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# My difficulty with *C. difficile*

The name for the bacterium that causes antibiotic-associated colitis and pseudomembranous colitis is derived—most appropriately—from the Latin word meaning "difficult" or "troublesome."

**ABSTRACT: Cases of *Clostridium difficile* antibiotic-associated colitis continue to be seen commonly and are now complicated by the enhanced virulence of some strains and the prevalence of these strains in certain regions. With the use of potent broad-spectrum antibiotics, severe and relapsing illnesses are becoming more common, especially among patients in institutional care. Metronidazole remains the drug of choice for initial treatment when treatment is warranted. Severe disease or repeated relapses are managed better with vancomycin. Novel therapies, including the use of probiotics, continue to be investigated. Prevention is essential to reduce the burden of illness and its associated economic costs, which are now considerable in most developed countries.**

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My difficulty with *Clostridium difficile* began as an unsuspecting resident immersed in a medical microbiology training program at the University of Toronto. My professors shared their practical insight via weekly seminars. A topic one day was *C. difficile*, and the professor was an exacting, knowledgeable, and cunning senior Scotsman—he had a jocular side he loved to share with us, but we always took his teaching seriously. He began by pronouncing the name of the bacterium with four syllables and a *K* rather than *S* sound (dif'fi.ki.le). The residents looked at each other with amusement, assuming that he was either a poor language scholar or stubbornly unwilling to use a French pronunciation given Toronto's position at the centre of the Canadian English language universe. To us, it seemed proper that *difficile* should be pronounced in the French way (difisil), and as the session progressed he continued to use the hard-sounding *K*. What mockery of the language, we mused, most of us having English-French capabilities. After all, the French version of *difficile* was consistent with almost every mention at local, national, and international microbiology meetings. Of course our professor was as perceptive as he was bright, and he noticed that every pronunciation of *difficile* made us smile. He then digressed on the etymology of *difficile*, explaining that it derived from the Latin *difficilis* (dif'fi.ki.lis) meaning "difficult" or "troublesome." It was synonymous with the Latin *difficiliter* or *difficulter*, and the correct pronounciation was therefore with a *K* sound as in so many Latin words spelled with a *C*. We would never think of the word thereafter as a simple French noun. That lecture was only five or so years after it became established in medical circles that *C. difficile* was the cause of antibiotic-associated colitis and pseudomembranous colitis.[1]

While securing an honored place in my mind as a polished Scotsman with abundant classical wisdom, he also impressed upon me the general mystique of *C. difficile*-associated disease. However, although I was intrigued by *C. difficile*, I would hardly have expected the bacterium to become renowned only 25 years later as one so formidable to medicine. Today the economic impact of *C. difficile*-

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associated disease is considerable.[2,3] Two typical clinical scenarios provide an introduction to some diagnosis and treatment information that the general practitioner may find useful.

### Scenario A

A 75-year-old female with a history of hypertension, systemic lupus, coronary artery bypass, and aortic valve replacement developed acute pancreatitis and was treated conservatively. With the finding of gallstones, she underwent elective cholecystectomy. She developed postoperative pneumonia for which she was given a 7-day course of moxifloxacin.

While completing her antibiotic treatment, she developed abdominal pain accompanied by fever and diarrhea. She was found to have some peritonism, and laboratory studies revealed the presence of neutrophilia and the *C. difficile* toxin. Metronidazole (250 mg t.i.d., a dose chosen because of her small stature) was given for 10 days. Her illness abated, but within a week of completing her course of antibiotics, the diarrhea recurred and her stool was found to contain blood and mucous. She was febrile, and again manifested some mild peritonism. An assay of stool samples revealed the *C. difficile* toxin again. A similar course of metronidazole was given, and her illness subsided over 4 days. There were no further recurrences.

### Scenario B

An 80-year-old male had a complicated and stormy clinical course over several years following prostate cancer treatment. He experienced renal calculi, aspiration pneumonia, and repeat urosepsis. His care had been complicated by the use of a chronic indwelling urinary catheter and a gastric feeding tube. As a consequence of several infections, he had been exposed to repeated antibiotic treatments, with the medication administered through the G-tube. Over 2 years he was exposed to numerous antibiotics, including cotrimoxazole, nitrofurantoin, ciprofloxacin, amoxicillin, gentamicin, meropenem, cefuroxime, and ceftazidime.

