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Treatment of *Clostridium Difficile* Colitis in the Critical Care Setting

Daniel M. Musher, MD[a,b,c,*], Saima Aslam, MD[a,b]

[a]*Infectious Disease Section, Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Boulevard, Houston, TX 77030, USA*
[b]*Department of Medicine, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA*
[c]*Department of Molecular Virology and Microbiology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA*

Clostridium difficile has emerged as an important cause of infection during the past 10 to 15 years [1]. This organism causes an acute inflammation of the colon, largely attributable to its release of toxins A and B into the lumen. A syndrome of acute diarrheal disease follows, which is debilitating and not infrequently lethal. Some authorities continue to use the phrase "*C difficile*–associated diarrhea" or "*C difficile*–associated disease" to describe this disease, but those terms are left over from the late 1970s when the cause was still uncertain. A better descriptive term is "*C difficile* colitis" (CDC).

CDC was originally recognized exclusively as a nosocomial infection and, subsequently, as a problem in extended care facilities [2]. Infection tends to occur in bedridden patients, especially those who have underlying diseases including malnutrition and other common debilitating conditions [3]. Early reports suggested that nearly all patients received antibiotics before infection. Subsequently, it was shown that chemotherapy and the use of drugs that inhibit gastric acidity strongly increase the risk of CDC [4]. In the past few years, an increasing number of community-acquired cases have been reported [5,6]; many of the patients who acquire this infection in the community have not received antibiotics in the preceding 90 days [6,7].

In the epidemiologic setting of a hospitalized patient who has received prior antimicrobial therapy or chemotherapy, the clinical syndrome of CDC is usually easy to recognize. Abdominal discomfort and diarrhea,

* Corresponding author. Infectious Disease Section, Michael E. DeBakey Veterans Affairs Medical Center, 2002 Holcombe Boulevard, Houston, TX 77030.
E-mail address: daniel.musher@med.va.gov (D.M. Musher).

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generally more than three loose or watery bowel movements per day, develop over a period of a few days. Fever is present in about half of patients during the first few days of symptoms but, interestingly, may abate by the time the diagnosis is considered, a stool sample is submitted, and results of *C difficile* toxin are positive. About 40% of hospitalized patients have leukocytosis (white blood cell $>12{,}500/mm^3$); in the authors' medical center, 25% of all patients who have peripheral white blood cell counts greater than $30{,}000/mm^3$ have CDC [8]. Because this infection occurs in patients who already have severe underlying diseases complicated by infection and antibiotic treatment, or malignancy and chemotherapy [3], the diarrhea itself contributes to further debilitation. As a result, CDC is associated with substantial mortality, nearly 20% in the first month after diagnosis and 27% in 3 months after diagnosis [9].

As with nearly every disease, the best approach is preventive. This article emphasizes treatment of CDC, considers diagnostic techniques, and describes means for preventing the spread of this infection in the intensive care setting.

Treatment

Stopping the antibiotic

In early reports [10–12], 15% to 23% of patients with CDC had spontaneous resolution of symptoms within 48 to 72 hours of stopping the offending antibiotic and without specific antimicrobial therapy. This approach is not recommended, except perhaps in outpatients who have very mild disease, certainly not in an intensive care setting. One cannot predict which patients will clear the infection spontaneously, and it is often not feasible to discontinue antibiotics. Furthermore, diarrhea contributes to contagion [13] and, in the hospital setting, delaying initial therapy prolongs the period of contagion. Finally, persons who develop CDC tend to be more debilitated and to have received more intensive antibiotic treatment than in the past, suggesting that an even smaller proportion than originally reported might respond to simple cessation of antibiotics.

Specific therapy

Vancomycin

In vitro, *C difficile* is susceptible to vancomycin (minimum inhibitory concentration $[MIC]_{90}$, 1 μg/mL; range, 0.06–4 μg/mL) [14]. Oral vancomycin was used to treat staphylococcal enterocolitis and clindamycin-associated diarrhea before the discovery that *C difficile* was responsible for the disease [15–17]. Recognition of the role of *Clostridium* was followed by additional studies using vancomycin for treatment [11,18–21]; doses ranging from 125 to 500 mg four times daily were found to be equally effective

[21]. Vancomycin (125 mg four times daily by mouth) cures 86% to 100% of patients with CDC [10–12,15,18–25] and is the only medication that has a Food and Drug Administration indication for this infection. Reports [26] of intermediate resistance to vancomycin (MIC, 4–16 μg/mL) have not provided clinical correlations. Orally administered vancomycin is minimally absorbed and has a mean stool concentration of up to 3100 μg/g [18], suggesting that the resistance reported to date is not clinically important.

