C. difficile Infection:
More Than Just Diarrhea

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The high rate of *Clostridium difficile* infection in health-care facilities appears to be increasing. A recent baseline survey of infection rates in Canadian facilities was established at 66.3 cases/100,000 patient days or 5.9/1,000 patient admissions.[1] Most of these infections are seen in the elderly, especially with prolonged hospital admission.

A number of studies have also shown increasing rates of *C. difficile* infection in the community. While the increased use of outpatient antibiotics and shorter hospital stays have likely contributed to this trend, it means that *C. difficile* infection must now be considered in the differential diagnosis of community-acquired diarrhea.

Garth's Case

Garth, an 85-year-old in-patient, is having multiple episodes of diarrhea. His stool assay has come back positive for *Clostridium difficile* toxin.

1. **What should be done?**
2. **What are the complications?**
3. **What can be done to improve treatment and prevention of these infections?**

For a followup on Garth, go to page 86.

What are the signs?

Usually, patients with *C. difficile* toxin-mediated disease present with:

- Frequent diarrhea, often many times per day, not usually associated with nausea or vomiting. Typically, the diarrhea is mild, but sometimes can be associated with explosive episodes of watery stool that are difficult for the patient to control. Bloody or melena stool is unusual.
- Low-grade fevers may be present, and while the fever may become more severe as the disease continues, temperatures rarely resemble the high-spiking temperatures seen in septicemic patients.
- A striking elevation of the white cell count, sometimes reaching up to 50,000.
- Preceding antibiotic therapy, which is a precipitating event for most *C. difficile* infections.

In the appropriate clinical situation, consider *C. difficile* as a differential diagnosis of leukocytosis.[2] Blood cultures remain negative as the organism confines its damage to the large intestine. Over time, the clinical condition may develop into pseudomembranous colitis. The toxins A and B (enterotoxin and cytotoxin, respectively) cause the deteri-

oration of tight cell junctions in the mucosa, cell death, and the recruitment of neutrophils, which leads to the production of pseudomembranes.

On examination, pseudomembranous colitis is recognized by:

- a distended abdomen,
- markedly elevated bowel sounds, and
- a thickened bowel wall with thumbprinting.

It can be diagnosed visually by colonoscopy or sigmoidoscopy (and biopsy), as well as an abdominal computerized tomography scan.

Consider C. difficile *as a differential diagnosis of leukocytosis*

Fluid loss into the intestines can be profound, resulting in hypotension and death if the systemic circulation is not supported. Occasionally, the pseudomembranous colitis will progress to toxic megacolon with absent bowel sounds and a markedly dilated colon. At this point, the danger of a perforation and/or hemorrhage renders toxic megacolon a medical and surgical emergency. Sepsis and hemorrhage are potential complications of toxic megacolon and these carry high mortality, even with surgical intervention.

Making the call

The diagnosis of *C. difficile* disease is usually made by laboratory tests, which detect toxin in the stool. Most diagnostic tests now use enzyme immunoassays to detect toxin antigens directly from stool specimens, however, the toxin assays are usually not as sensitive as biologic assays. Considering the bioassay takes more time and is only available in selected laboratories, the most practical approach is to use antigen detection to make the diagnosis. Culture detection of the organism alone is not enough to confirm the presence of *C. difficile*-related disease because some isolates may not be responsible for significant toxin production and may reflect only colonization.

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Followup on Garth

There are often problems associated with the management of this toxin-mediated disease, but usually it can be managed with a short course of oral metronidazole.

How is C. difficile *treated?*

Since antibiotic therapy is the precipitating event for most *C. difficile* infections, any current antibiotics should be discontinued, if possible. The discontinuation of antibiotics often enables mild *C. difficile*-related diarrhea to resolve spontaneously. In addition to stopping current antibiotics, primary treatment, consisting of oral metronidazole (500 mgm three times daily for 10 days), should also be initiated for any symptomatic individual found to have toxin for *C. difficile* infection.

Although 25% of individuals may have another subsequent episode of *C. difficile*

infections after this course of therapy, it does not mean the infection is resistant to metronidazole. Various studies have shown that approximately half of these subsequent *C. difficile* episodes are related to re-infection. Therefore, it is recommended that the same course of treatment be repeated for any subsequent infection. If relapses continue with mild symptoms, treatment can be extended to three weeks.