Shortly after an episode of catheter-associated urinary infection and subsequent treatment with cotrimoxazole, the patient developed *C. difficile*-associated diarrhea. Treatment with metronidazole (500 mg t.i.d. for 10 days) through the G-tube was initially successful, although relapse occurred 1 week later. Repeated episodes of *C. difficile*-associated diarrhea required repeated courses of metronidazole. Vancomycin (125 mg q.i.d. for 10 days) was also administered through the G-tube after it was determined that the metronidazole courses were promptly followed by relapse. The vancomycin course, too, was followed by relapse. During each of the metronidazole and vancomycin treatments, the clinical illness resolved within 3 to 5 days. The addition of oral probiotics from different sources did not appear to be of value. Given that relapses occurred regardless of whether metronidazole or vancomycin was used, a decision was made to administer a long tapering dose of vancomycin: 125 mg q.i.d. for 14 days, 125 mg b.i.d. for 1 week, 125 mg o.d. for 1 week, 125 mg every 2 days for 2 weeks, and 125 mg every 3 days for 2 weeks. Again, the gastrointestinal illness resolved in several days, but on this occasion the tapered treatment was not followed by relapse.

## Recent trends and concerns

The pathogenetic mechanisms by which *C. difficile* causes disease and the risk factors for the initiation of infection are largely understood by most, and little has changed in practical terms for general practitioners (**Table 1**).[4,5] The likelihood of developing infection largely turns on the spectrum of antibiotic that is used for the treatment of other infections and the antibiotic's ability to suppress most large bowel flora excepting *C. difficile*. Although *C. difficile*-associated diarrhea has been associated with most antibiotics, it is more commonly associated with oral cephalosporin-like antibiotics, clindamycin, and quinolones, and with aggressive parenteral administration and multiple antibiotic treatments in medical institutions (**Table 2**). Other causes of antibiotic-associated diarrhea may require consideration in certain contexts.[6] For example, when there is no obvious and specific bacterial cause for antibiotic-associated diarrhea, factors to consider include promotility effect, yeast overgrowth, small bowel overgrowth, and intestinal intolerance of constituents of pills, capsules, or

**Table 1. Risk factors for *C. difficile*-associated disease.**

- Antibiotic exposure—previous, current, intermittent.
- Type of antibiotic.
- Advanced age, especially over 65 years.
- Hospital/institutional care—especially prolonged stay.
- Previous *C. difficile* illness.
- Multiple existing illnesses.
- Institutional exposure to another patient with *C. difficile*-associated disease
- Immunocompromised status, including changes associated with cancer chemotherapy.
- Lack of circulating neutralizing antitoxin antibody, poor antitoxin response, or both.
- Procedures or treatments, other than antibiotics, that modify normal flora of the bowel, especially the colon.
- Proton pump inhibitor therapy (of debate).

**Table 2. Antibiotics grouped according to their relative risk of causing *C. difficile*-associated disease.**

**Greater risk**
- clindamycin
- advanced cephalosporin-like antibiotics
- carbapenems
- fluoroquinolones

**Moderate risk**
- macrolides
- amoxicillin/clavulanic acid
- amoxicillin/ampicillin
- tetracyclines
- first-generation cephalosporins
- cotrimoxazole

**Minimal risk**
- penicillin
- aminoglycosides
- nitrofurantoin
- rifampin
- fusidic acid
- vancomycin
- metronidazole

suspensions. In rare cases, bacteria other than *C. difficile* may be responsible, including *Staphylococcus aureus*, *Clostridium perfringens*, and *Klebsiella oxytoca*.

The experience in Quebec during this past decade made headlines and caused some to look again at epidemiological and pathogenetic issues.[7,8] First, there appeared to be a considerable increase in the number of infections, although these were largely confined to teaching hospitals. Second, there were concerns about whether a new and more virulent strain of *C. difficile* was emerging. Institutional care was a risk factor but so too was quinolone use. Concerns were raised about possible fundamental changes in the epidemiology of *C. difficile*. Through several local and international studies, it has been proposed that a hypervirulent type of *C. difficile* has emerged (one with relatively increased toxin production) and that it is quinolone resistant.[8-10] Examples of this emerging strain have been found outside of Quebec, but most *C. difficile*-associated disease is still caused by other common strains.

