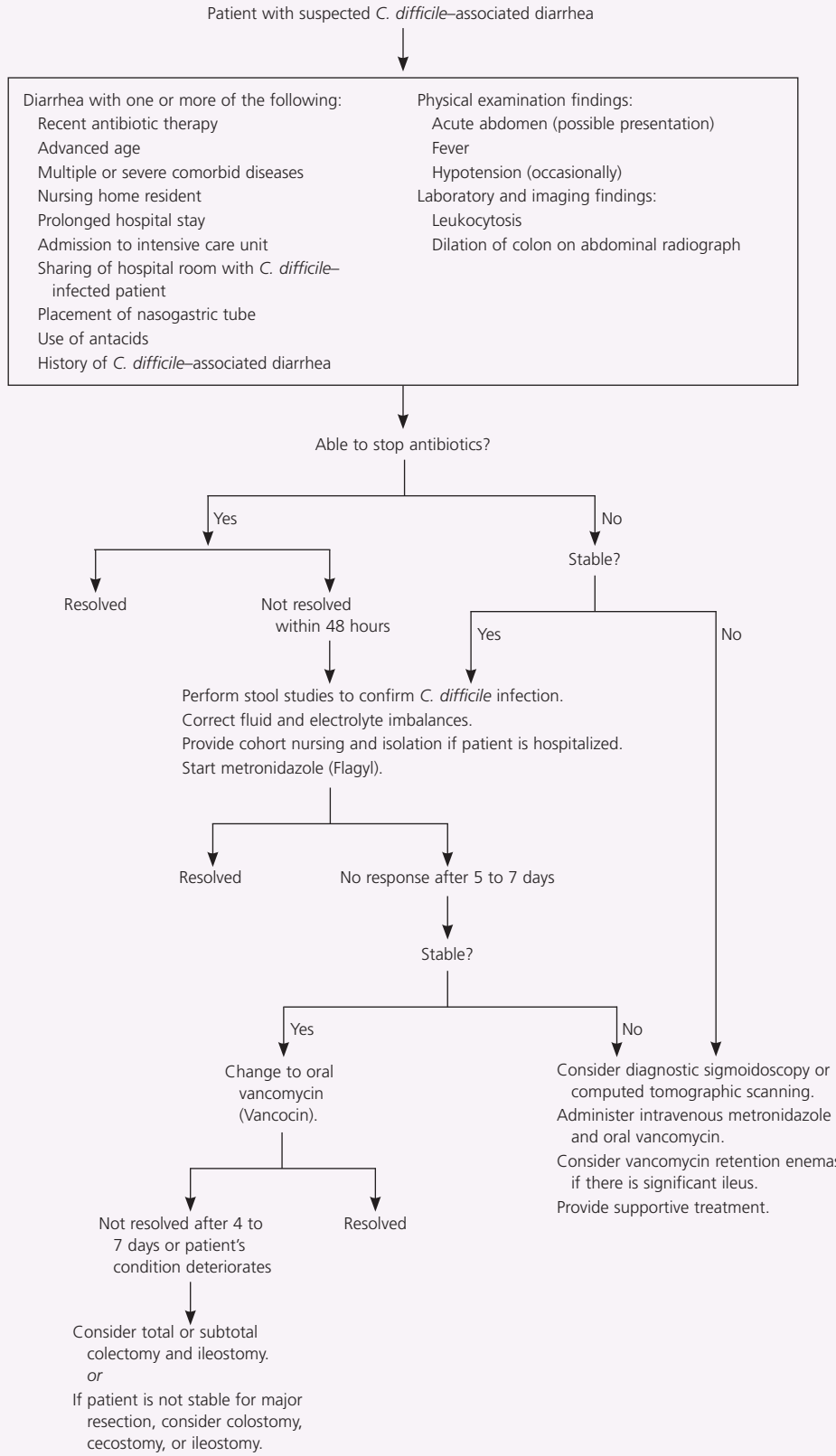

Figure 3. Suggested algorithm for the diagnosis and treatment of *Clostridium difficile*–associated diarrhea.

Adapted with permission from Viswanath YK, Griffiths CD. The role of surgery in pseudomembranous enterocolitis. Postgrad Med J 1998;74:216-9.

ods in 25 percent of successfully treated patients.[8]

The gold standard for the diagnosis of *C. difficile*–mediated disease is a cytotoxin assay. Although this test is highly sensitive and specific, it is difficult to perform, and results are not available for 24 to 48 hours.

