Antimicrobial Therapy of *Clostridium difficile*-Associated Diarrhea

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* Clostridium difficile*-associated diarrhea (CDAD) is the most common etiologically defined cause of hospital-acquired diarrhea. Caused by the toxins of certain strains of *C difficile*, CDAD represents a growing concern, with epidemic outbreaks in some hospitals where very aggressive and difficult-to-treat strains have been found recently [1–9].

Incidence of CDAD varies ordinarily between 1 and 10 cases in every 1,000 admissions, raising rates of morbidity and significantly increasing costs [10,11]. Length of stay of in-patients with CDAD is prolonged from 18 to 30 days [12,13] and the disease has an estimated extra cost per episode for the hospital budget of £4,107, as calculated by a British group, and $3,340, as calculated by a group in the United States [14,15].

* Clostridium difficile* is a gram-positive sporulated rod that grows in strict anaerobic conditions, forming colonies that are circular to irregular [16] (Fig. 1), with a characteristic odor redolent of horse feces (a smell “like a horse stable”) [17].

Strains with clinical interest are the toxin-producing ones. Two main toxins are responsible for virulence in most *C difficile* isolates. These are named toxin A and toxin B [18–20]. Although traditionally toxin A has been considered as enterotoxic and toxin B as cytotoxic, both are cytotoxic for a variety of cellular types, both induce an increase in vascular permeability, and both cause hemorrhage [21]. Besides, both toxins may act
sinergically in the destruction of digestive-tract cells [22]. Researchers have identified toxin-A–negative and toxin-B–positive strains that still retain their ability to produce disease [23,24].

In approximately 5% of strains at some institutions, a third toxin or group of toxins, named binary toxins, is present. The pathogenic meaning of this toxin or toxins is still not well defined, though the toxin or toxins might be responsible for increasing disease severity [25–31].

Clinical manifestations of *C difficile*-associated disease

Clinical manifestations of infection by *C difficile* are numerous and range from asymptomatic carrier status to fulminant colitis, including the most common of all, CDAD, with or without pseudo-membranes in the wall of the colon [32–34]. The severity of the disease depends on two factors. These are the host characteristics, especially immune status, and the pathogen characteristics, especially virulence, inoculum, and ability to produce toxins.

CDAD may present as a mild disease, similar to antimicrobial-related diarrhea not due to *C difficile*, which usually comes to an end on the withdrawal of antibiotic administration, most frequently acquired in hospital but occasionally in the community [35–38].

The most common clinical presentation of CDAD is a moderate-to-severe nosocomial diarrhea. Patients with CDAD usually present with malaise, abdominal cramps or pain, nausea, vomiting, brown or clear watery diarrhea, fever, and leukocytosis. In these cases, endoscopic examination of the colon commonly reveals unspecific inflammatory lesions (unspecific colitis) [34].

In more severe cases (<20% of CDAD), pseudo-membranes are present in the wall of the colon and endoscopy shows white-yellowish plaques (2–10 mm) in any segment of the colon [34]. Small bowel or other segments of the digestive tract are very rarely involved [32].

One of the most severe clinical presentations of CDAD is as an impending fulminant colitis with a sudden rise in the peripheral white blood
count to between 30,000 and 50,000 per cubic millimeter (leukemoid reaction) [39–41]. In a very elegant and clarifying work by Wanahita et al [41] involving 400 inpatients with leucocytosis >15,000/mm³ in an institution, the investigators showed that *C. difficile* was a very frequent underlying condition, often in the absence of diarrhea. Patients with a leukemoid reaction have a mortality rate of approximately 50%, significantly higher than that of other forms of CDAD [41].

The isolation of *C. difficile* from nonfecal samples is very uncommon and its final clinical significance unclear [42–44].