Metronidazole

Reports of the MIC_{90} of metronidazole for *C difficile* ranges from 0.20 to 2.0 μg/mL with a median less than 1 μg/mL; [27–32]. A recent study [14] showed that 100% of 110 isolates were inhibited by less than or equal to 0.5 μg/mL. There are scattered reports of resistance [26,28,30] with MICs ranging from 8 to 64 μg/mL, but there is no clinical correlation. Our data [9] and those from Hecht and colleagues [14] have shown that all isolates, including those from clinical failures and the newly described epidemic strain *C difficile* NAP-1 [33], remain fully susceptible.

In 1982, Cherry and colleagues [34] described 13 patients with CDC who responded to 1.5 to 2 g of oral metronidazole daily for 7 to 10 days, although two (15%) had recurrent disease. Soon thereafter, a randomized trial [10] in 92 patients compared oral metronidazole, 250 mg four times daily, with oral vancomycin, 500 mg four times daily, for 10 days. Rates of response (88% for vancomycin and 90% for metronidazole) and recurrence within a 21-day follow-up period (12% for vancomycin and 5% for metronidazole) were similar. A subsequent study confirmed a response rate of 94% [35], and a Cochrane database analysis found no difference between metronidazole and vancomycin in treating CDC [36].

The apparent equivalence of these two drugs, the remarkable price differential, and concern over the selection of vancomycin-resistant bacteria, especially within hospitals [37,38], led to a recommendation that metronidazole be used as first-line therapy for CDC [39]. More recent articles, however, have reported a much lower rate of success with metronidazole therapy [9,40,41]. In these case series, about one quarter of patients failed to respond to 2 weeks of metronidazole, and another one quarter had recurrence of CDC within 2 months. At the time of this writing, an important double-blind, prospective comparison has just confirmed that this drug is distinctly inferior to oral vancomycin in moderately severe or severe cases [25], raising further question about whether it has a continued place in treating this disease [42], especially in critically ill patients (see later).

Pharmacokinetics provide a possible explanation for the high failure rate with metronidazole. In healthy adults, after oral administration, metronidazole is completely absorbed from the gastrointestinal tract; fecal concentrations are undetectable [43,44]. Levels of this drug in feces are, however, significantly higher in CDC, with concentrations exceeding the MIC for *C difficile* (mean concentration, 9.3 μg/g; range, 0.8–24 μg/g) [45]. In

semiformed stool, drug levels are somewhat lower (mean, 3.3 μg/g; range, 0.5–10.4 μg/g) and are undetectable in about 50% of patients during convalescence (mean, 1.2 μg/g; range, 0–10.2 μg/g). The presence of metronidazole in diarrheal stool specimens may reflect increased gastrointestinal transit time leading to incomplete absorption or seepage of plasma containing the drug across the inflamed colonic mucosa [45]; the authors favor the latter explanation. The main point is, that as CDC responds to metronidazole therapy, the drug concentration in the feces rapidly falls, and increasing the dose or prolonging therapy is not likely to prevent relapses in patients who have responded to therapy.

Because metronidazole is fully absorbed in the small intestine and yet appears in feces during diarrhea, one might hypothesize that parenteral metronidazole might also be useful in treating CDC. In three patients who received intravenous metronidazole [45], fecal concentrations ranged from 6.3 to 24 μg/g of stool during acute illness but were significantly lower in formed stool. A retrospective review of 10 patients with CDC initially treated with intravenous metronidazole [46] revealed clinical improvement in nine, an observation that has been supported by substantial personal experience (unpublished data). Treatment with intravenous metronidazole has an important place in treating critical care or postoperative patients.