First-line therapy consists of metronidazole, 500 mg orally three or four times daily for 10 to 14 days.

C. difficile can be cultured. However, culture is not specific for pathogenic toxin-producing *C. difficile* strains and, therefore, is not clinically helpful except for strain typing in outbreaks of nosocomial infection.[9]

A combination immunoassay that is currently in development tests for *C. difficile*–specific glutamate dehydrogenase (sensitivity: 97 percent) and toxins A and B (specificity: 97 to 99 percent). The advantages of this test are same-day turnaround and a high negative predictive value.[16]

An important indicator of impending fulminant colitis is a sudden rise in the peripheral WBC count to between 30,000 and 50,000 per mm^3 (30 to 50 $\times$ 10^9 per L), often accompanied by significant bandemia.[4,17] Because progression to shock can occur even in patients who have had relatively benign symptoms for weeks, early warning signs such as the leukemoid reaction are invaluable.[4]

In patients with fulminant *C. difficile*–associated diarrhea, flexible sigmoidoscopy can provide an immediate diagnosis.[4,13] The finding of pseudomembranes is pathognomonic for *C. difficile* colitis *(Figure 1)*. CT scanning also can diagnose fulminant disease quickly. When considered with the clinical history, the presence of ascites, colon wall thickening, or dilation can help categorize the severity of the colitis.[4]

Treatment

The treatment of *C. difficile*–associated diarrhea depends on the clinical presentation *(Figure 3)*.[18] In otherwise healthy adults, the first step is to discontinue the precipitating antibiotic, if possible, and administer fluids and electrolytes to maintain hydration. With this conservative therapy, diarrhea can be expected to resolve in 15 to 23 percent of patients.[19]

Specific pharmacotherapy for *C. difficile*–associated diarrhea should be initiated in older patients, patients with multiple medical problems, and patients in whom antibiotics need to be continued. Specific treatment also should be initiated if diarrhea persists despite discontinuation of the precipitating antibiotic or if there is evidence of colitis (i.e., fever, leukocytosis, characteristic findings of colitis on CT scanning or endoscopy).[6] Use of opiates and antidiarrheal medications should be avoided or minimized because decreased intestinal motility can exacerbate toxin-mediated disease.

First-line therapy consists of metronidazole, 500 mg orally three or four times daily for 10 to 14 days.[20,21] Metronidazole is an inexpensive drug with a greater than 90 percent positive response rate[21] *(Table 3)*.[13,19-21]

Vancomycin also is an effective treatment, with a response rate of greater than 90 percent.[21] If a patient is pregnant or does not respond to or tolerate metronidazole, vancomycin should be initiated in a dosage of 125 to 500 mg orally four times daily for 10 to 14 days.[6]

Response to therapy can be assessed by the resolution of fever, usually within the first two days. Diarrhea should resolve within two to four days. Treatment is continued for 10 to 14 days. Therapeutic failure is not determined until treatment has been given for at least five days.[19]

Twenty to 25 percent of patients with *C. difficile* infection will have recurrent infection.[6,9] Recurrence seldom is caused by treatment-resistant strains; usually, it is due to the germination of persistent *C. difficile* spores in the colon after treatment or to reinfection because of reingestion of the pathogen.[9] Management of recurrent *C. difficile* infections remains controversial, although most relapses respond to another course of antibiotics given in standard dosages for 10 to 14 days. Up to 5 percent of patients have more than six recurrences.[6]

In patients with recurrent *C. difficile* infection, enemas containing human stool have been used to restore normal microflora in the colon. This approach has had good response rates; however, the enemas are unwieldy to perform, and there is a risk of

