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Edited by
Janet Schlechte, M.D.
Kevin Bebout, R.Ph.
Mary Ross, M.B.A.

Pharmacy and Therapeutics
Subcommittee Members:

TREATMENT OF ANTIBIOTIC-ASSOCIATED COLITIS

Jacqueline Stark, PharmD and Sarah J. Johnson, PharmD

Clostridium difficile is the organism responsible for antibiotic-associated colitis (AAC).¹ When antibiotics disrupt the normal intestinal flora, *C. difficile* can colonize the gut and release toxins that result in colonic mucosal injury and inflammation causing sequelae ranging from uncomplicated diarrhea to sepsis and death.^{2,3} The typical symptoms are diarrhea with fever, abdominal pain, and leukocytosis; however, some patients remain asymptomatic.^{2,3}

Who Is at Risk?

C. difficile is one of the most common nosocomial infections.¹ Patients with a long hospital stay or who have had exposure to antibiotics are most likely to develop *C. difficile* colitis.^{1,3} While clindamycin was the first antibiotic shown to cause *C. difficile* colitis,¹ the disease has now been associated with all classes of antibiotics, particularly with commonly used broad-spectrum antibiotics such as third-generation cephalosporins and fluoroquinolones.¹

Diagnosis

The diagnosis of *C. difficile* is established by bioassay of stool for *C. difficile* cytotoxins in conjunction with symptoms.³ Ideally, a toxin-specific enzyme-linked immunosorbent assay (ELISA) is used to detect toxin A or toxin B in stool infiltrates. However, it is important to note that false negative tests in patients with *C. difficile*-associated diarrhea do occur. Other nonspecific laboratory findings include leukocytosis, hypoalbuminemia, and fecal leukocytes.³

Treatment of Antibiotic-Associated Colitis

Treatment should be based on the patient's symptoms and classification of the severity of disease. Table 1 provides guidance on classifying disease severity, as well as disease management based on disease severity. If the patient has a stool bioassay positive for the *C. difficile* cytotoxins, but there are no symptoms present, the patient should not be treated for *C. difficile*.¹ However, if the patient is *C. difficile* positive and does have symptoms, treatment is recommended.³ General guidelines for treatment include:

- Non-essential antibiotics should be discontinued.¹
- Laxatives and antiperistaltic agents should be discontinued.¹
- Fluid and electrolytes should be replaced.¹

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- For antibiotic treatment, both metronidazole and oral vancomycin are appropriate antibiotic choices depending on the severity of the disease.^{1,4}
 - **Metronidazole**
 - **First line therapy in mild to moderate disease: metronidazole 500 mg every 6 hours orally for 10 to 14 days¹**
 - ✓ Vancomycin use should be limited in order to prevent the spread of vancomycin-resistant enterococcus.
 - ✓ The cost of daily metronidazole therapy is under \$1, while oral vancomycin can cost up to \$5 per day for solution and \$42 per day for oral capsules.
 - If a patient is treated for mild disease with metronidazole therapy and there is no improvement after 4 days, or if the patient becomes more symptomatic, the patient should be reassessed to see if the criteria for severe disease are met.
 - If the patient has a **recurrence of mild disease**, metronidazole can be given again as most patients will respond to the same previous therapy. However, if relapse is accompanied by symptoms of severe disease, it should be treated with oral vancomycin.¹
 - **Oral Vancomycin**
 - **First line therapy for severe disease: vancomycin 125 mg every 6 hours orally or via nasogastric tube¹**
 - An Infectious Disease, General Surgery, or Gastrointestinal Medicine Service consult should be considered.
 - Use of oral vancomycin is restricted at UIHC due to concern about inducing vancomycin-resistant enterococci and other resistant organisms.
 - Intravenous vancomycin should not be used for the treatment of *C. difficile* colitis because inadequate drug concentrations reach the infected area.³
 - It may be necessary to use oral vancomycin first line for patients who have:¹
 - ✓ Contraindication to metronidazole use (e.g., severe hepatic dysfunction, allergy, or potential for an alcohol-induced disulfiram-like drug interaction).
 - ✓ Recurrent relapse (more than two previous episodes; Infectious Disease consult should be considered).
 - ✓ Endoscopic evidence of pseudomembranous colitis.
 - ✓ Toxic megacolon, colectomy, or septic shock requiring ICU admission and vasopressor therapy.
 - **Oral vancomycin plus IV/oral metronidazole may be needed for treatment of severe disease with ileus**

Prevention

Spread of *C. difficile* in health care facilities occurs primarily from person-to-person contact or through contamination of the patient care environment. ***C. difficile* spores are resistant to alcohol-based hand sanitizers.** Therefore, health care workers should **wash hands with soap and water** in order to remove the spores from the surface of contaminated hands and to prevent spread of the infection.¹

Summary

- *C. difficile* is one of the most common nosocomial infections and is associated with antibiotic use and long hospital stays.
- *C. difficile* is diagnosed through symptoms and a positive stool bioassay.
- Treatment depends on severity of disease.
 - Mild to moderate disease: metronidazole 500mg every 6 hours orally for 10 to 14 days.
 - Severe disease: vancomycin 125mg every 6 hours orally or via NG tube.
- Alcohol-based hand sanitizers do not kill *C. difficile* spores, so it is important to wash hands with soap and water to avoid spreading the infection.