**Risk factors for CDAD**

The main risk factor associated with symptomatic infection by *C. difficile* is antimicrobial treatment within the previous 6 to 8 weeks, which occurs in over 90% of patients. The administration of antibiotics decreases the “resistance to colonization,” diminishing microbial competence [45,46]. The antimicrobials most frequently associated with CDAD are summarized in Table 1 [47,48]. Anti-microbials least associated with CDAD are aminoglycosides, cotrimoxazole, benzyl penicillin, and ureido or piperacil penicillins.

There seems to be an obvious difference among quinolones with low antianaerobic activity, which do not alter the intestinal microflora, and those with antianaerobic activity, though not active against *C. difficile*. The latter have been associated with epidemic outbreaks of CDAD as once happened in a hospital after substituting treatment with levofloxacin for treatment with gatifloxacain [49,50] (see Table 1). On the other hand, levofloxacin has been described as a potentially responsible factor in an epidemic outbreak described in 2005 [7].

Other therapeutic drugs, such as antineoplastic agents (5-fluorouracil), antifungal agents (amphotericin B or fluconazole) or antiviral agents, have also been described as predisposing to CDAD, though the exact pathogenic mechanism remains unknown. The authors have examined CDAD

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patients who were only being administered antituberculous drugs containing rifampin.

Advanced age is another risk factor for the infection and a very high proportion of patients with CDAD are over 65 years old [51–54]. The increased susceptibility of the elderly to the infection may be related to the presence of underlying diseases, to the higher exposure to antimicrobials, or to the presence of lower antibody titers against *C difficile*.

Oncologic diseases, hemodialysis, immunosuppression, ulcerative colitis, malnutrition, solid-organ transplantation and HIV infection are among the predisposing conditions to CDAD [2,55–68].

Prolonged hospital stay also increases the risk of CDAD. Incidence is lower among patients with a higher titer of anti-*Clostridium* antibodies in serum and in these patients relapses are less frequent [69–73].

**Confirmation of *C difficile*-associated disease**

Five issues should be taken into consideration when CDAD is suspected:

- Diarrhea that occurs 48 hours or more after the beginning of the hospital stay may also be community-acquired.
- The diarrhea is related to previous use of antimicrobials, though not necessarily to a simultaneous use.
- Diagnosis should exclude other entities that present with diarrhea, such as parenteral nutrition and enteropathogens.
- Diagnosis requires *C difficile* toxin in feces, either directly in the sample, or in *C difficile* strains isolated from samples with a negative direct cell culture assay, retested for toxin production.
- Good therapeutic response to treatment with oral vancomycin or metronidazole is now being reconsidered because some healthcare centers report an increasing percentage of patients with a low response to metronidazole.

**Laboratory methods**

The choice sample for the diagnosis of CDAD is a fresh sample of diarrheic stools, readily sent to the laboratory [17,74–79]. The benefit of sending several stool samples for toxin detection per episode is very limited [80,81].

The gold standard for the diagnosis of the disease is the toxin-B cytotoxicity test in cell cultures [82,83]. An alternative technique for laboratories without cell cultures is the use of enzyme-linked immunosorbent assays (ELISAs) [76,84,85]. They have an excellent specificity, although their sensitivity allows for the detection of toxin quantities over 100 to 1000 pg (the cellular culture detects 10–20 pg of toxin A and 1 pg of toxin B when used with the appropriate antisera). Therefore, the false-negative rate
amounts to 10% to 40%. There are ELISA assays that detect either toxin A or both toxins A and B [86].

Molecular techniques have also been successfully employed in the diagnosis of CDAD [87–90]. Their complexity and cost prevent them from being adopted in the laboratory on a routine basis, so they should be used for confirmation only, or be restricted to highly qualified reference laboratories.

The Infectious Diseases Society of America [91] and the Society for Health Care and Epidemiology of America [92] have published guidelines for the correct use of detection techniques of *C. difficile* [45]. According to these guidelines:

- With few exceptions, only diarrheic stools should be examined.
- Microbiological tests, except those required for epidemiological studies, are not needed to confirm that the patient has been cured once the symptoms have subsided.
- Only samples from patients over the age of 1 year should be examined.
- ELISA techniques are an alternative to the standard method, although their sensitivity is quite lower.
- Diarrhea that develops after 3 days of hospitalization should be tested only for *C. difficile* toxin (the “3-day rule”), with the exception of elderly patients, patients with HIV, or neutropenic patients.