## Diagnosis

The *C. difficile* toxin assay for stool samples remains the laboratory cornerstone for diagnosis.[11] Equally important, however, is the clinical context, where the development of a diarrheal illness following antibiotic use must be highlighted. There are occasions when microbes other than *C. difficile* may be implicated in antibiotic-associated diarrhea and also when toxin assays are negative initially. A toxin assay result may also be positive when no clinical illness prevails.

The methodology for laboratory testing was once considerably variable and confused both general practitioners and microbiologists alike. At this time, although some limitations remain, the technologies are unlikely to change much and we can be generally confident about testing.

## Treatment

With the evolution of novel antibiotics over the last 25 years, most physicians in general practice have encountered patients with antibiotic-associated diarrhea on several occasions. Indeed, *C. difficile*-associated diarrhea can occur even with the most commonly used of all antibiotics, amoxicillin. A preventive approach is the best initial strategy, and the reduction of antibiotic use will inevitably reduce the incidence of *C. difficile*-associated disease. Reducing antibiotic use in "grey-zone" indications, choosing a narrow-spectrum antibiotic (e.g., penicillin V versus broader-spectrum amoxicillin for strep throat), and shortening the duration of treatment will all contribute to lessening the pressure on normal commensal bacteria and thus avoiding *C. difficile* overgrowth.

A contemporary dilemma has resulted with the widespread dissemination of methicillin-resistant *Staphylococcus aureus* (MRSA) in the community. The prevalence of MRSA has significantly increased the use of clindamycin as a first-line agent in the treatment of common skin and soft tissue infections. Compared with other agents, oral clindamycin puts patients at greater risk for *C. difficile*-associated disease. If an antibiotic is required, most infections will respond to a short course of 5 to 7 days. More indolent infections may require surgical intervention (e.g., drainage) or a re-evaluation and subsequent prolongation of treatment.

When antibiotic-associated diarrhea occurs, most illnesses will remit if the current antibiotic is discontinued. Remission will often occur without the need for any supportive maneuvers, especially those often recommended for children. Given the predominantly large bowel nature of *C. difficile*-associated diarrhea, the time-honored approach based on the dairy-free BRAT diet (bananas, rice, applesauce, toast) and clear fluids is not warranted, although adequate hydration remains useful. Illnesses that require specific treatment, however, are more likely to occur among patients with complicated medical conditions, especially elderly patients and those confined to medical institutions. When treatment of *C. difficile*-associated diarrhea is initiated, the reduction, simplification, and cessation of preceding antibiotic use can be very helpful. Oral treatment with metronidazole or vancomycin have remained the standards for several decades when diarrhea continues despite other approaches.

### Metronidazole and vancomycin

A prescription for oral metronidazole is preferable economically (approximately $40 retail for a standard adult

course), and the success rate for metronidazole in mild to moderate infections is over 90%. A typical adult course of treatment would be 500 mg 3 times a day for 10 days (pediatric course: 30 mg/kg/a day divided into four administrations). *C. difficile* has remained susceptible to metronidazole despite the use of this antibiotic for *C. difficile*-associated diarrhea and many other indications. Metronidazole use does not generally promote other significant forms of resistance and rarely have other bacteria developed resistance to metronidazole when they are found to be initially susceptible to the agent. On a historical basis, however, response rates to metronidazole may be changing toward ones suggesting reduced efficacy.

In contrast, vancomycin is very expensive (approximately $325 retail for a standard adult course) regardless of administration route. Further, oral administration can potentially promote the emergence of vancomycin-resistant bacteria (e.g., vancomycin-resistant enterococci), which have become a topic of conversation and concern much like MRSA, although the practical clinical consequences are less of a concern at this time. Vancomycin-resistant bacteria are more likely to be associated with complex care in hospitals and residential care facilities. Nevetheless, oral (not intravenous) vancomycin is associated with a response rate of over 95%, thereby rivaling the efficacy of metronidazole when used in a standard dose of 125 mg 4 times a day for 10 days (pediatric course: 40 to 50 mg/kg/a day divided into four administrations; maximum dose 500 mg a day). Among patients with severe diarrhea, response rates with vancomycin are generally 10% to 15% better than with metronidazole. The timing of response toward cessation of diarrhea is also marginally and clinically better (improved resolution by an average of 1 or 2 days only). Some experts have therefore reserved vancomycin treatment for when there is an advanced illness, when metronidazole use is contraindicated, and when treating some relapsing illnesses.