TABLE 3
Treatment of *Clostridium difficile* Colitis

Drug	*Dosage*	*Mode of administration*	*Efficacy*	*Side effects*	*Price**	*Advantages and disadvantages*
Metronidazole (Flagyl)	500 mg orally every six to eight hours for 10 to 14 days Alternatives: 250 mg every six hours for 10 to 14 days and 500 mg IV every eight hours for 10 to 14 days	Oral and IV	> 90%	Nausea, vomiting Metallic taste Potentiation of warfarin (Coumadin) Disulfiram-like reaction	$256 (36 to 40): 500 mg orally every six hours for 14 days $678 (103 to 644): 500 mg IV every eight hours for 14 days	Effective by IV administration Less expensive than vancomycin More side effects than vancomycin
Vancomycin (Vancocin)	125 to 500 mg orally every six hours for 10 to 14 days	Oral only† Nasogastric tube Retention enema	> 90%	Minimal; can include unpleasant taste, mouth irritation, nausea or vomiting; rarely, rash	$1,724: 500 mg orally every six hours for 14 days	Safe for use in pregnant women High cost Use may lead to resistance
Vancomycin retention enemas			Uncertain		Variable	

IV = intravenous.

**—Estimated cost to the pharmacist based on average wholesale prices in Red book. Montvale, N.J.: Medical Economics Data, 2004. Cost to the patient will be higher, depending on prescription filling fee.*

†—*Vancomycin is not secreted into the bowel; therefore, IV administration is not effective.*

Information from references 13, and 19 through 21.

transmitting retroviruses or other infectious agents.[22] One potential benefit of enemas is a decrease in the use of vancomycin for recurrent *C. difficile* infections and therefore a theoretical decrease in the emergence of vancomycin-resistant bacteria.

Approximately 3 percent of patients develop severe *C. difficile*–associated diarrhea. The mortality rate in these patients ranges from 30 to 85 percent.[19] Initial treatment of severe cases must be aggressive, with intravenous metronidazole and oral vancomycin used in combination.[11] If ileus occurs, vancomycin can be administered by nasogastric tube with intermittent clamping, retention enemas, or both.[23] If medical therapy fails or perforation or toxic megacolon develops, surgical intervention with colectomy and ileostomy is indicated but carries a high mortality rate.[4,9,18]

Prevention

Prevention of *C. difficile* infection is challenging. Established guidelines should be followed to minimize exposure to the pathogen, particularly in debilitated patients. Preventive measures include the judicious use of antibiotics, hand washing between patient contacts, rapid detection of *C. difficile* by immunoassays for toxins A and B, isolation of patients who have *C. difficile*–associated diarrhea, use of precautions when in contact with the patient and surrounding environment, proper disinfection of objects (e.g., sodium hypochlorite, alkaline glutaraldehyde, ethylene oxide), education of staff members, and use of continued precautions until the diarrhea ceases.[1,6]

A multidiscipline antibiotic management program to restrict the inappropriate use of antibiotics (e.g., third-generation cephalosporins) can lead to a significant decrease in nosocomial infections caused by *C. difficile*.[24] In particular, restriction of clindamycin use has been shown to decrease the incidence of *C. difficile*–associated diarrhea.[25] Family physicians can do much to decrease the occurrence of *C. difficile*–mediated disease

by restricting the use of broad-spectrum antibiotics in their patients.

Probiotic use is a more controversial mode of prevention. Lactobacilli have been shown to reduce the incidence of antibiotic-associated diarrhea, but have not been proven to decrease the incidence of *C. difficile*–associated diarrhea.[26] Anecdotally, many physicians report success with lactobacilli and use this preventive measure routinely, especially in patients at higher risk for severe disease.

The author thanks Christie Schroeder, M.P.H., for her invaluable research and editorial skills that were of great assistance throughout the development of this manuscript.

The author indicates that he does not have any conflicts of interest. Sources of funding: none reported.