Several culture media allow for the easy isolation of *C. difficile* from feces [17,93,94], but culture is not frequently performed in CDAD cases and is considered unnecessary by many laboratories around the world. The authors recommend the complementary use of culture for the isolation of *C. difficile* because it is highly sensitive and allows for the isolation of strains in patients with negative direct assay test. The use of culture permits a “second look” cytotoxicity assay, which, in the authors’ institution, has improved the diagnosis of CDAD by 15% [95]. The isolation of *C. difficile* also enables antimicrobial susceptibility testing and facilitates epidemiologic studies [95,96].

In most cases, endoscopy is not required to confirm the diagnosis of CDAD and is therefore an unnecessary risk for the patient.

Image techniques can be useful for the diagnosis of CDAD. The prevalence of an abnormal colon on CT in adult inpatients with *C. difficile* colitis is close to 50%. Segmental colonic wall thickness (>4 mm) is the main finding. The areas most commonly involved are the rectum and sigmoid colon. Positive scans are associated with increased white blood cell count, abdominal pain, and diarrhea, but specific CT findings could not predict surgical treatment [97].

**Antimicrobial activity of different drugs against *C. difficile***

A high percentage of *C. difficile* strains are resistant to antimicrobials, such as cephalosporins, clindamycin, macrolides, telithromycin, aminoglycosides,
tetracyclines, cotrimoxazole, ertapenem, imipenem, and chloramphenicol [98–106]. Most fluoroquinolones now in use have a low activity against this pathogen, though some of the most recently synthesized, with a good antianaerobic coverage, show lower minimal inhibiting concentration, as compared with those already in use [99,107–115]. Meanwhile, the microorganism shows in vitro susceptibility to ampicillin, meropenem, metronidazole, penicillin, piperacillin, piperacillin–tazobactam, teicoplanin, and vancomycin [98,99,103,116,117].

Among new antimicrobials, ramoplanin is particularly interesting. It is a new peptide that inhibits the synthesis of the cell wall by sequestrating peptidoglycan biosynthesis lipid intermediates. It is poorly absorbed by the digestive tract and cannot be administered intravenously. Therefore, it is a good choice for endoluminal dispensing in CDAD. Ramoplanin demonstrates excellent in vitro activity against \textit{C difficile}, including strains resistant to metronidazole and with intermediate resistance to vancomycin [118,119]. Daptomycin and telavancin also show good activity against \textit{C difficile} [120–122] as also do linezolid and the newer oxazolidinones, which are at present in different research phases [123–125].

Nitazoxanide, a nitrothiazolic compound with antimicrobial activity against \textit{C difficile} comparable to that of metronidazole and vancomycin, has shown very good results in experimental animal models infected with \textit{C difficile} [126,127].

Until recently, the activity of vancomycin and metronidazole, both first-line drugs for the therapy of CDAD, was not questioned and susceptibility testing was not even recommended. However, resistance to metronidazole, present in some equine isolates, was reported in 1997 [128]. Reviewing antimicrobial susceptibility profiles of 415 clinical \textit{C difficile} isolates obtained during an 8-year period, the authors found a resistance rate to metronidazole (minimal inhibiting concentration \(\geq 16 \text{ micrograms/mL}\)) of 6.3\%. The authors did not find any strains with full resistance to vancomycin, although strains with intermediate resistance amounted to 3.1\%. Resistance was more frequent in isolates from HIV patients and clonal dissemination could not be proved among the isolates with decreased susceptibilities to the antimicrobials tested in any of the cases [62]. The authors believe that resistance to metronidazole is heterogeneous and can be lost in strains after a prolonged period of storage (due to freezing and defrosting) [129]. The authors do not know the clinical interpretation of this resistance and its influence in the poor response to metronidazole or in recurrent disease.

