



International Foundation for Functional Gastrointestinal Disorders

IFFGD
700 W. Virginia St., #201
Milwaukee, WI 53204

Phone: 414-964-1799
Toll-Free (In the U.S.): 888-964-2001
Fax: 414-964-7176
Internet: www.iffgd.org

C. Difficile (167)

© Copyright 2001-2012 by the International Foundation for Functional Gastrointestinal Disorders

Reviewed, 2006

Clostridium Difficile Infection

By: Charalabos Pothoulakis, M.D., Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Clostridium difficile, or *C. difficile* (a gram-positive anaerobic bacterium), is now recognized as the major causative agent of colitis (inflammation of the colon) and diarrhea that may occur following antibiotic intake. *C. difficile* infection represents one of the most common hospital (nosocomial) infections around the world. In the United States alone, it causes approximately three million cases of diarrhea and colitis per year. This bacterium is primarily acquired in hospitals and chronic care facilities following antibiotic therapy covering a wide variety of bacteria (broad-spectrum) and is the most frequent cause of outbreaks of diarrhea in hospitalized patients. One of the main characteristics of *C. difficile*-associated colitis is severe inflammation in the colonic tissue (mucosa) associated with destruction of cells of the colon (colonocytes).

Recently, an unusually high number of *C. difficile*-associated disease epidemics with elevated severity have been reported in several hospitals in the U.S. and Canada related to a new potent strain of *C. difficile* described as "epidemic strain." The number of cases of severe *C. difficile*-associated disease in healthy persons living in the community might also be on the rise. Together, these results underscore the importance of judicious use of antibiotics and early recognition of *C. difficile*-associated disease cases.

The disease involves, initially, alterations by antibiotic therapy of the beneficial bacteria that are normally found in the colon. The alterations lead to colonization by *C. difficile* when this bacterium or its spores are present in the environment. In hospitals or nursing home facilities where *C. difficile* is prevalent and patients frequently receive antibiotics, *C. difficile* infection is very common. In contrast, individuals treated with antibiotics as outpatients have a much smaller risk of developing *C. difficile* infection. Laboratory studies show that when *C. difficile* colonize the gut, they release two potent toxins, toxin A and toxin B, which bind to certain receptors in the lining of the colon and ultimately cause diarrhea and inflammation of the large intestine, or colon (colitis). Thus, the toxins are involved in the pathogenesis, or development of the disease.

A highly virulent strain of *C. difficile* has been recently associated with epidemic disease at several hospitals, including hospital outbreaks in North America, Canada, and several European countries. An important characteristic of this new virulent strain is its association with fluoroquinolones (a group of broad-spectrum antibiotics) and its resistance to these antibiotics, as well as its increased incidence and severity rates among hospitalized patients. For example, a *C. difficile*-associated disease epidemic that started in 2002 and involved more than 30 hospitals in the province of Quebec, Canada is associated with a high mortality rate relative to the number of new cases. Analysis of stool samples from Sherbrooke Hospital in Quebec revealed that the epidemic strain (known as

NAP1/027) was isolated in 67% of the cases, while the same strain has been also isolated from outbreaks in Montreal in Canada, the U.S., the U.K., and the Netherlands. (This strain is associated with much higher release of toxin A and B as well as another toxin, called binary toxin, whose role in *C. difficile*-associated disease is not known.) Mortality rates in Quebec's hospitals quadrupled and *C. difficile*-associated disease incidence were five times higher than the historic incidence. The most important risk factor for the *C. difficile*-associated disease epidemics in these hospitals appears to be the use of fluoroquinolones, which are the most frequently used antibiotic in the U.S.

Fluoroquinolones are used to treat bacterial infections in many different parts of the body. These antibiotics are available only by prescription. Common products include the following:

Generic Name	Brand Name
Ciprofloxacin	Cipro, Cipro I.V.
Gatifloxacin	Tequin
Levofloxacin	Levaquin
Lomefloxacin	Maxaquin
Moxifloxacin	Avelox
Norfloxacin	Noroxin
Ofloxacin	Floxin, Floxin I.V.

Source – U.S. Natl. Library of Medicine and NIH. Fluoroquinolones (Systemic). www.nlm.nih.gov/medlineplus/druginfo/uspd/202656.html (Medline Plus 2005; accessed June 28, 2006).

Transmission Factors

An important characteristic of *C. difficile*-associated disease is its high prevalence among hospitalized patients. Thus, *C. difficile* contributes significantly to hospital length of stay, and may be associated in some elderly adults with chronic diarrhea, and occasionally other serious or potentially life-threatening consequences. One study demonstrated that 20% of patients admitted to a hospital for various reasons were either positive for *C. difficile* on admission or acquired the microorganism during hospitalization. Interestingly, only one-third of these patients developed diarrhea while the remainder were asymptomatic carriers serving as a reservoir of *C. difficile* infection. The organism and its spores were also demonstrated in the hospital environment, including toilets, telephones, stethoscopes, and hands of healthcare personnel.

While patient-to-patient spread and environmental contamination can be some of the reasons of cross-infection in *C. difficile*-associated disease, antibiotic therapy is the major risk factor for this disease. Thus, antibiotic use only when necessary is the most effective measure of preventing *C. difficile* infection. However, considering the severity and impact in the

recent *C. difficile* associated disease epidemics more attention should be placed not only on careful use of antibiotics, but also on isolation of involved patients, cleaning with anti-*C. difficile* sporicidal agents, and washing hands with soap and water in addition to alcohol-based disinfectants.

