

CASE 2.4
Gastrointestinal Infection—*Clostridium difficile* | Level 1

SELF-ASSESSMENT ANSWERS

1. Develop a pharmacologic plan for the treatment of the CDI.

C. difficile is a gram-positive, spore-forming anaerobic bacillus. The treatment of a CDI would include antibiotics such as oral or IV metronidazole, oral vancomycin, or oral fidaxomicin. Because this is J. W.'s first episode of *C. difficile* and he is hemodynamically stable, oral metronidazole 500 mg po three times daily for 10 to 14 days would be an appropriate plan. Metronidazole is the recommended drug of choice for mild-to-moderate infections. Oral vancomycin is warranted for severe infections, and oral vancomycin and IV metronidazole can be used in combination for severe, complicated infections. Fidaxomicin was approved for treatment of CDIs in mid-2011, but current U.S. guidelines lack inclusion of the drug. It was shown to be noninferior to vancomycin for initial cure of a CDI in two Phase III clinical trials. However, institutions generally reserve it for patients who experience multiple recurrent infections or fail metronidazole and/or vancomycin therapy. It is important to note that J. W. should discontinue taking the antiperistaltic agent Imodium because it may obscure symptoms or precipitate complications such as toxic megacolon.

2. Which one of the following statements is *true* regarding *C. difficile* enterocolitis testing and diagnosis?

- C. difficile* enterocolitis is typically diagnosed in clinical settings by isolation of the organism from the stool.
- Isolation of the *C. difficile* organism is rare in neonates or infants.
- False-negative testing results for *C. difficile* are common.
- The majority of patients in whom the *C. difficile* organism could be isolated will remain asymptomatic for diarrhea.
- Laboratory testing for *C. difficile* is recommended in all ICU patients because outbreaks commonly occur in this setting.

Answer d is correct. Although *C. difficile* is not part of the bowel normal flora, it can be isolated in virtually all populations including healthy persons (d). As such, testing of asymptomatic patients and nondiarrheal stools is not recommended. It commonly colonizes neonates and infants with an estimated carriage rate of 30% to 70% (b).

Pathogenic strains cause enterocolitis by secretion of cytotoxins A or B, and the diagnosis is based on isolation of the toxin rather than the organism in most clinical settings (a). Strains that do not produce toxins are nonpathogenic for colitis. Although false-positive testing results (c) are a concern with present testing methodology, a negative testing result can be trusted. Because not all strains of the bacteria are pathogenic for disease and over 50% of patients in whom the organism can be isolated are asymptomatic for diarrhea or evidence of colitis, they can be defined as carriers versus being infected.

3. Name at least three risk factors for developing a CDI.

Antimicrobial exposure is a modifiable risk factor for CDIs. Almost all antibiotics have been associated with CDIs. Fluoroquinolones antimicrobials have emerged in the past decade as an important risk factor for CDI, having been associated with NAP1/BI/027 strain that causes severe enterocolitis. Cancer chemotherapy has immunosuppressant and antimicrobial effects, as does the treatment for HIV disease, and both are well-accepted risk factors for the disease. Advanced age has been long known to be an important risk factor for CDI. Duration of hospitalization is also a risk factor. Proton pump inhibitor therapy has been found in several studies to be associated with an increased risk of CDI, and the FDA recently added warnings to this class of acid-suppressing medications. However, a link between CDI and the H₂ blockers has not been established to date. Other risk factors include gastrointestinal surgery or manipulation of the gastrointestinal tract.

4. Which of the following statements is true regarding metronidazole (Flagyl) treatment of *C. difficile* enterocolitis?

- The drug is effective only if given by the oral route of administration.
- Relapse rate following a course of metronidazole is less than 2%.
- The drug is an appropriate first choice in patients of all conditions and ages with *C. difficile* enterocolitis.