**Antimicrobial treatment of CDAD**

The first step in the treatment of patients with CDAD is to withdraw antimicrobials whenever possible. Up to 25\% of CDAD episodes may resolve with this simple measure [70,130,131]. The therapeutic response usually involves the resolution of fever on the first day and of diarrhea on
the fourth or fifth day. It is not feasible to predict which subset of patients will respond to the withdrawal of antibiotics. On the other hand, for hospitalized patients who are especially ill, it is hardly possible to stop antimicrobial therapy altogether. Thus, this is not a common practice in the health care setting. Patients for whom antimicrobial therapy cannot be discontinued are less likely to overcome diarrhea when treated with metronidazole [132].

The second step is the administration of either metronidazole or vancomycin, first-line drugs for the treatment of CDAD. Oral metronidazole (500 mg thrice daily or 250 mg four times per day) and oral vancomycin (125 mg every 6 h) have similar efficacy, with response rates near 90% to 97%, according to commonly cited reports [131,133,134]. However, in the last few years, response rates have changed in some hospitals in certain geographic areas [135]. The normal duration of therapy is 10 to 14 days, although no well-performed studies have established the possible advantage of shortening or lengthening this course. Some investigators advocate longer therapy (14 days) to avoid recurrence. All antimicrobials should be administered orally because C. difficile is in the lumen of the colon. If the intravenous route is required, only metronidazole is effective, as intravenous vancomycin achieves only low concentrations in the colon lumen [136]. The therapeutic response usually involves the resolution of fever and of diarrhea on the fourth or fifth day [136].

In patients who are not critically ill, metronidazole is preferred to vancomycin because of metronidazole’s lower cost and because it minimizes the risk of selecting vancomycin-resistant enterococci. The indications for oral vancomycin are pregnancy, breast-feeding, metronidazole intolerance, or therapeutic failure of metronidazole after 3 to 5 days of treatment.

In a Cochrane analysis that included nine prospective and comparative studies in patients with CDAD, metronidazole, bacitracin, teicoplanin, fusidic acid, and rifaximin were each as effective as vancomycin for initial symptomatic resolution [137].

Most infections by C. difficile respond to either treatment with vancomycin or metronidazole, and the lack of therapeutic response requires the confirmation of the diagnosis and the exclusion of ileitis or toxic megacolon, as these conditions may prevent the drugs from reaching sufficiently high levels in the colon lumen. Patients with ileitis may benefit from increasing the transport of the antibiotic to the colon lumen by using high doses of oral vancomycin (500 mg four times per day) or by the instillation of vancomycin or metronidazole in the colon lumen by means of enemas.

Other drugs to be used

Bacitracin was used in the treatment of CDAD in the 1980s. However, since then, vancomycin has been preferred because persistence of toxins in the stools is higher in patients on bacitracin than for those on vancomycin. Nevertheless, the rate of recurrence in patients treated with bacitracin is not higher than that in patients on vancomycin [138–140].
Teicoplanin is an alternative to vancomycin though with no clear benefit and with the disadvantage of not being available at present in the United States [133,141,142]. Fusidic acid is associated with more recurrences, is worse tolerated by patients when compared with vancomycin [133], and shows similar results when compared with metronidazole [143].

Nitazoxanide, an antihelminthic and antiprotozoal agent with activity against a broad range of parasites, also shows in vitro activity against *C difficile* [126,127,144,145]. After its oral administration, nitazoxanide reaches high concentrations in the lumen of the colon. It has achieved cure rates of 75% in patients who failed metronidazole treatment. However, relapse occurs in one out of three patients. In a recently published prospective, randomized, double-blind study, nitazoxanide (500 mg two times per day) was compared with metronidazole (250 mg four times per day) for 10 days in treating hospitalized patients with *C difficile* colitis. The study found that nitazoxanide was at least as effective as metronidazole in treating *C difficile* colitis [134,146,147].