When simple maneuvers fail, most illnesses will resolve with a single course of either oral metronidazole or vancomycin (**Figure**).[4,12-14] Significant challenges arise, however, when relapsing disease occurs.[14,15] Our two clinical scenarios illustrate this. In Scenario A, a simple repeat course of metronidazole was sufficient to prevent relapse in the context of no need for further antibiotic administration. This supports most authorities' recommendation of a repeat course of metronidazole if the disease is mild to moderate. In Scenario B, complications occurred in the face of a variable but persistent need for antibiotic administration. Difficulties arise with repeat infections or when an active illness does not appear to be responding to a reasonable course of metronidazole.

Relapses of an existing illness or repeat infections may be difficult to predict. Some disease episodes may worsen despite what appears to be a reasonable antibiotic treatment. Lack of response to metronidazole or repeated failure of metronidazole treatment merits a standard dose of oral vancomycin. Relapse after standard vancomycin requires a different approach.[4,13,14] A tapered or pulsed vancomycin regimen is favored. With this method, an initial standard course of vancomycin is given and not terminated at 10 days. Instead, a reduced dose is continued immediately after, and further reduced doses are administered over many weeks. In theory, and given the ability of the spore-forming *C. difficile* to exist in a non-vegetative bacterial cell state at times,

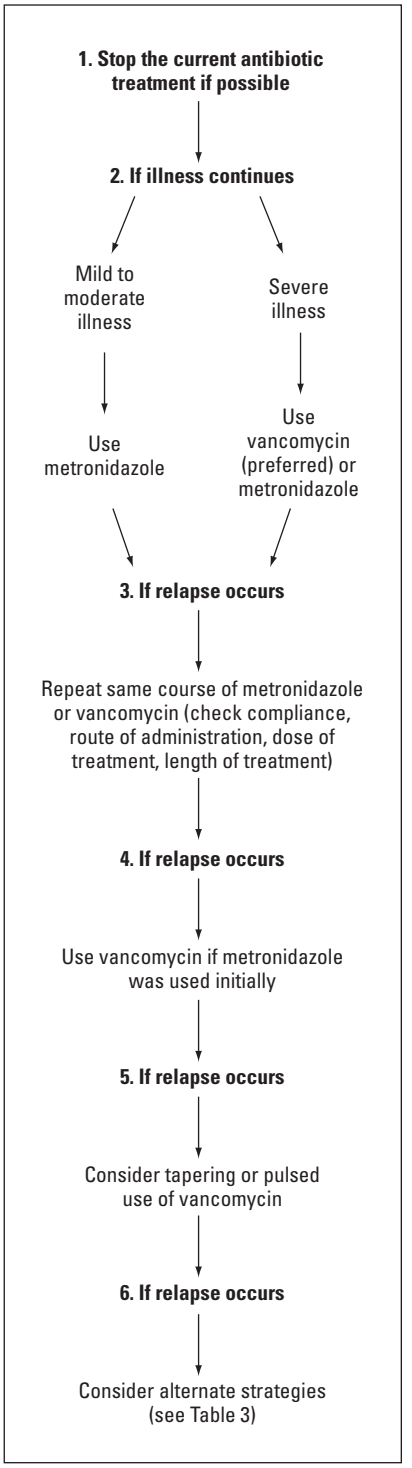


**Figure. Treatment strategies for initial and recurrent *C. difficile*-associated disease.**

Adapted from Kelly CP, LaMont JT,[4] McFarland LV,[12] Johnson S[14]

**Table 3. Alternate strategies proposed or being assessed for *C. difficile*-associated disease.**

**Antimicrobials**
- teicoplanin (analogous to vancomycin)
- fusidic acid (orally, a third choice)
- bacitracin (an old therapy; not highly effective)
- other experimental treatments including rifamixin, tigecycline, telavancin, nitazoxanide, ramoplanin

**Toxin-binding resins**
- cholestyramine (low-value adjunct)
- tolevamer (under trial)

**Immunotherapy**
- gammaglobulins (mainly intravenous immunoglobulin)
- monoclonal antibodies (experimental)
- vaccines (experimental)

**Fecal transplantation** (anecdotal success; largely experimental)

**Replacement with nontoxigenic *C. difficile*** (experimental)

**Colectomy**

the slow reduction of vancomycin provides a pulse of antibiotic that eliminates or at least better controls *C. difficile* populations as the spores in the bowel germinate periodically. As well, such a tapering of vancomycin slowly allows other microbial flora to reconstitute during such a long interval and thus overpopulate *C. difficile* in the large bowel. There are many variables that potentially affect relapses, but continued antibiotic use, and hence pressure, is probably the most important.