- The failure rate for metronidazole treatment of *C. difficile* enterocolitis appears to be increasing.
- A 3- to 5-day course of metronidazole therapy may be used in patients presenting with mild *C. difficile* enterocolitis.

Answer d is correct. Current treatment guidelines recommend metronidazole for the initial treatment of mild-to-moderate disease. Metronidazole can be used in the treatment of *C. difficile* enterocolitis by either the oral or IV route (a). The relapse rate following a course of metronidazole is estimated to be between 10% to 20% (b), and evidence suggests failure rates to metronidazole have been increasing (d). Metronidazole is not recommended for use in all patient populations (c). The drug is not recommended for patients who are pregnant; in these situations, oral vancomycin is preferred. Treatment duration of therapy of 10 to 14 days is recommended in all *C. difficile* patients treated with metronidazole regardless of disease severity; there are insufficient data to support a duration of therapy shorter than 10 days (e).

- 5. A medical resident asks you when vancomycin should be used as an appropriate alternative to metronidazole for *C. difficile* enterocolitis. Vancomycin should be considered for therapy in all except which one of the following patient types?**
- The patient is intolerant to metronidazole.
 - The patient has failed to respond to an adequate course of metronidazole.
 - The patient has gastrointestinal tract complications and must be treated with IV drug therapy.
 - The patient has severe, life-threatening *C. difficile* enterocolitis.
 - The patient is suffering a second recurrence of *C. difficile* enterocolitis.

Answer c is correct. Although oral vancomycin is considered equally effective as metronidazole for treatment of *C. difficile* enterocolitis (c), it is regarded as second-line therapy for most initial disease episodes because of concern for the

development of vancomycin-resistant enterococci colonization, as well as its increased cost. Unlike metronidazole, vancomycin should not be used by the IV route for treatment of *C. difficile* enterocolitis because adequate drug concentrations are not achieved in the intestinal lumen. Vancomycin is recommended alone or with metronidazole when the patient has severe life-threatening enterocolitis and with recurrences (d, e), based on data that the duration of diarrhea may be shortened. The use of oral vancomycin is appropriate in patients who are intolerant to metronidazole (a). Although the initial CDI episode response rates for metronidazole are typically greater than 90%, and the drug may be utilized for the first disease recurrence, vancomycin is recommended in patients who have their second disease recurrence (b).

6. Which of the following statements is **true** regarding options for the treatment of *C. difficile* enterocolitis?
- a. Treatment with recommended pharmacotherapeutic agents is always required when *C. difficile* enterocolitis is diagnosed.
 - b. Fidaxomicin is a newer treatment option that is superior in efficacy to vancomycin for treatment of an initial episode of *C. difficile* enterocolitis.
 - c. Fidaxomicin has been proven to be a cost-effective treatment for all patients with recurrent *C. difficile* enterocolitis.
 - d. Probiotics have been proven to help prevent *C. difficile* enterocolitis when added to antimicrobial therapy.
 - e. Combination therapy with oral vancomycin plus IV metronidazole is recommended for initial treatment of severe, complicated *C. difficile* enterocolitis.

Answer e is correct. The initial action that should be taken in a patient with suspected *C. difficile* enterocolitis is to discontinue the offending antimicrobial agent, and this action alone will result in improvement in approximately 30% of patients (a). Fidaxomicin is a newer treatment option that has been shown to be equally effective but not superior to vancomycin therapy for treatment of initial episodes of *C. difficile* enterocolitis (b). Due to a cost greater than that for either vancomycin or metronidazole, it will not be a cost-effective alternative for most patients with *C. difficile* enterocolitis (c). Probiotics have been used with antimicrobial therapy to prevent *C. difficile* enterocolitis development, but evidence has been conflicting, and they are presently not recommended in guidelines for this purpose (d). Combination therapy with vancomycin plus metronidazole may be used in disease recurrences and is recommended for initial treatment of severe, complicated *C. difficile* enterocolitis (e).

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