Tiacumicins B and C are members of a novel group of 18 macrolide antibiotics with in vitro activity against *C difficile*. The in vivo activities of the tiacumicins were favorably compared with that of vancomycin in a hamster model of antibiotic-associated colitis [148,149].

Rifaximin is a synthetic antibiotic derived from rifamycin to achieve low gastrointestinal absorption while retaining good antibacterial activity. It has a broad spectrum of antibacterial action, including action against aerobic and anaerobic gram-positive and gram-negative microorganisms. Potential indications include *C difficile* infections [117,149–151].

**Nonantimicrobial treatment**

Antimotility agents (eg, loperamide) are not indicated, since they impair response and increase the risk of toxic megacolon [152,153].

Intravenous immunoglobulins have been used in patients with severe disease or multiple recurrences, but no prospective and comparative studies establish their role in the treatment of this disease [154–156]. In spite of this, the administration of 200 to 500 mg/kg, in one or more doses, has been used in patients with refractory disease as an adjuvant therapy to conventional treatment.

A hyperimmune bovine gammaglobuline that neutralizes the effects of *C difficile* toxins has been studied, but it only prevents the disease in rodents [157–159]. The feasibility of 40% immune whey protein concentrate (immune WPC-40) to aid in the prevention of relapse of *C difficile* diarrhea has also been evaluated. Immune WPC-40 was made from milk after immunization of Holstein-Frisian cows with *C difficile*-inactivated toxins and killed whole-cell *C difficile*. Immune WPC-40 contained a high concentration of specific sIgA antibodies and was effective in neutralizing the cytotoxic effect of *C difficile* toxins in cell assays in vitro [160–162]. WPC-40 was administered to 11 patients who failed treatment or had a history of relapsing *C difficile*
after a 14-day treatment course. All patients were cured and none of them suffered another episode of diarrhea. The potential use of monoclonal antibodies has also been evaluated [163].

Colestipol, colestyramine and other exchange resins able to bind to *C difficile* toxin, may also bind to antimicrobials used to treat CDAD. Therefore, their clinical use is not recommended [164–167]. Nothing can be established from studies in which patients have received corticosteroids as part of the treatment for CDAD [168].

Data regarding the role of oligofructose in the prevention of CDAD relapses are still conflicting [169,170]. In a study performed by Lewis et al [169], consecutive inpatients with CDAD were randomly assigned to receive oligofructose or placebo for 30 days, in addition to specific antibiotic treatment. Relapses were more common in those taking placebo. The oligosaccharide is well tolerated and increases fecal bifidobacterial concentrations [170].

Another promising line of research explores the use of synthetic oligosaccharide sequences that are attached to an inert support and are able to bind to toxin A in the lumen of the colon. One of them is Synsorb 90, which can effectively neutralize toxin-A activity from stool samples [171]. Tolevamer (GT160-246), a polyanionic polymer chain with a high molecular weight, has been evaluated in vitro and in animal models. These evaluations show that tolevamer neutralizes the activity of *C difficile* toxin A [172,173].

Tolevamer has already been administered to humans [174,175] both for the treatment of a first episode as well as for the treatment of recurrent disease. In a recently published multicenter, double-blind, study, patients with CDAD were randomized to receive 3 g of tolevamer per day (n = 97), 6 g of tolevamer per day (n = 95), or 500 mg of vancomycin per day (n = 97). Tolevamer administered at a dosage of 6 g per day was found to be no less effective than vancomycin with regard to time-to-resolution of diarrhea and was associated with a trend toward a lower recurrence rate [176]. A second international study is taking place.

Surgery is a last resort for the treatment of unmanageable CDAD with toxic megacolon or colon perforations. Fulminant *C difficile* colitis can result in bowel perforation and peritonitis with a high mortality rate. The indications for surgery are systemic toxicity and peritonitis, radiological and clinical evidence of progressive toxic colonic dilatation, and progressive colonic dilatation with bowel perforation. The most frequent surgical techniques are either hemicolectomy or total colectomy. In both cases, the postoperative mortality may be >30% [177,178]. Very occasionally, colonic surgery may complicate with *C difficile* enteritis [179–182].

