DECISIONS

A woman with community-acquired *Clostridium difficile* infection

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A 66-year-old woman who recently completed a course of levofloxacin to treat community-acquired pneumonia presents to her family physician with a two-day history of watery diarrhea. Her stool tests positive for *Clostridium difficile* toxin. She takes pantoprazole daily for symptoms of dyspepsia and is otherwise healthy. You consider the relevant components of managing her case.

What are this patient's risk factors for *C. difficile* infection?

The patient's history includes multiple risk factors for *C. difficile* infection. The most recognized modifiable risk factor for such infections is the use of antibiotic agents in the preceding three months.[1] Although all antibiotic agents have been implicated in contributing to *C. difficile* infection, it is most frequently associated with the use of clindamycin, fluoroquinolones, broad-spectrum penicillins and cephalosporins.[1] Disruption of the gastrointestinal flora by proton pump inhibitors, feeding tubes or previous abdominal surgery also increases the risk of infection.[1] Patient characteristics such as age (≥ 65 yr), underlying immunosuppression, inflammatory bowel disease and recent or prolonged stays in hospital increase risk. However, community-acquired infection can occur and should remain a diagnostic consideration for acute diarrhea, even in the absence of risk factors.[2]

How should her first episode of *C. difficile* infection be treated?

The management of *C. difficile* infection begins with discontinuing or shortening the course of the offending antibiotic. Given her loose, unformed stools and the positive test for *C. difficile,* the patient should be given a 10- to 14-day course of oral metronidazole.[1] For patients who are severely ill with a suspected *C. difficile* infection, unlike this patient, treatment should be given empirically while waiting for test results to confirm the diagnosis. The choice of antimicrobial agent is based on the severity of disease (Table 1).[1,3] Unfortunately, there is no uniform definition of severity. The most commonly used definition is a white blood cell count greater than 15×10^9 cells/L, or serum creatinine levels 1.5 times higher than those before the illness began.[1] For patients with severe or complicated disease, subtotal colectomy should be considered if symptoms progress despite appropriate antimicrobial therapy.[4] Drugs that attenuate bowel motility, such as opioids and antiperistaltic agents, should be avoided.

How does the physician know whether the treatment is working?

Once a course of treatment with antibiotic agents has been started, it is imperative to monitor the patient for the resolution of her diarrhea and assess whether any complications of *C. difficile* infection develop, such as ileus or peritonitis. The mean duration of diarrhea is three to four days, with most cases resolving by day 7.[1,5] Persistent diarrhea warrants considering alternative causes. Retesting the stool is discouraged, because the organism and its associated toxins can persist long after symptoms have resolved. As many as 40% of patients will continue to show positive results in toxin assays up to six weeks after their diarrhea has resolved.[5]

Should this patient have a recurrent infection, what are her options for treatment?

For the treatment of recurrent infection, either metronidazole or vancomycin is recommended. Management is guided by the number of recurrences and severity of infection (Table 1). The definition of recurrent infection, which occurs in 25% of cases, is complete abatement of symptoms with appropriate therapy, followed by the reappearance of diarrhea with a positive test for *C. difficile*.[1] Probiotics (e.g., *Saccharomyces*

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boulardii) may reduce the risk of recurrence when used as adjunctive therapy for patients with at least one recurrence.[1] However, the use of *Saccharomyces* should be avoided for patients with immunosuppression (e.g., transplant recipients), as well as those who are seriously ill, as it has been associated with fungemia.[2]

How can the spread of this patient's infection be prevented?

If admitted to hospital, this patient should be isolated with contact precautions. In general, preventing *C. difficile* infection relies on two factors: limiting transmission of the organism and minimizing exposure to antimicrobial agents in people colonized by the bacteria. Hand hygiene is the most effective means of preventing transmission.[1] Because *C. difficile* spores are resistant to alcohol sanitizers, health care workers are urged to use soap and water to physically remove spores from their hands after contact with patients.[1] Patients in hospital should be isolated with contact precautions when *C. difficile* infection is suspected; this course of action should continue until infection is ruled out or the diarrhea resolves. Equipment that has been in contact with an infected patient should be cleaned with a hypochlorite-based solution. Recommendations for household contacts are not addressed in the most recent guidelines; however, the aforementioned measures may be adapted to the outpatient setting.

What are novel strategies for managing *C. difficile* infection?

Several novel therapies have shown promise in the management of *C. difficile* infection, although most are currently not widely used in Canada. A randomized controlled trial of a 10-day course of fidaxomicin versus vancomycin found similar rates of cure for both drugs. The rate of recurrence with fidaxomicin was significantly lower than with vancomycin; however, this was a secondary outcome of the study.[3] Other randomized trials have shown that monoclonal antibodies to *C. difficile* toxins A and B reduce the risk of recurrence. Rifaximin, a minimally absorbed oral macrolide, given for two weeks after a course of vancomycin, has decreased the risk of recurrence in patients with repeated relapses.[5] Observational studies have

Table 1: Managing *Clostridium difficile* infection according to severity[1]

Type of infection	Severity	Treatment	Duration of treatment	Author comments
Initial episode or first recurrence	Mild to moderate*	Metronidazole (500 mg orally, 3 times/d)	10–14 d	Avoid metronidazole after first recurrence because of potential cumulative neurotoxicity; consider vancomycin when metronidazole is ineffective, poorly tolerated or contraindicated; fidaxomicin may be equally effective;[3] time to resolution may be shorter with vancomycin
	Severe†	Vancomycin (125 mg orally, 4 times/d) with or without metronidazole (500 mg intravenously, 3 times/d)		
Complicated‡	Ileus, toxic megacolon, signs of shock	Vancomycin (500 mg orally or rectally, 4 times/d) with metronidazole (500 mg intravenously, 3 times/d)	10–14 d	Consider colectomy for progressive infection in patients with severe illness
Second or later recurrence‡	Mild to moderate*	Vancomycin, tapering§ or pulsed regimen	Example tapering regimen:[3] 125 mg 4 times/d for 14 d 125 mg 2 times/d for 1 wk 125 mg 1 time/d for 1 wk 125 mg every 2 d for 1 wk 125 mg every 3 d for 2 wk	Consider *Saccharomyces boulardii* (500 mg, 2 times/d) as adjunctive therapy[3]
	Severe†	Vancomycin (500 mg orally or rectally, 4 times/d) with metronidazole (500 mg intravenously, 3 times/d)	When acute phase has resolved, consider tapering regimen as above	Avoid *S.boulardii* in patients who are critically ill

*Peak leukocytosis < 15×10^9 cells/L, peak serum creatinine < 1.5 times premorbid level.
†Peak leukocytosis > 15×10^9 cells/L and peak serum creatinine level ≥ 1.5 times premorbid level.
‡Expert consultation recommended (author opinion).
§Regimen may vary across institutions.[3]

suggested that fecal transplant is highly effective in reducing recurrence;[1] however, to date, there are no standardized regimens or published randomized trials evaluating this therapy.

Case revisited

Because the patient has diarrhea, and test results for *C. difficile* were positive, her case warrants antibiotic therapy. Without evidence of previous infection or signs to suggest severe or complicated infection, she should be given a 10- to 14-day course of oral metronidazole. The indication for her pantoprazole should be reassessed, and she should be counselled on the expected duration of diarrhea, risk of recurrence and methods of preventing the spread of infection. In addition, avoiding the unnecessary use of antibiotic agents is crucial to preventing recurrent infection.

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