Nitazoxanide

Nitazoxanide is licensed to treat protozoan and helminthic infections [47] and is probably the only drug that effectively treats cryptosporidiosis in AIDS patients. This drug blocks anaerobic metabolic pathways and has been shown to be effective against *C difficile* in vitro (MIC_{90}, 0.06; range, 0.03–0.5 μg/mL) [14]. Approximately two thirds of the oral dose is excreted in feces as tizoxanide, an active metabolite that has similar antibacterial activity [14]. A prospective, double-blind control trial showed that oral nitazoxanide 500 mg twice daily for 10 days is at least as effective as metronidazole in treating CDC [3], and a case series showed the efficacy of this drug in patients who failed metronidazole therapy [48]. This drug is relatively free of complications, and bacteria resistance has not been observed.

Rifaximin

Rifaximin is only minimally absorbed in the gastrointestinal tract after oral administration. This drug is effective in vitro against gram-negative and gram-positive flora, including anaerobic bacteria and *C difficile* [14,49] and has been shown to provide effective treatment for traveler's diarrhea [50]. The MIC_{90} for *C difficile* is 0.008 μg/mL (range, <0.002–0.05 μg/mL) [14]. Reports to date in treating CDC are limited. In an open trial, 10 patients were treated with rifaximin, and nine were cured [51]. Eight patients who had multiple recurrences of CDC were treated with a course of vancomycin followed by 2 weeks of rifaximin; six were cured and a seventh was cured by a second course of the same treatment [52]. Resistance to

rifaximin, however, appeared in the isolate from the patient who failed therapy, even though prior in vitro studies suggested that this was not likely to occur [31]. A double-blind prospective trial comparing rifaximin with vancomycin is nearing completion at the time of this writing.

OPT-80

OPT-80 is also a nonabsorbed antimicrobial that is highly effective against *C difficile* in vitro (MIC_{90}, 0.008; range, 0.001–0.06 μg/mL) with little effect against other gram-positive anaerobes and none against gram-negative ones [53]. Based on these characteristics, this might seem to be the best of the agents currently in development. A trial comparing OPT-80 with vancomycin is currently in progress.

Treatments based on blocking toxin activity

In a critical care setting, an ideal therapy, either by itself or as an adjunct to antimicrobial therapy, might be one that blocks toxin activity, because it could lead to the most immediate reversal of disease. Several compounds that exhibit this property have been studied, but there are no convincing data to date that any has a place in the treatment of CDC.

Agents that bind toxin

Colestipol and cholestyramine, anion exchange resins, bind the toxin produced by *C difficile* in vitro, but they seem to lack clinical efficacy [54–56], and their potential is further compromised by the possibility that they also bind orally administered drugs that are used to treat CDC, such as vancomycin [57]. Tolevamer is a polyanionic compound that binds *C difficile* toxins in the colon without affecting intestinal absorption of most drugs. In a large randomized, double-blind trial comparing this drug with vancomycin, however, it seemed to be inferior (unpublished information, but available on a Genzyme Web site that deals with this compound). A more relevant scientific question, namely whether tolevamer in addition to vancomycin was associated with a better outcome than vancomycin alone, especially in very ill subjects was not addressed by the study.

Antibody to toxin

Anti–*C difficile* bovine immunoglobulin neutralizes the effects of toxin B in a cell cytotoxicity assay and has been used to treat and prevent CDC in rodents [58,59]. Monoclonal antibody to toxin A or to toxin B has shown promising results in experimental animals [60]; phase II studies in humans are currently in progress. Again, such agents should probably used together with an effective antimicrobial that eradicates the *C difficile* or, at least, returns it to its minor place in the colonic flora. The current study uses the monoclonal antibody alone, and it is feared that, even if effective control is achieved, the rate of relapse will be unacceptably high.

Miscellaneous therapies

In a small number of cases, pooled human immunoglobulin (200–300 mg/kg) has been administered to patients with CDC [61–63]; in two studies that included seven patients with refractory CDC, five seemed to be cured by this treatment [62,63]. Somewhat surprisingly, Salcedo and colleagues [62] found anti–*C difficile* toxin activity in all samples of pooled intravenous immunoglobulin. A recent retrospective study at one medical center showed no benefit from intravenous immunoglobulin [64]. Intravenous methylprednisolone has also been used to treat CDC in a single pediatric case [65].

Vancomycin enemas and colonic infusions of normal feces have also been recommended in refractory cases [66] based on a remarkably few case reports [67–69]. Nevertheless, in critically ill subjects with CDC, especially if bowel motility is compromised, intracolonic vancomycin is recommended. One case series has described apparent success with nasogastric administration of feces from a healthy donor [70].