**Treatment of relapsing episodes**

One of the main complications of CDAD is recurrence, which is described in 8% to 50% of cases [11,131,139,141,183–192]. Recurrences are multiple in a significant percentage of the patients. Risk factors for
recurrence are (1) advanced age, (2) remaining on antimicrobial therapy after a first CDAD episode, (3) low albumin levels, (4) a long hospital stay, (5) admittance to an intensive care unit, and (6) a severe underlying disease [72,187,193–195]. It is essential to know whether the relapse is a result of a reactivation of the disease by a previous clon or if it is due to the acquisition of a new clon. Different typing techniques have shown that 10% to 50% of recurrences are caused by a new strain (“reinfections”) [196–199]. In a series of HIV patients with CDAD, a third of the recurrences were reinfections [184].

One of the major explanations for recurrences is the patient’s inability to produce a good immune response [70,72,73]. The risk of recurrence is similar for patients on metronidazole or on vancomycin [183,200]. Recurrence appears 3 to 21 days (mean: 6 days) after completion of therapy. Most patients with a relapse respond to another 10-day course of therapy with the same antimicrobial agent but 3% to 5% of patients may have up to five subsequent relapses [201].

In patients with a poor response or with a third relapse, both the patient and the patient’s family require a therapeutic alternative [202]. An option is to keep on using the same agent, though on a different dosage or with a longer duration. Some protocols recommend a double dose of vancomycin for 10 days; others prolong the administration of vancomycin for 3 weeks; and still others follow a decreasing dosage scheme on vancomycin 500 mg daily during the first week, 250 mg daily during the second week, 125 mg daily during the third week, followed by 125 mg every 3 days for 21 days [202]. There are no reports on prolonged or intermittent use of metronidazole.

A different approach is the use of a different drug or the use of nonantimicrobial agents. Bacitracin, fusidic acid, teicoplanin, and rifampin have been used mostly for the treatment of first episodes of CDAD and their use has been mentioned.

A meta-analysis from six randomized trials showed that probiotics had significant efficacy for CDAD (relative risk = 0.59, 95% CI 0.41, 0.85, \(P = .005\)) [203]. Two randomized studies of patients with CDAD recurrences evaluated intestinal recolonization with *Saccharomyces boulardii* [200,204]. In one of them, *S. boulardii* was administered for 4 weeks after treatment with vancomycin (2 g daily) for 10 days. Recurrences decreased but only when vancomycin was administered at such a high dose [204]. The efficacy of *S. boulardii* to decrease recurrences has been shown in several studies [64,200]. This probiotic has been widely prescribed because it is inexpensive and many believe it has no risks. The authors’ group has recently published a study on one of its complications, fungemia by *Saccharomyces*, that may present as small epidemic outbreaks, particularly in intensive care unit patients with intravascular catheters [205].

Following studies of several small groups of patients, some investigators reported that the administration of *Lactobacillus rhamnosus* or *Lactobacillus plantarum* stopped recurrences [206,207]. However, in two prospective and
comparative studies with this probiotic and placebo, recurrences did not decrease [208,209].

Local bacteriotherapy is the name for the lavage of the lumen of the colon or for the administration of enemas prepared with fresh feces from healthy volunteers [210–213]. Related reports almost always concern isolated cases or short series. No relevant study supports recommendations on this method, which has obvious drawbacks, including the additional risk of transmitting other infectious agents.

Characteristics of aggressive recent epidemic outbreaks

In 1998, Ya Nair et al [187] reported a series of 8 out of 36 patients (22%) on metronidazole who did not have a good response to the treatment, and 7 patients had a relapse within 2 months. In 2004, Noren et al [196] found a 25% recurrence rate in patients on metronidazole in Sweden.

