Clostridium difficile Infection: A Practical Approach

Marisa Ann Azad BSc(Hons); Christine H. Lee MD, FRCPC
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Clostridium difficile: meet the microbe

Clostridium difficile is a Gram-positive, anaerobic, spore-forming bacillus and is ubiquitous. *C. difficile* infection (CDI) is one of the most frequent causes of health care-associated infections, and its rates are growing in the community. The case fatality rate associated with CDI is 6%, and there are growing reports of treatment failures with standard antibiotic therapy.[1] The incidence, recurrence, and severity of CDI have increased over the past 10 years and may be due to the emergence of the hypervirulent strain, NAP1/027.[1,2]

The majority of cases of CDI result from antibiotic-induced alteration of intestinal flora. CDI is frequently associated with the use of fluoroquinolones, cephalosporins, broad-spectrum penicillin-derivatives, and clindamycin, although most antibiotics can elicit CDI. A recent, large Canadian study showed that approximately 4.4% of patients at the time of hospital admission were colonized with the organism without having the actual infection.[3] The rate of carriage state of CDI can be 15 to 50% for hospitalized patients and the residents of long-term care facilities.[3-5]

The clinical course of CDI

C. difficile is transmitted through the ingestion of spores (fecal-oral route). In general, CDI results from:

Terry's Case

A 62-year-old man developed shortness of breath, a productive cough, and a low-grade fever (T = 37.9 ^{0}C) during his routine hemodialysis session. He was started on oral levofloxacin 250 mg q.d. by his nephrologist. A laboratory investigation showed a white blood cell count of 11.6 × 109/L; the sputum culture did not grow any significant respiratory pathogens. When the chest radiograph showed pulmonary edema and no air space disease, levofloxacin was stopped. Seven days after the discontinuation of the antibiotic, he started having watery diarrhea up to 12 times daily, that was associated with abdominal pain, anorexia, profound fatigue, and a temperature of > 38.1 ^{0}C. His white blood cell count was 15.3 × 109/L.

(a) A disruption in the intestinal flora,
(b) The colonization and multiplication of *C. difficile*, and
(c) The release of *C. difficile* toxins that cause mucosal inflammation.[6]

Most CDIs develop one to two weeks following the initiation of the antibiotic; however, CDI can occur 10 to 12 weeks following the completion of the antibiotic.[7] Patients can present with watery diarrhea, abdominal pain and cramps, anorexia, malaise, and in severe cases, fever, and hypotension. A patient with severe CDI may cease to have diarrhea as a result of ileus. Persons over 65-years-of-age, immunocompromised, and hospitalized

Questions and Answers

1. When should I empirically start antibiotics for suspected CDI?

If the patient has fever, multiple watery bowel movements, a WBC > 15,000, and no other explanation for leukocytosis and diarrhea, then the patient should be empirically initiated on oral vancomycin 125 mg q.i.d. until the laboratory confirmation of *C. difficile* toxin is available.

2. What is the recovery time for most CDI patients?

The patient's diarrhea and overall clinical status should improve by day five of initiation of antibiotic therapy. If there is no improvement by day five, then switch the antibiotic or consider an alternate diagnosis for diarrhea.

3. Should I send a repeat stool for examination at the end of treatment to determine cure?

If the patient has recovered completely at the end of treatment, then a repeat stool sample should not be sent, as there is no test of cure for CDI at this time.

patients who receive multiple courses of antibiotics are at higher risk of CDI compared to otherwise healthy individuals. Other risk factors for CDI are underlying comorbidities, such as renal insufficiency, inflammatory bowel diseases, and use of proton pump inhibitors. Individuals with risk factors for CDI are also more susceptible to multiple recurrences.

Laboratory investigation

C. difficile infection is diagnosed using clinical and laboratory findings. A thorough history to rule out other causes of diarrhea is paramount. Patients can develop CDI without having received any antibiotics; underlying CDI should be considered when a patient presents with three or more watery bowel movements in 24 hours for more than two days, even in the absence of recent antibiotic use. When a patient with CDI has a white blood cell count > 15.0 x 109/L or serum creatinine > 1.5 times the baseline, the likelihood of developing severe CDI increases.[8] Therefore, a complete blood count and serum creatinine should be performed when managing a patient with confirmed or suspected CDI to predict the severity of the illness.