Summary of treatment recommendations

Treatment of critically ill patients with metronidazole, a drug that only arrests disease in 20% to 25% of patients and then has a high relapse rate, is probably no longer appropriate. Vancomycin is proved to be effective, and should probably be used under the ethical concept that the interests of an individual patient must be weighed more heavily than a theoretic concern for the general good. Nitazoxanide, rifaximin, or OPT-80 may become acceptable alternatives if approved for such use, and might be preferred because of the desire to avoid vancomycin in the hospital environment.

Making the diagnosis

Because of the importance of prompt therapy in preventing the spread of infection, clinicians need to be aware of how diagnoses are made, how promptly, and how reliably [71]. In the early days of testing for *C difficile* toxin, the cytotoxicity assay, which evaluated the presence of toxin based on the effects of a filtered fecal sample on tissue-cultured cells, became the gold standard. This test was regarded as being close to 100% sensitive and 100% specific. By comparison, early ELISAs were much less sensitive; three fresh specimens were required to achieve a sensitivity of 75%–85%. These ELISAs have been improved. It was found that, among those several that are commercially available in the United States, the sensitivity on a single fecal sample is around 95%, and the specificity is greater than 95% [71]. Furthermore, recently developed rapid tests, based on adapting ELISA to a card, are similarly reliable.

Laboratories that test many samples each day should probably continue to use ELISA. For laboratories that have no more than one to two assays,

the immunocard is probably a more efficient method. Furthermore, this one can be done at any time (end of the day, off shift, and so forth) and by a less extensively trained technologist.

Surgical management

In the absence of appropriate treatment and, in some patients, even despite optimal medical treatment, CDC may progress to severe sepsis, peritonitis, toxic colonic dilatation, or bowel perforation; mortality may exceed 50% [72,73]. It seems that the number of patients who have life-threatening disease is now increasing [74–76]. Careful monitoring of these patients is vital, because they may require early surgical intervention [77,78]. Total colectomy has the lowest mortality in the treatment of fulminant CDC compared with more limited colonic resection [79,80]; in a case series of 14 patients who underwent surgical management of fulminant colitis, the 30-day mortality was 10% for 10 patients treated with a total colectomy versus 100% in the four treated with a hemicolectomy. Early surgical consultation is recommended for the critically ill patient with CDC.

Practical hints for managing *Clostridium difficile* colitis in intensive care settings

Clostridium difficile is a hardy organism in its vegetative state and even hardier once it sporulates; this organism can be exceedingly difficult to eradicate once it is in the environment. As a general matter, diarrhea poses the threat of contagion; it is difficult to prevent soiling one's own clothing, not to mention hands, wrists, arms, and stethoscopes while examining or treating patients. Prevention of development and spread of this infection are extremely important and are a vital concern for every health care provider in the intensive care setting.

Minimizing unnecessary use of antibiotics is probably the highest priority, closely followed by reducing the use of proton pump inhibitors. Every physician must weigh risks against benefits when prescribing these agents, and one of the major risks, proved with absolute certainty in the literature during the past two decades, is CDC. The possibility of this infection needs to be considered at the first signs of abdominal discomfort or tenderness, unexplained leukocytosis, or diarrhea.

When diarrhea develops, isolation measures should immediately be instituted (Box 1). A fecal specimen should be submitted promptly for testing. The authors have found that nurses may need to be reminded to obtain stool samples; it is helpful to teach the nursing staff the importance of early detection, isolation, and treatment. Except in special situations, looking for ova and parasites or culturing for *Shigella* and *Salmonella* is a waste of resources. Metronidazole may be ordered empirically at the time the diarrhea