In situations where relapses are associated with moderate to severe disease, or when there has been no improvement after metronidazole treatment, oral vancomycin, 125 mgm orally/four times daily for 10 days, should be prescribed. Vancomycin is not recommended as first-line therapy due to the possibility of developing vancomycin-resistant enterococci, and because of its higher cost. While there is some evidence that treatment with oral vancomycin may result in earlier symptomatic relief of diarrhea following onset of treatment compared to metronidazole, this is not enough rationale for selecting vancomycin as a first-line treatment. Relapses following vancomycin treatment can be followed by extending treatment of vancomycin to three or more weeks and observing the effects.

Prolonged use of metronidazole can be associated with toxicity, such as peripheral neuropathy.

For more complicated sequelae for *C. difficle* infections, where the gut is not working and oral treatment is not likely to be of assistance, intravenous metronidazole (500 mgm every 8 hours) can be used, often in association with vancomycin.[3] If *C. difficile* infections become life threatening, consideration may need to be given to a colectomy.

For optimal management, clinical diagnosis of *C. difficile* must be considered in any institutionalized patient with diarrhea. Early diagnostic testing and rapid reporting of results for prompt treatment are of paramount importance. In cases where individuals become moderately to severely ill with diarrhea in an institution, consideration should be given to simultaneously obtaining a specimen and starting appropriate antibiotic management for *C. difficile*, rather than waiting one to two days for diagnosis prior to starting therapy.

How are relapses managed?

Anti-motility drugs, such as imodium, should be avoided. Care must also be taken that patients in relapse situations aren't overmedicated. Prolonged use of metronidazole can be associated with toxicity, such as peripheral neuropathy.

Some individuals can continue oral vancomycin treatment for prolonged periods of time on gradually tapering doses. While there are few scientific studies demonstrating such treatment methods, doses tapering down incrementally from 125 mgm four times a day to 125 mgm daily, over a period of two to four weeks at each dosing level, works for some patients. Some individuals are unable to discontinue low-dose vancomycin without experiencing a relapse.

What are some prevention considerations?

C. difficile is our most important nosocomial enteric infection and, as such, good infection control practices are required to prevent further cases. Consequently, good handwashing is key in all facilities where *C. difficile* infections are detected. While the use of 70% alcohol-based gel is generally the preferred hand cleansing method, alcohol does not kill the spores of *C. difficile*. Therefore, handwashing with soap for an adequate duration is always recommended.

C. difficile produces hardy spores, capable of surviving for months after being shed into the environment. The use of chlorine-based products to disinfect the environment has been found to be an optimal approach. Other studies have also shown the effectiveness of peracetyl ions and acidified nitrate, both of which are safe for use in the hospital environment. While glutaraldehyde has also shown effectiveness, it may cause respiratory or skin problem for health-care workers.[4]

Alcohol-based gel does not kill C. difficile spores; handwashing with soap for an adequate duration is recommended.

Detergents may not adequately kill spores.

It is important to avoid the inappropriate use of antibiotics. Care must be taken not to over-interpret laboratory results of individuals who show organism colonization, but remain asymptomatic.

Control strategies also include restricting or discontinuing certain classes or selected antibiotics that have been found to predispose *C. difficile* outbreaks in various institutional settings (*i.e.* clindamycin, cephalosporins). Conversely, some antibiotics (piperacillin/tazaboctam) have been shown not to be associated with *C. difficile* outbreaks.[5] Some strategies have attempted to use rotation of antibiotic classes to avoid *C. difficile* infections, but few of these studies have shown benefit.

Another predisposing factor for acquisition for *C. difficile* organisms is the use of nasogastric feeding tubes. These tubes can become colonized, especially by contamination from hospital health-care workers. Some studies have also shown that the nutritional elements in nasogastric feeding tubes will provide additional growth advantages for *C. difficile* organisms.

Take-home message

- Symptoms of *C. difficile* include frequent diarrhea, fever, elevated white cell count, and preceding antibiotic therapy.
- *C. difficile* must be considered in any elderly patient with diarrhea. Early diagnostic testing, rapid reporting of results, and prompt treatment cannot be over-emphasized.
- First-line treatment follows oral metronidazole (500 mg three times daily for 10 days).
- Preventative measures include good handwashing, environmental sanitization, and cautious antibiotic use.

The skinny on C. difficile

C. difficile is a preventable and treatable nosocomial infection. There are rapid tests now available for diagnosis. Rates of these infections appear to be increasing and the

clinical management of cases is often more difficult as a result of frequent relapses or re-infections in some individuals

Increased surveillance is required to determine trends and the financial impact of *C. difficile* disease. Additional research is needed to determine the most effective ways to provide environmental decontamination and prevent infections. CME

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