Overview

To address the continuing problem of Clostridium difficile infection (CDI) within our health authority, the VIHA Antimicrobial Review Subcommittee (VIHA-ARS) of the Pharmacy and Therapeutics Committee has developed a treatment algorithm (see below) to provide direction in managing these infections.

Background

After treatment with antibiotics, many patients develop gastrointestinal symptoms ranging from mild diarrhea to severe bloody diarrhea with fever and abdominal pain. Many cases of the milder forms of gastrointestinal illness and most of the severe forms are caused by CDI.

C. difficile is a gram positive, anaerobic, spore-forming bacillus that is resistant to most antibiotics. When a person takes an antibiotic, the normal colonic flora are reduced giving C. difficile, if present, the opportunity to proliferate. If it lacks the gene for toxin production then disease does not develop. However, if it produces cytotoxin A and/or B, it may cause colitis. C. difficile does not invade the colonic mucosa and it only has the potential to cause disease if toxin is produced. Even when toxin is produced, some people become carriers or develop mild self-limited diarrhea while others develop severe colitis and may have multiple relapses.

The clinical course appears to depend on the host immune response to toxin. While most colonized patients won’t develop CDI, they represent a large reservoir of C. difficile with the potential to contaminate the environment. The spores survive desiccation for months and are resistant to conventional disinfectants. Poor hand hygiene and suboptimal cleaning practices can then easily result in transmission to susceptible patients.

Virulence Factors

C. difficile may produce up to six different types of toxins but the main virulence factors are toxin A (tcdA) and toxin B (tcdB). Usually, C. difficile isolates from patients with CDI produce both toxin A and B, but variants A+B- and A-B+ have also been found in symptomatic patients.

The “Quebec strain” of C. difficile (BI/NAP-1/027) is particularly virulent and is now also widespread in British Columbia. The strain has a dysfunctional tdcC gene inactivating the down regulation of tcdA and tcdB. These strains produce 16 times more toxin A and 23 times more toxin B than other C. difficile strains. Another novel characteristic of this strain is that it is resistant to fluoroquinolones. There is concern that increasing fluoroquinolone use is associated with increasing CDI.
Risk Factors

Risk factors for CDI are generally divided into three main groups:

1. Host factors: age greater than 65 years; female sex; multiple comorbidities; immune compromised;
2. Disruption of normal intestinal microflora: antibiotic exposure within 3 months; medications affecting intestinal tract; loss of intestinal function (ileus, obstruction); chemotherapy; antacids/proton pump inhibitors; procedures (surgery, nasogastric tube, enemas);
3. Increased exposure to *C. difficile*: admission to hospital; admission to Long Term Care (LTC) facility; poor hand hygiene; infected hospital roommate; prior CDI episodes.

Lab Diagnosis

Patients with suspected CDI should have a stool sample submitted. Formed stool is not appropriate and if submitted will be rejected. The specimen must be liquid enough to move in the container when the container is tilted (Bristol stool chart #7). In VIHA, the sample is first tested using a rapid membrane enzyme immunoassay for the detection of *C. difficile* antigen and toxins A and B. The antigen test detects glutamate dehydrogenase as a screen for the presence of *C. difficile*. If the test is negative, no further testing is necessary. In a recent comparison with nucleic acid amplification test (NAT) methods, the negative predictive value of the antigen test was 99%. The turn around time (TAT) for the initial rapid screen test is less than 24 hours and STAT tests can be arranged following consultation with the medical microbiologist on call. All toxin positive tests are notified to the ward for inpatients and to the physician's office for outpatients.

If the antigen test is positive but the initial toxin screen test is negative then the patient maybe colonized with a non toxin producing strain of *C. difficile* or the toxin production may be below the detection threshold of the initial toxin screen test. In VIHA, to increase the sensitivity for detection of CDI, a supplemental nucleic acid amplification test (NAT) is performed on all samples when the antigen test is positive and the initial rapid toxin A and B screen is negative. The NAT detects the presence of the toxin B gene, not the presence of free toxin in the stool. Clinical correlation is required to determine if the patient’s illness still meets the case definition when positive NAT results are reported.

Treatment

**Initial episode**
- Mild-to-moderate infection: Metronidazole 500 mg orally 3 times daily (or 250 mg orally 4 times daily) for 10 to 14 days
- Severe infection or unresponsiveness to or intolerance of metronidazole: Vancomycin 125 mg orally 4 times daily for 10 to 14 days

**First recurrence†**
- Mild-to-moderate infection: Metronidazole 500 mg orally 3 times daily for 10 to 14 days
- Severe infection or unresponsiveness to or intolerance of metronidazole: Vancomycin 125 mg orally 4 times daily for 10 to 14 days

**Second recurrence†**
- Vancomycin 125 mg orally 4 times daily for 14 days
- If patient has previously received vancomycin proceed to tapering therapy described below
TREATMENT SECTION CONTINUED…

Third / subsequent recurrence(s)†

- Vancomycin in tapered and pulsed doses:
  - 125 mg orally 4 times daily for 14 days
  - 125 mg orally 2 times daily for 7 days
  - 125 mg orally once daily for 7 days
  - 125 mg orally once every 2 days for 14 days

† A probiotic such as Saccharomyces boulardii (Florastor) 500 mg orally 2 times daily for at least 4 weeks may be added as adjunctive therapy in recurrent CDI. However, the efficacy of probiotics in preventing recurrent *C. difficile* infection is not established because of inconsistent study results. Probiotics are generally safe but should NOT be prescribed to immunocompromised patients, to patients in critical care settings, to patients with central lines in place nor to patients with bloody diarrhea or severe abdominal pain. There have been reports of bacteremia and fungemia associated with probiotics in such settings.