Enzyme immunoassay (EIA) for the detection of toxins A and B is commonly employed, especially by the community-based laboratories, as it is rapid and easy to perform. However, the sensitivity of EIA is between 66 and 90%.[9] A majority of academic centre laboratories in Canada are currently using polymerase chain reaction (PCR) for the detection of the toxin or its gene. The sensitivity of PCR is approximately 90%; however, it can also be positive in setting off colonization. Therefore, the laboratory test result must be coupled with the clinical presentation. A diagnosis of CDI is made only when a patient has a positive *C. difficile* toxin test or pseudomembranes on endoscopy and three or more unformed (loose or watery) stools within 24 hours.

Treatment

Asymptomatic carriers (colonization) require no treatment. Approximately 15% of patients with very mild symptoms may be managed by discontinuing the causative antibiotic, whenever possible. This particular group of patients may not require any specific CDI treatment.[7] For patients with mild to moderate CDI, the treatment is oral metronidazole or oral vancomycin for 10 to 14 days. Metronidazole is generally used as a first-line therapy in non-severe CDI, as oral metronidazole is inexpensive, and the efficacy of oral metronidazole and oral vancomycin for uncomplicated CDI is similar.[10] For severe cases, oral vancomycin 125 to 500 mg every six hours is the drug of choice.[10] Approximately 25 to 60% of patients develop recurrent CDI following

treatment.[11] Usually, CDI recurrence develops one to three weeks after the cessation of antibiotic therapy. Patients who have had more than one episode of recurrent CDI have a 65% chance of experiencing subsequent recurrences.[12] Pulse-tapered administration of oral vancomycin has been used for recurrent CDI; however, the response to this regimen is suboptimal. Fidaxomicin, a narrow-spectrum, macrocyclic antibiotic, which is available in Canada, has been shown to reduce recurrent CDI by 50% compared to oral vancomycin for non-NAP1/027 related primary, or first recurrent episode of CDI.[13] For multiple recurrent CDI cases, fecal transplant using the liquid component of stool sample collected from a healthy, screened donor is a promising treatment. According to the recent systemic reviews, fecal transplants result in a 91% cure rate.[14,15]

Summary and scope of CDI

Research is needed to more effectively treat CDI and prevent recurrences. Appropriate antibiotic utilization is essential to prevent CDI. Implementation of proper hand hygiene for both patients and health care providers is also important to prevent development of the infection and transmission of the organism.

Back to Terry's Case

Terry's stool was sent for *C. difficile* toxin testing, and he was empirically initiated on oral vancomycin 125 mg q.i.d., because he was unwell. *C. difficile* toxin gene tested positive by PCR. Terry's diarrhea and abdominal discomfort resolved completely on day five of treatment. Over the next five months, he experienced three episodes of recurrent CDI, despite 14 days of oral vancomycin for the first two episodes of recurrence. For the third episode of recurrence, he was treated with a tapering dose of oral vancomycin. On day 10 of the last dose of vancomycin, he developed recurrent diarrhea. He underwent fecal transplant and remained free of diarrhea at his 12-month follow-up.

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Marisa Ann Azad received a BSc(Hons) degree in Cellular, Molecular, and Microbial Biology from Thompson Rivers University in 2010 where her research focused on the design and bioactivity of antimicrobial peptides. She is currently enrolled in McMaster University's combined MD/PhD program in Biochemistry and Biomedical Sciences. Working with Dr. G.D. Wright, her PhD. aims to characterize different proteins involved with microbial drug resistance.

Dr. Christine H. Lee is an Associate Professor, Department of Pathology and Molecular Medicine at McMaster University. She is also the Medical Director for Infection Prevention and Control at St. Joseph's Healthcare, Hamilton, and the Director of the Microbiology Laboratory at Hamilton Regional Laboratory Medicine Program.