C. difficile and Diarrhea:

What You Need to Know

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Diarrhea is one of most frequent complications associated with antibiotic therapy. *Clostridium difficile* is often responsible for diarrheas and colitis following antibiotic therapy.

The incidence of diarrhea due to *C. difficile* is on the rise. Recent literature indicates that, in certain cases, the clinical picture of the infection is more severe, with an increased rate of mortality.[1]

In August 2004, the Institut National de Santé Publique du Québec implemented a surveillance program to monitor *C. difficile*-associated diarrhea i… Quebec. The program has allowed us to … stand the scope of the proble… for facilities to … infec…

…produces spores … years after its discovery … was linked to pseudomembranous …itis. The source of *C. difficile* can be endogenous (in the digestive tract of newborns and adults) or environmental (on inanimate surfaces and hands of healthcare staff).

The sequence of events leading to *C. difficile*-associated diarrhea is as follows:

- modification of the intestinal flora due to antibiotics or chemotherapy,
- acquisition of a strain of toxin-producing *C. difficile* and
- weak antibody response of host to the toxins produced by the bacterial strain.

Elliot's Emergency

- Elliot, 68, is admitted to the coronary care unit for an acute coronary syndrome.
- He is diabetic and, at his physical examinati…
- …wait …e scan.
- …
- Elliot presents with fever and abdominal cramps, as well as five liquid stools in the past eight hours.

How can you help Elliot?

For the answer, go to page 50.

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Cover Photograph: Intestinal tract (Firstlight Images®)

The toxins that remain non-neutralized by the host destroy the epithelial layer of the colon. They also induce a marked inflammatory response in the colic mucosa, which then gives rise to pseudomembranes that frequently accompany colitis infections.

The antibiotics most often found to cause *C. difficile*-associated diarrhea are the following:

- beta-lactams (some penicillins and second- and third-generation cephalosporins),
- clindamycin,
- macrolides and
- respiratory quinolones.

What is the epidemiology?

The April 2005 surveillance report on *C. difficile*-associated diarrhea, published by the Institut National de Santé Publique du Québec, gives an overview of the scope of the situation.[2]

Between August 22, 2004, and February 5, 2005, slightly more than 3,000 cases of *C. difficile*-associated diarrhea were recorded for the 88 hospitals that participated in the program. If expressed in terms of 10,000 persons/day, the rate varied between 11 and 16 cases in the course of the observation period. The most affected regions in Quebec are the southern and western parts of the province. Two further characteristics that concern hospital centres influence the incidences of nosocomial *C. difficile*-associated diarrhea:

- the size of the hospital centre (higher incidence in centres having 250 beds or more) and
- the proportion of elderly in the hospital (higher incidence in centres where at least 35% of patients are 65 years and older).

What are the clinical manifestations of C. difficile?

Once a host has acquired the *C. difficile* bacteria, he or she can present a range of manifestations, from asymptomatic to severe, including fulminant colitis, which can be recurrent and sometimes even fatal.

Symptoms normally set on five to 10 days after beginning antibiotic therapy, although cases have been recorded from the first day of taking antibiotics until 10 weeks after stopping the treatment.

Helping Elliot

Elliot is a hospitalized patient who has abdominal complications that set five days after starting a broad-spectrum antibiotic therapy with clindamycin. This clinical picture is highly suggestive of *C. difficile*-associated diarrhea.

After sending a stool sample to the microbiology laboratory to look for the presence of toxins, Elliot's antibiotic therapy needs to be re-evaluated. Elliot is to be administered an empirical treatment of metronidazole, 250 mg, orally, four times daily. The fluid and electrolyte balance should be monitored closely and adjusted promptly.

The signs and symptoms frequently observed with infected patients are:

- diarrhea (at least three liquid stools in 24 hours),
- fever,
- abdominal pain/cramps,
- anorexia/nausea and
- general malaise.