Box 1. Practical hints for preventing spread of *C difficile* in the ICU setting

1. Reduce use of antibiotics to only what is necessary
2. Reduce use of proton pump inhibitors similarly
3. Consider *C difficile* infection at first signs of abdominal discomfort, unexplained increase in white blood cell count, or diarrhea
4. Promptly isolate patient and submit fecal specimen for testing
5. Insist that laboratory assays for *C difficile* toxin daily
6. Treat with metronidazole before results available
7. Treat with oral vancomycin if diagnosis proved
8. Repeat fecal assay if negative, continue metronidazole
9. Stop treatment if second test is negative
10. Continue isolation for CDC for at least a week into Rx and longer if diarrhea persists

is recognized; if the toxin assay is positive, treat with vancomycin. If negative, continued metronidazole until a second specimen can be assayed is reasonable; if results are negative again and the patient has not responded, metronidazole may be discontinued. Several years ago, it was noted that some patients who fit the clinical picture of CDC with negative testing may respond to this drug [81]; that work was done at a time that the sensitivity of ELISA was not yet as good as it is now. Consistent with the data on the relative efficacy of vancomycin versus metronidazole, the authors believe that as soon as CDC is documented in a patient in the ICU, treatment with vancomycin should begin. This approach meets all guidelines because it avoids empiric use of vancomycin, yet promptly treats critically ill patients with the most effective agent.

Finally, if there is an outbreak of CDC in an ICU (the United States Centers for Disease Control and Prevention tends to define an outbreak as ≥ 2 cases within a short period of time), physicians need to involve themselves in the nitty-gritty of housekeeping procedures to be sure that terminal cleaning (cleaning beds and the environment after discharge of patients) is being done properly, including wiping down of all surface areas with bleach.

Strategies to treat recurrent *Clostridium difficile* colitis

Various strategies have been proposed to treat recurrent CDC. If a patient fails after being treated with vancomycin, longer courses of treatment may be given, although this approach is not expected to be effective against organisms that have sporulated. Vancomycin has been given in a pulsed

dose or a tapered regimen, based on the concept that drug given every few days or in a decreasing dose allows the *C difficile* spores to germinate and be susceptible to being killed by the antibiotic [82]. The reader should note that this same approach was followed with penicillin for bacterial endocarditis in the 1950s (Louis Weinstein, personal communication, 1967), but it was abandoned by the mid-1960s. A combination of vancomycin and rifampin has also been reported as effective treatment in a few cases [83]. The authors' experience has been that this is a vexing problem with no satisfactory resolution at present. It should be noted that the meaning of repeated detection of *C difficile* toxin in the feces of patients who have been treated for CDC is uncertain. In their recent study, Zar and colleagues [25] included such detection at 10 days as a treatment failure, but reanalysis of their data suggested that there were very few patients who had toxin but were otherwise apparently cured of their infection [84].

Summary

CDC is a debilitating infection with a remarkably high associated mortality. Infection is contagious and spreads especially rapidly in an intensive care setting because patients who are there have all the associated risk factors, including major underlying illnesses, prior antibiotic therapy, and use of agents that suppress gastric acidity. Prevention of disease is the responsibility of every health care provider in the critical care setting. Reduction of nonindicated use antibiotics and proton pump inhibitors and meticulous attention to infection control measures are central to this effort. Early recognition, implementation of isolation precautions, and testing of feces for *C difficile* toxin should be a priority, and currently available tests are highly reliable. Failures with metronidazole therapy are common and, once a diagnosis of CDC is established, prompt treatment with a more effective drug (at present vancomycin, but perhaps eventually nitazoxanide or one of the newer ones in development) seems appropriate. Diagnoses should be made rapidly, metronidazole instituted promptly while awaiting diagnosis, and vancomycin given as soon as CDC is proved to be present.

References

[1] Bartlett JG. Narrative review: the new epidemic of *Clostridium difficile*-associated enteric disease. Ann Intern Med 2006;145:758–64.

[2] Laffan AM, Bellantoni MF, Greenough WB III, et al. Burden of *Clostridium difficile*-associated diarrhea in a long-term care facility. J Am Geriatr Soc 2006;54:1068–73.

[3] Musher DM, Logan N, Hamill RJ, et al. Nitazoxanide in the treatment for *Clostridium difficile* associated disease. Clin Infect Dis 2006;43:421–7.

[4] Dial S, Delaney JA, Barkun AN, et al. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. JAMA 2005;294:2989–95.

[5] Severe *Clostridium difficile*–associated disease in populations previously at low risk–four states. MMWR Morb Mortal Wkly Rep 2005;54:1201–5.