Clinical Features

A wide range of conditions is associated with *C. difficile* infection. Most cases develop 4 to 9 days after the beginning of antibiotic intake. It should be noted, however, that some patients develop diarrhea after antibiotics are discontinued and this may lead to diagnostic confusion. Although nearly all antibiotics have been implicated with the disease, second and third generations of cephalosporins, clindamycin, and fluoroquinolones, are the commonest antibiotics associated with *C. difficile*-associated disease.

The most common presentation of the disease is either mild colitis, or simple diarrhea that is watery and contains mucus but not blood. Examination by sigmoidoscopy usually reveals normal colonic tissue. General symptoms are commonly absent and diarrhea usually stops when antibiotics are discontinued. *C. difficile* can also cause non-specific colitis quite reminiscent of other intestinal bacterial infections such as *Shigella* or *Campylobacter*. This is a more serious illness than simple antibiotic-associated diarrhea; patients experience watery diarrhea 10 to 20 times a day and lower, crampy, abdominal pain. Low-grade fever, dehydration, and non-specific colitis are common manifestations.

Pseudomembranous colitis represents the characteristic manifestation of full-blown *C. difficile*-associated colitis. Sigmoidoscopic examination reveals the presence of characteristic plaque-like pseudomembranes, scattered over the colonic tissue. The presence of these plaques is a distinctive indicator of *C. difficile* infection in patients with diarrhea following antibiotic treatment.

The most serious manifestation of *C. difficile* infection, fulminant colitis (severe sudden inflammation of the colon), is frequently associated with very serious complications. This can be a life-threatening form of *C. difficile* infection and occurs in 3% of patients; most are elderly and debilitated from other diseases. Patients with this form of the disease experience severe lower abdominal pain, diarrhea, high fever with chills, and rapid heart beat. Timely treatment of fulminant colitis is essential; this condition can be life threatening.

C. difficile Infection In Patients With Other Intestinal Diseases

It is well documented that *C. difficile* may complicate the course of ulcerative colitis or Crohn's disease and it is responsible for 4% to 12% of diarrhea in AIDS patients. In this case, patients develop the typical symptoms of *C. difficile* colitis, including diarrhea, abdominal pain, and fever reminiscent of exacerbation of inflammatory bowel disease. The reason for this complication is not entirely clear. It may be that the frequent hospitalizations and exposure to antibiotics of patients with inflammatory bowel disease or AIDS places them at increased risk for the infection. So far there is no evidence to indicate that *C. difficile* can complicate the symptoms associated with irritable bowel syndrome (IBS).

Laboratory Diagnosis

The laboratory diagnosis of *C. difficile* infection is primarily related to the demonstration of *C. difficile* toxins in the stool of suspected patients. The detection of *C. difficile* toxins in the

stool can be made by a laboratory test (cytotoxicity assay) where the toxins can be easily observed in the microscope. This tissue culture assay is considered the gold standard because of its high sensitivity and specificity. Since there is no correlation between levels of *C. difficile* toxins in the stool and severity of the disease, the results are reported simply as "positive" or "negative." However, time is a drawback of this assay since it requires 24 to 48 hours to read the results.

Over the past few years several rapid tests that take just a few hours, and which do not require specialized personnel to run, have been developed (immuno-enzymatic assays) for the detection of *C. difficile* toxins in the stool. These tests are commercially available in the form of diagnostic kits. Although they are relatively less sensitive and demonstrate lower specificity compared to the laboratory tests, they are very useful not only in the every day practice when specialized personnel is not available, but also in emergency situations and in rapid screening of patients during spreading of the disease in hospitals.

Therapy

Therapy of *C. difficile* is directed against eradication of the microorganism from the colonic microflora. No therapy is required for asymptomatic carriers. In noncomplicated patients with mild diarrhea, no fever, and modest lower abdominal pain, discontinuation of antibiotics (if possible) is often enough to alleviate symptoms and stop diarrhea. When severe diarrhea is present and in cases of established colitis, the patients should receive the antibiotics, metronidazole or vancomycin, for 10 to 14 days. Several clinical trials have shown that these antibiotics are equally effective in cases of mild to moderate *C. difficile* infection and more than 95% of patients respond very well to this treatment. Diarrhea following treatment with either vancomycin or metronidazole is expected to improve after 1 to 4 days with complete resolution within 2 weeks. However, some patients do not respond despite aggressive medical therapy and require surgical intervention.

Therapy For Relapsing *C. difficile* Infection

Although *C. difficile* infection usually responds well to treatment with metronidazole or vancomycin, approximately 15% to 20% of patients will experience re-appearance of diarrhea and other symptoms weeks or even months after initial therapy has been discontinued. The usual therapy for relapse is to repeat the 10 to 14 day course of either metronidazole or vancomycin and this is successful in most patients. However, a subset of patients continues to relapse whenever antibiotics are discontinued and this represents a therapeutic challenge. Some authorities recommend switching to the alternative antibiotic from the one used initially. A variety of other therapies have also been described for relapsing disease. It is hoped that development of vaccines against *C. difficile* toxins may someday control the problem of *C. difficile* infection in hospitals.

Opinions expressed are an author's own and not necessarily those of the International Foundation for Functional Gastrointestinal Disorders (IFFGD). IFFGD does not guarantee or endorse any product in this publication nor any claim made by an author and disclaims all liability relating thereto.

This article is in no way intended to replace the knowledge or diagnosis of your doctor. We advise seeing a physician whenever a health problem arises requiring an expert's care.

IFFGD is a nonprofit education and research organization. Our mission is to inform, assist, and support people affected by gastrointestinal disorders. For more information, or permission to reprint this article, write to IFFGD, 700 W. Virginia St., #201, Milwaukee, WI 53204. Toll free: 888-964-2001. Visit our websites at: www.iffgd.org or www.aboutibs.org.