The most severe recent event has been the emergence of a new epidemic C difficile strain in Canada and the United States. In 2004, Pépin et al reported a spectacular rise in especially virulent CDAD cases, with a high fatality rate in a hospital in Quebec [214]. They reviewed the progression of CDAD in the period from January 1991 through December 2003. Incidence increased from 35.6 per 100,000 population in 1991 to 156.3 per 100,000 population in 2003. In the subgroup of patients aged 65 years or more, the increase was from 102.0 to 866.5 per 100,000 inhabitants. The percentage of complicated cases rose from 7.1% (12:169) in 1991 and 1992 to 18.2% (71:390) in 2003 (P < .001), and the proportion of patients who died within 30 days after the CDAD episode rose from 4.7% (8:169) in 1991 and 1992 to 13.8% (54:390) in 2003 (P < .001). The investigators, after adjusting for age and other confounding factors, suggest that the evolution was worse in patients on metronidazole [214]. Pépin et al also published a second study [193] in which failure rates (poor response or relapse) dramatically increased in patients on metronidazole during the period from 2003 to 2004. Among the patients initially treated with metronidazole, the proportion of those who had to switch to vancomycin or for whom vancomycin was added because of a disappointing response was steady between 1991 and 2002 (9.6%), though it rose to 25.7% from 2003 to 2004 (P < .001). The rate of poor outcome (failure plus recurrence) increased from 20.8% to 47.2% (P < .001) and was particularly dramatic in patients over 65 years old (58.4%). This was also the case in other hospitals in the area and has raised a great concern, leading Canadian health authorities to include C difficile and its related illnesses in the group of compulsory communicable diseases [215–219].

In a later study, the same Canadian group [220] showed that metronidazole was as effective as vancomycin for the treatment of patients with a first recurrence of CDAD, yet the risk of complications with any treatment of CDAD may be higher than has previously been documented.
The same findings have been reported in the United States. In a prospective observational study of 207 patients who developed CDAD in a Houston, Texas, hospital and who were treated with metronidazole, only 103 (50%) were cured by the initial course of therapy, 46 (22%) presented with a therapeutic failure with persistence of symptoms despite treatment for more than 10 days, and 58 (28%) responded initially but had a recurrence within the ensuing 90 days. Mortality in patients with CDAD reached 27% and was higher among those with a poor response during the initial course of therapy (33% versus 21%; \( P < .05 \)) [221].

The epidemic in Quebec was caused by a particular clone (toxinotype III, North American PFGE type 1/PCR, ribotype 27 (NAP1/027)) that is a hyperproducer of toxins A and B. This same strain was found in several states of the United States, in the United Kingdom, in the Netherlands, in Belgium, and in France [135,221,222].

Neither the Canadian nor the American research reported the systematic isolation of \( C \) difficile strains. Thus, susceptibility testing to metronidazole or genotyping of isolates on a large scale has not been possible.

The present epidemic strain is a toxin hyperproducer, shows an increased resistance to fluoroquinolones, and is responsible for the outbreaks at more than seven American hospitals in different states from 2001 to 2004 [6,7,135,223–225]. This same strain was the one that caused the Quebec outbreak [215,219] and an additional outbreak in England [226].

Preliminary results from a study of \( C \) difficile strains isolated during a 2-month period in 2005 from 38 hospitals of 14 European countries were presented in 2006 at the European Congress of Clinical Microbiology and Infectious Diseases meeting in Nice, France [227]. Barbut et al found that 25 out of 486 isolates collected in Europe were toxinotype III, and 20 of those belonged to ribotype 27. All of these were isolated in Belgium and the Netherlands, but for one that was recovered in Ireland. The polymerase chain reaction ribotype 027, toxinotype III strain has a characteristic antimicrobial susceptibility pattern, since it is resistant to the newer fluoroquinolones (moxifloxacin) and to erythromycin, but susceptible to clindamycin.

References