[6] Delaney JAC, Dial S, Barkun A, et al. Antimicrobial drugs and community-acquired *Clostridium difficile*-associated disease, UK. Emerg Infect Dis 2007;13:761–3.
[7] Dial S, Delaney JA, Schneider V, et al. Proton pump inhibitor use and risk of community-acquired *Clostridium difficile*-associated disease defined by prescription for oral vancomycin therapy. CMAJ 2006;175:745–8.
[8] Wanahita A, Goldsmith E, Musher D. Leukocytosis in a tertiary care hospital with particular attention to the role of infection caused by *Clostridium difficile*. Clin Infect Dis 2002;34: 1585–92.
[9] Musher DM, Aslam S, Logan N, et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. Clin Infect Dis 2005;40:1586–90.
[10] Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium-difficile*-associated diarrhoea and colitis. Lancet 1983;2: 1043–6.
[11] Bartlett JG. Treatment of antibiotic-associated pseudomembranous colitis. Rev Infect Dis 1984;6(Suppl 1):S235–41.
[12] Olson MM, Shanholtzer CJ, Lee JT Jr, et al. Ten years of prospective *Clostridium difficile*-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982–1991. Infect Control Hosp Epidemiol 1994;15:371–81.
[13] Musher DM, Musher BL. Contagious acute gastrointestinal infections. N Engl J Med 2004; 351:2417–27.
[14] Hecht DW, Galang MA, Sambol SP, et al. In vitro activities of 15 antimicrobial agents against 110 toxigenic *Clostridium difficile* clinical isolates collected from 1983 to 2004. Antimicrob Agents Chemother 2007;51:2716–9.
[15] Bartlett JG. *Clostridium difficile*: clinical considerations. Rev Infect Dis 1990;12(Suppl 2): S243–51.
[16] Wallace JF, Smith RH, Petersdorf RG. Oral administration of vancomycin in the treatment of staphylococcal enterocolitis. N Engl J Med 1965;272:1014–5.
[17] Khan MY, Hall WH. Staphylococcal enterocolitis: treatment with oral vancomycin. Ann Intern Med 1966;65:1–8.
[18] Tedesco FJ, Barton RW, Alpers DH. Clindamycin-associated colitis: a prospective study. Ann Intern Med 1974;81:429–33.
[19] Silva J Jr, Batts DH, Fekety R, et al. Treatment of *Clostridium difficile* colitis and diarrhea with vancomycin. Am J Med 1981;71:815–22.
[20] Fekety R, Silva J, Buggy B, et al. Treatment of antibiotic-associated colitis with vancomycin. J Antimicrob Chemother 1984;14(Suppl D):97–102.
[21] Fekety R, Silva J, Kauffman C, et al. Treatment of antibiotic-associated *Clostridium difficile* colitis with oral vancomycin: comparison of two dosage regimens. Am J Med 1989;86:15–9.
[22] Young GP, Ward PB, Bayley N, et al. Antibiotic-associated colitis due to *Clostridium difficile*: double-blind comparison of vancomycin with bacitracin. Gastroenterology 1985;89: 1038–45.
[23] Dudley MN, McLaughlin JC, Carrington G, et al. Oral bacitracin vs vancomycin therapy for *Clostridium difficile*-induced diarrhea: a randomized double-blind trial. Arch Intern Med 1986;146:1101–4.
[24] de Lalla F, Nicolin R, Rinaldi E, et al. Prospective study of oral teicoplanin versus oral vancomycin for therapy of pseudomembranous colitis and *Clostridium difficile*-associated diarrhea. Antimicrob Agents Chemother 1992;36:2192–6.
[25] Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis 2007;45:302–7.
[26] Pelaez T, Alcala L, Alonso R, et al. Reassessment of *Clostridium difficile* susceptibility to metronidazole and vancomycin. Antimicrob Agents Chemother 2002;46:1647–50.
[27] Dzink J, Bartlett JG. In vitro susceptibility of *Clostridium difficile* isolates from patients with antibiotic-associated diarrhea or colitis. Antimicrob Agents Chemother 1980;17:695–8.