Leukocytosis normally develops with a cell count of around 15,000 cells/mm. In rare cases, acute infections of *C. difficile* bacteria do not generate diarrhea, however, they manifest a toxic megacolon. This condition, which involves considerable dilatation of the colon with wall edema and loss of haustrations, has a mortality greater than 50%.[3]

Approximately 20% of patients suffering from *C. difficile*-associated diarrhea have a relapse following treatment.

What about diagnostic methods?

The most common diagnostic method of *C. difficile*-associated diarrhea is the detection of the toxin from stool samples. The cytopathic effect on a cell layer exposed to the stool sample is now considered as the gold

Preventing *C. difficile*-associated diarrhea

The main measures to prevent and control *C. difficile* infections in health-care environments are:

- Early screening of patients presenting with compatible symptoms
- Rigorous application of basic practices, in particular, hand-washing
- Additional precautions (gowns, gloves) with all patients suspected or proven to be infected and symptomatic
- Adequate disinfection of the environment (buffered solution highly concentrated in bleach, namely 1600 ppm)
- Use of material that is either disposable or used exclusively for one patient
- Staff training
- Appropriate use of antibiotics

standard for diagnosing *C. difficile* infections. The test sensitivity is higher than 90%,[4] although it can be weaker depending on the sample quality, the cell line used and the inoculation delay of the samples.

Many immunoenzymatic tests are now on the market to detect the toxins produced by *C. difficile* faster and at a lesser cost than the aforementioned method. However, these are less sensitive than the cell culture.

What is the role of endoscopy in the diagnosis of C. difficile-associated diarrhea?

The endoscopic visualization of exudative plaques or pseudomembranes on the colic mucosa indicates a pseudomembranous colitis. The lesions typically revealed by endoscopies are swollen, yellowish and have a diameter between 2 mm and 10 mm with normal mucosa between the lesions. In more severe cases, the lesions unite to form plaques (Figure 1). The absence of these plaques with some patients renders the endoscopic diagnosis of *C. difficile*-associated diarrhea more difficult. Given the cost and discomfort of the endoscopy for the patient, the American College of Gastroenterology recommends limiting this method of diagnosing *C. difficile*-associated diarrhea to the following situations:[5]

Important

To effectively fight *C. difficile* bacteria, hands should be washed for at least 15 seconds with an antiseptic soap after taking off gloves. The efficacy of antiseptic alcohol gels in preventing the transmission of *C. difficile* has not been studied and can not replace hand-washing.

Figure 1. Plaques seen in endoscopy of patient with C. difficile-related diarrhea. (Reproduced with the permission of The Infectious Diseases Society of America.)

- a rapid diagnosis is needed and test results are delayed or insensitive tests are used,
- the patient has an ileus and stool is not available or
- other colonic diseases that can be diagnosed with endoscopy are being considered.

What is the treatment?

Both metronidazole and vancomycin are effective for the treatment of diarrhea or colitis associated with *C. difficile*. From a cost perspective and also to avoid the emergence of vancomycin-resistant enterococcus, oral metronidazole is the therapy of choice for most cases. The success rate is over 90%, with a relapse rate between 10% and 30%. The success rate following an oral vancomycin therapy lies between 86% and 100%, with a relapse rate similar to that of the metronidazole treatment.

Second generation antibiotics can contribute to the therapeutic success in cases of allergy, intolerance or inefficacy of first generation agents:

- bacitracin,
- teicoplanin,
- fusidic acid or
- rafampin with vancomycine.

Actual benefits of other therapeutic modalities have not been proven, including:

- anion-exchange resins,
- probiotics,
- vancomycin enema,
- immunoglobulins and
- intrarectal or nasogastric administration of stool.

Patients who cannot tolerate an oral therapy usually receive intravenous metronidazole. Nevertheless, there is little literature to support this practice and therapeutic failures with this treatment have been recorded.[6]

In cases where a patient in treatment shows clinical deterioration, it is sometimes appropriate to administer an intravenous antibiotic therapy to effectively counter the digestive flora as well as carry out a colectomy. A publication from an American health centre reports that 1.9% of patients hospitalized with *C. difficile*-associated colitis have had to undergo a colectomy.[7]

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