## Alternate strategies

There are many treatment and prevention strategies at different stages of implementation or trial (**Table 3**).[16-18] At this time none of these can replace metronidazole or vancomycin treatment, and indeed some have been proposed solely to augment these antibiotics. By far, the most popular of these is treatment with probiotics.[19]

Probiotics are viable, low-virulence-potential microbes, either yeast or bacteria.[19,20] Their use in this context is predicated on the supposition that introducing a relatively nonpathogenic microbe may lead to colonization of the bowel in sufficient numbers to either displace or at least sufficiently compete with *C. difficile*. In a general sense, probiotics are quickly creeping into everyday use in many processed foods, especially dairy items, but the common ones linked to *C. difficile* prevention or treatment include *Saccharomyces boulardii* (a yeast) and bacteria of the *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* species.[21] Numerous studies have examined the use of probiotics for prevention or treatment, many lacking the stringency of science that academics would endorse. While interest in such "natural" products continues, probiotics have not found a sure place in either prevention or treatment recommendations;[22] some researchers say there is no evidence to support their use.[23] Of the examples that have been scientifically scrutinized, only specific species and administration methods have been assessed, and thus the minor benefit that the microbes and regimens studied may confer cannot be assumed to apply to all probiotics. For instance, only particular strains of *Lactobacillus* species have been assessed, and yet there are numerous *Lactobacillus* species and innumerable strains of the latter species in total. Certainly no probiotic alone suffices for the treatment of active *C. difficile*-associated disease.[12] Likewise, a probiotic alone has little, if any, protective effect against subsequent antibiotic-associated diarrhea or *C. difficile*-associated disease. A probiotic (mainly *S. boulardii*) added to vancomycin or metronidazole treatment has been shown to provide a modest benefit for prevention of recurrent *C. difficile* disease.[24] Still, probiotics are of controversial value in managing multiple relapses. Given the live nature of probiotic agents, care must be taken when administering them to severely immunocompromised patients.

Various alternate agents, including antibiotics other than metronidazole and vancomycin, have been assessed. Some of these have been used on their own while others have been used solely as adjuncts to metronidazole or vancomycin. Cholestyramine used as a toxin-binding agent is an older approach but without much success in active disease; other binding agents are being actively investigated. Toxin neutralization is appealing in theory, but only intravenous immunoglobulin has been used in severe disease with anecdotal reports of success; in future, vaccination with modified toxin may prove to provide some benefit. The radical approach of total colectomy has been chosen in intractable serious disease, although bowel surgery is usually beneficial only when the integrity of the bowel has been or is near compromise. Fecal transplantation is essentially a microbial recolonization scheme whereby donor-processed stool is administered enterally to regenerate lost colonic flora.[25-27] It has been tried with success in cases of severe illness after most other treatments have failed, but is considered experimental in Canada.

## Prevention

Whereas active treatment of existing disease is imperative, one cannot underestimate the importance of prevention (**Table 4**). Prevention requires a concerted effort at all levels of health care to minimize spread and to provide a safe and clean environment for patient care.

**Table 4. Prevention strategies for *C. difficile*-associated disease.**

- Limit antibiotic use.
- Shorten length of antibiotic treatment.
- Use disease-specific antibiotic with narrower spectrum activity.
- Use effective doses of antibiotic for treatment.
- Practice contact isolation in institutions where patients have an active *C. difficile*-associated illness.
- Practise good hygiene, especially hand washing.
- Appropriately decontaminate at-risk objects.
- Enhance knowledge base for caregivers and patients.

## Summary

The increase in cases of *C. difficile* antibiotic-associated illness requires general practitioners to limit their use of broad-spectrum antibiotics and prescribe the most equally effective therapeutic agent and dose possible. Although *C. difficile* illness can be treated successfully with metronidazole and vancomycin, relapses are common and prevention is still the best option.

**Competing interests**

None declared.

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