Table 1: Disease Severity and Recommended Treatment for *C. difficile* Colitis¹

Severity	Severity Criteria	Treatment Regimen
Mild-to-moderate disease	<ul style="list-style-type: none"> • Diarrhea (> 3 unformed stools per day) • Abdominal discomfort • Increase in WBC • Fever 	<ul style="list-style-type: none"> • Stop non-essential antibiotics, laxatives, and antiperistaltic agents (e.g., diphenoxylate, atropine, loperamide) • Initiate metronidazole 500 mg every 6 hours orally for 10 to 14 days • Allow 4 to 6 days for symptoms to resolve • If no improvement in 4 days, reassess and consider changing to oral vancomycin if patient fits criteria for severe disease • If recurrent relapse*, consider changing to oral vancomycin if patient fits criteria for severe disease
Severe disease	<p>Above criteria, <u>plus</u> at least <u>one</u> of the following:</p> <ul style="list-style-type: none"> • Endoscopic evidence of pseudomembranous colitis • At least <u>three</u> of the following criteria identifying severe disease: <ul style="list-style-type: none"> ▪ Symptoms of dehydration (e.g., elevated serum creatinine) ▪ WBC > 20,000 cells/mm³ ▪ Age ≥ 65 years ▪ Fever > 38.3°C (100.9°F) ▪ Plasma Albumin < 2.5 mg/dL ▪ Admission to the ICU • Toxic megacolon, colectomy, or septic shock requiring ICU admission and vasopressor therapy 	<ul style="list-style-type: none"> • Stop non-essential antibiotics, laxatives, and antiperistaltic agents (e.g., diphenoxylate, atropine, loperamide) • Consider Infectious Disease, General Surgery, or Gastrointestinal Medicine Service consult • Initiate vancomycin 125 mg every 6 hours orally or via NG tube • Ileus: Metronidazole 500 mg IV or via NG tube every 8 hours <u>PLUS</u> vancomycin 125 mg orally or via NG tube every 6 hours

*Most patients with recurrent disease will respond to previous therapy; however, if relapse is accompanied by symptoms of severe disease, treat as severe disease.¹

References

1. *Gastroenterol Clin North Am.* 2006; 35:315-35.
2. *CID.* 2007; 40:1598-600.
3. *Pharmacotherapy.* 2007; 27:1029-39.
4. *CID.* 2007; 45:302-7.

Written by: Jacqueline Stark, PharmD, Pharmacy Practice Resident, Department of Pharmaceutical Care and Sarah J. Johnson, PharmD, Clinical Pharmacy Specialist, Department of Pharmaceutical Care
 Reviewed by: Phil Polgreen, MD, Assistant Professor, Division of Infectious Diseases

For information regarding newly marketed drugs, drug-drug interactions, foreign drug identification, adverse drug reactions, alternative medications or other medication-related questions, contact the **DRUG INFORMATION CENTER (6-2600)**. The Center is open Monday through Friday from 8:00 a.m. - 12:30 p.m. and 1:00 p.m. - 4:30 p.m. (except holidays).

ADVERSE DRUG REACTION? CALL THE DRUG INFORMATION CENTER AT 6-2600

FLUOROQUINOLONES NO LONGER RECOMMENDED FOR TREATMENT OF GONOCOCCAL INFECTIONS¹

In the United States, gonorrhea is the second most commonly reported notifiable disease. Since 1993, fluoroquinolones (i.e., ciprofloxacin, or levofloxacin) have been used frequently in the treatment of gonorrhea because of their high efficacy, ready availability, and convenience as a single-dose, oral therapy. However, prevalence of fluoroquinolone resistance in *Neisseria gonorrhoeae* has been increasing and is becoming widespread in the United States, necessitating changes in treatment regimens. Beginning in 2000, fluoroquinolones were no longer recommended for gonorrhea treatment in persons who acquired their infections in Asia or the Pacific Islands (including Hawaii); in 2002, this recommendation was extended to California. On the basis of the most recent evidence, CDC no longer recommends the use of fluoroquinolones for the treatment of gonococcal infections and associated conditions such as pelvic inflammatory disease (PID). Consequently, only one class of drugs, the cephalosporins, is still recommended and available for the treatment of gonorrhea.

Because fluoroquinolones are no longer recommended, the options for treating gonococcal infections in the United States are limited.² For the treatment of uncomplicated urogenital and anorectal gonorrhea, CDC no longer recommends a single intramuscular dose of ceftriaxone 125 mg or a single oral dose of cefixime 400 mg. However, 400 mg tablets of cefixime are not available; cefixime is only available in a suspension formulation. Some evidence suggests that a single oral dose of cefpodoxime 400 mg or cefuroxime axetil 1 gm might be additional oral alternatives for the treatment of urogenital and anorectal gonorrhea.²

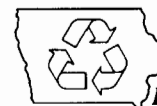
For pharyngeal gonorrhea, CDC now recommends a single intramuscular dose of ceftriaxone 125 mg; pharyngeal gonococcal infections often are asymptomatic and more difficult to eradicate than urogenital and anorectal infections.¹

A single oral dose of azithromycin 2 gm is effective against uncomplicated gonococcal infections, but CDC does not recommend widespread use of azithromycin because of concerns regarding rapid emergence of resistance, as evidenced by the increase in azithromycin MICs documented since 1999 in the United States and internationally. However, azithromycin might be an option for treatment of uncomplicated gonococcal infections from any site (i.e., urogenital, anorectal, and pharyngeal) in persons with documented severe allergic reactions to penicillins or cephalosporins.

Persons in whom gonococcal infection is diagnosed should be treated for possible coinfection with *Chlamydia trachomatis* with a single dose of azithromycin 1 gm by mouth or with doxycycline 100 mg twice a day, by mouth for 7 days, if chlamydial infection has not been ruled out.²

References

1. MMWR 2007;56:332-6.
2. MMWR 2006;55(No. RR-11).



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