REFERENCES

1. Hurley BW, Nguyen CC. The spectrum of pseudomembranous enterocolitis and antibiotic-associated diarrhea. Arch Intern Med 2002;162:2177-84.
2. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of *Clostridium difficile* infection. N Engl J Med 1989;320:204-10.
3. Bartlett JG, Chang TW, Gurwith M, Gorbach SL, Onderdonk AB. Antibiotic-associated pseudomembranous colitis due to toxin-producing clostridia. N Engl J Med 1978;298:531-4.
4. Dallal RM, Harbrecht BG, Boujoukas AJ, Sirio CA, Farkas LM, Lee KK, et al. Fulminant *Clostridium difficile*: an underappreciated and increasing cause of death and complications. Ann Surg 2002;235:363-72.
5. Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to *Clostridium difficile*. Clin Infect Dis 2002;34:346-53.
6. Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. N Engl J Med 2002;346:334-9.
7. Clabots CR, Johnson S, Olson MM, Peterson LR, Gerding DN. Acquisition of *Clostridium difficile* by hospitalized patients: evidence for colonized new admissions as a source of infection. J Infect Dis 1992;166:561-7.
8. Wilcox MH. Gastrointestinal disorders and the critically ill. *Clostridium difficile* infection and pseudomembranous colitis. Best Pract Res Clin Gastroenterol 2003;17:475-93.
9. Kelly CP, Pothoulakis C, LaMont JT. *Clostridium difficile* colitis. N Engl J Med 1994;330:257-62.
10. Kyne L, Warny M, Qamar A, Kelly CP. Association between antibody response to toxin A and protection against recurrent *Clostridium difficile* diarrhoea. Lancet 2001;357:189-93.
11. Kelly CP, LaMont JT. *Clostridium difficile* infection. Annu Rev Med 1998;49:375-90.
12. Wistrom J, Norrby SR, Myhre EB, Eriksson S, Granstrom G, Lagergren L, et al. Frequency of antibiotic-associated diarrhoea in 2462 antibiotic-treated hospitalized patients: a prospective study. J Antimicrob Chemother 2001;47:43-50.
13. Kyne L, Farrell RJ, Kelly CP. *Clostridium difficile*. Gastroenterol Clin North Am 2001;30:753-77,ix-x.
14. De Girolami PC, Hanff PA, Eichelberger K, Longhi L, Teresa H, Pratt J, et al. Multicenter evaluation of a new enzyme immunoassay for detection of *Clostridium difficile* enterotoxin A. J Clin Microbiol 1992;30:1085-8.
15. Altaie SS, Meyer P, Dryja D. Comparison of two commercially available enzyme immunoassays for detection of *Clostridium difficile* in stool specimens [published correction appears in J Clin Microbiol 1994;32:1623]. J Clin Microbiol 1994;32:51-3.
16. Massey V, Gregson DB, Chagla AH, Storey M, John MA, Hussain Z. Clinical usefulness of components of the Triage immunoassay, enzyme immunoassay for toxins A and B, and cytotoxin B tissue culture assay for the diagnosis of *Clostridium difficile* diarrhea. Am J Clin Pathol 2003;119:45-9.
17. Wanahita A, Goldsmith EA, Marino BJ, Musher DM. *Clostridium difficile* infection in patients with unexplained leukocytosis. Am J Med 2003;115:543-6.
18. Viswanath YK, Griffiths CD. The role of surgery in pseudomembranous enterocolitis. Postgrad Med J 1998;74:216-9.
19. Florea NR, Kuti JL, Nightingale CH, Nicolau DP. Treatment of *Clostridium difficile*-associated disease (CDAD). Conn Med 2003;67:153-5.
20. Guerrant RL, Van Gilder T, Steiner TS, Thielman NM, Slutsker L, Tauxe RV, et al., for the Infectious Diseases Society of America. Practice guidelines for the management of infectious diarrhea. Clin Infect Dis 2001;32:331-51.
21. Wenisch C, Parschalk B, Hasenhundl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea [published correction appears in Clin Infect Dis 1996;23:423]. Clin Infect Dis 1996;22:813-8.
22. Gustafsson A, Berstad A, Lund-Tonnesen S, Midtvedt T, Norin E. The effect of faecal enema on five microflora-associated characteristics in patients with antibiotic-associated diarrhoea. Scand J Gastroenterol 1999;34:580-6.
23. Apisarnthanarak A, Razavi B, Mundy LM. Adjunctive intracolonic vancomycin for severe *Clostridium difficile* colitis: case series and review of the literature. Clin Infect Dis 2002;35:690-6.
24. Carling P, Fung T, Killion A, Terrin N, Barza M. Favorable impact of a multidisciplinary antibiotic management program conducted during 7 years. Infect Control Hosp Epidemiol 2003;24:699-706.
25. Climo MW, Israel DS, Wong ES, Williams D, Coudron P, Markowitz SM. Hospital-wide restriction of clindamycin: effect on the incidence of *Clostridium difficile*-associated diarrhea and cost. Ann Intern Med 1998;128(12 pt 1):989-95.
26. Surawicz CM. Probiotics, antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in humans. Best Pract Res Clin Gastroenterol 2003;17:775-83.