**Frequently Asked Questions**

1. **What are the main clinical symptoms of *Clostridium difficile* infection (CDI)?**

   Clinical symptoms include: watery or loose stools (ie. more than three times/day); fever; nausea; abdominal pain or cramping.

2. **Aside from antibiotic exposure what other factors put patients at increased risk for CDI?**

   The risk for disease increases with: increasing age, severity of underlying diseases, degree of immunocompromise, abdominal surgery or gastrointestinal procedures, presence of a nasogastric tube, anti-ulcer medications (eg. proton pump inhibitors), duration of hospital stay or living in a long term care facility or prior history of CDI.

3. **How is CDI usually treated?**

   Initial therapy should, if possible, include discontinuing the inciting antibiotic regimen. CDI will resolve spontaneously in about 20% of patients within 2-3 days of discontinuing the offending antibiotic(s) but most patients require specific antibiotic therapy with po metronidazole or vancomycin for at least 10 days. After treatment, repeat *Clostridium difficile* testing is NOT recommended if the patients’ symptoms have resolved, as patients may remain colonized.

4. **Do asymptomatic patients with a positive *Clostridium difficile* toxin test result require treatment?**

   No, patients without symptoms do NOT require treatment.

5. **Which antibiotic is preferred in the treatment of mild to moderate CDI?**

   Metronidazole and vancomycin show similar efficacy in patients with mild infection. Due to the risk of emergence of VRE associated with excess vancomycin usage, *metronidazole remains the preferred agent in patients with mild-to-moderate infection*. Vancomycin may be considered as first line therapy in patients who are greater than 75 years old, have comorbidities or who are immunosuppressed. (Incidentally, a 14 day course of metronidazole 500 mg PO TID costs approximately $4.00 versus a 14 day course of vancomycin 125 mg PO QID which costs approximately $400.00.)
**Clostridium difficile Infection (CDI)**

6. **How long should patients with CDI be treated?**

   In order to reduce the likelihood of recurrence it is important that patients with CDI complete at least 10 days of therapy.

7. **What antibiotic is preferred in the treatment of severe CDI?**

   Vancomycin is recommended as first line therapy in patients with severe infection because of quicker symptom resolution and lower risk of treatment failure.

8. **How do you decide if the CDI is severe?**

   Determination of disease severity is based on clinicial judgement and may include any or all of: a marked peripheral leukocytosis; renal dysfunction; severe abdominal pain; fever; hypotension; ileus; or toxic megacolon.

9. **In severely ill patients with CDI should any additional antibiotic therapy be considered along with the po vancomycin?**

   Severely ill patients with ileus may have markedly delayed passage of oral antibiotics from the stomach to the colon. These individuals may benefit from the addition of intravenous metronidazole at a dose of 500 mg every eight hours. Vancomycin therapy per rectum may also be considered although the safety and efficacy of this practice has not been established. Vancomycin 500 mg retention enemas may be given every 4 to 8 hours.

10. **Is there any benefit to combining po metronidazole with po vancomycin in more severe infections?**

    No, there is no evidence that adding po metronidazole to po vancomycin improves outcomes.

11. **When should surgery be considered?**

    Surgery should be considered in patients with severe CDI who fail to improve with medical therapy or if toxic megacolon or colonic perforation is suspected. Toxic megacolon should be considered if the patient develops abdominal distention with diminution of diarrhea; this may reflect paralytic ileus resulting from loss of colonic muscular tone.

12. **What other conditions may resemble CDI?**

    The differential diagnosis for CDI includes: benign or simple antibiotic-associated diarrhea; acute and chronic diarrhea caused by other enteric pathogens; adverse drug reactions (other than antibiotics); ischemic colitis; idiopathic inflammatory bowel diseases; and intra-abdominal sepsis.

13. **Is there any role for antimotility agents in the treatment of CDI?**

    These agents should be avoided. There is little evidence that such agents lead to symptomatic improvement and several anecdotes and case series have associated their use with the development of toxic megacolon in patients with CDI.

14. **Is there any role for cholestyramine in the treatment of CDI?**

    This agent should also be avoided as it is of no proven benefit and may theoretically bind and reduce the activity of the antibiotic therapy.
15. What is the role of probiotics in the management of CDI?

A probiotic such as *Saccharomyces boulardii* (Florastor) 500 mg orally 2 times daily for at least 4 weeks maybe added as adjunctive therapy in recurrent CDI. However, the efficacy of probiotics in preventing recurrent CDI is not established because of inconsistent study results. Probiotics are generally **safe but should NOT be prescribed to immunocompromised patients, to patients in critical care settings, to patients with central lines in place nor to patients with bloody diarrhea or severe abdominal pain**. There have been reports of bacteremia and fungemia associated with probiotics in such settings.

16. Where can I find more information?

http://infectionnet.org/

Prevention: The Most Important Strategy

Given the significant morbidity and mortality associated with CDI it is critical that appropriate measures be undertaken to prevent infection and transmission. A multifaceted approach of prudent antimicrobial use along with stringent infection control including hand hygiene, early institution of contact precautions and disinfection of rooms with a sporocidal agent are all essential in preventing CDI and controlling its spread.

Summary

Increasing incidence and several recent outbreaks of CDI at VIHA facilities highlight the importance of early diagnosis, prompt institution of stringent infection control practices, and rational antibiotic therapy. New guidelines favour oral metronidazole as the preferred therapy for mild to moderate disease and oral vancomycin as the preferred therapy for those with severe disease or risk factors. The hypervirulent "Quebec strain" of *C. difficile* is widely present in VIHA and British Columbia and is associated with more severe disease and death. It is incumbent on all health care workers to adhere to optimal infection control and on all prescribers to practice good antimicrobial stewardship so as to prevent CDI and limit its transmission.

References and Further Reading

Clostridium difficile Infection (CDI)

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