[28] Wong SS, Woo PC, Luk WK, et al. Susceptibility testing of *Clostridium difficile* against metronidazole and vancomycin by disk diffusion and Etest. Diagn Microbiol Infect Dis 1999;34: 1–6.
[29] Cheng SH, Chu FY, Lo SH, et al. Antimicrobial susceptibility of *Clostridium difficile* by E test. J Microbiol Immunol Infect 1999;32:116–20.
[30] Barbut F, Decre D, Burghoffer B, et al. Antimicrobial susceptibilities and serogroups of clinical strains of *Clostridium difficile* isolated in France in 1991 and 1997. Antimicrob Agents Chemother 1999;43:2607–11.
[31] Marchese A, Salerno A, Pesce A, et al. In vitro activity of rifaximin, metronidazole and vancomycin against *Clostridium difficile* and the rate of selection of spontaneously resistant mutants against representative anaerobic and aerobic bacteria, including ammonia-producing species. Chemotherapy 2000;46:253–66.
[32] Jamal WY, Mokaddas EM, Verghese TL, et al. In vitro activity of 15 antimicrobial agents against clinical isolates of *Clostridium difficile* in Kuwait. Int J Antimicrob Agents 2002; 20:270–4.
[33] McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med 2005;353:2433–41.
[34] Cherry RD, Portnoy D, Jabbari M, et al. Metronidazole: an alternate therapy for antibiotic-associated colitis. Gastroenterology 1982;82:849–51.
[35] Wenisch C, Parschalk B, Hasenhundl M, et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. Clin Infect Dis 1996;22:813–8.
[36] Bricker E, Garg R, Nelson R, et al. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. Cochrane Database Syst Rev 2005; CD004610.
[37] Preventing the spread of vancomycin resistance. A report from the Hospital Infection Control Practices Advisory Committee prepared by the Subcommittee on Prevention and Control of Antimicrobial-Resistant Microorganisms in Hospitals; comment period and public meeting–CDC. Notice. Fed Regist 1994;59:25758–63.
[38] Gerding DN. Is there a relationship between vancomycin-resistant enterococcal infection and *Clostridium difficile* infection? Clin Infect Dis 1997;25(Suppl 2):S206–10.
[39] Fekety R. Guidelines for the diagnosis and management of *Clostridium difficile*-associated diarrhea and colitis. American College of Gastroenterology, Practice Parameters Committee. Am J Gastroenterol 1997;92:739–50.
[40] Nair S, Yadav D, Corpuz M, et al. *Clostridium difficile* colitis: factors influencing treatment failure and relapse. A prospective evaluation. Am J Gastroenterol 1998;93:1873–6.
[41] Pepin J, Alary ME, Valiquette L, et al. Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Quebec, Canada. Clin Infect Dis 2005;40:1591–7.
[42] Gerding DN. Metronidazole for *Clostridium difficile*-associated disease: is it okay for mom? Clin Infect Dis 2005;40:1598–600.
[43] Mattila KJ, Valtonen VV, Nieminen MS, et al. Role of infection as a risk factor for atherosclerosis, myocardial infarction, and stroke. Clin Infect Dis 1998;26:719–34.
[44] Loft S, Dossing M, Poulsen HE, et al. Influence of dose and route of administration on disposition of metronidazole and its major metabolites. Eur J Clin Pharmacol 1986;30: 467–73.
[45] Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. Gut 1986;27:1169–72.
[46] Friedenberg F, Fernandez A, Kaul V, et al. Intravenous metronidazole for the treatment of *Clostridium difficile* colitis. Dis Colon Rectum 2001;44:1176–80.
[47] White CA Jr. Nitazoxanide: a new broad spectrum antiparasitic agent. Expert Rev Anti Infect Ther 2004;2:43–9.
[48] Musher DM, Logan N, Mehendiratta V, et al. *Clostridium difficile* colitis that fails conventional metronidazole therapy: response to nitazoxanide. J Antimicrob Chemother 2007;59: 705–10.

[49] Ripa S, Mignini F, Prenna M, et al. In vitro antibacterial activity of rifaximin against *Clostridium difficile*, *Campylobacter jejunii* and *Yersinia* spp. Drugs Exp Clin Res 1987;13: 483–8.
[50] DuPont HL, Jiang ZD, Okhuysen PC, et al. A randomized, double-blind, placebo-controlled trial of rifaximin to prevent travelers' diarrhea. Ann Intern Med 2005;142:805–12.
[51] Boero M, Berti E, Morgando A, et al. Treatment for colitis caused by *Clostridium difficile*: results of a randomized open study of rifaximine vs vancomycin. Microbiol Med 1990;5: 74–7.
[52] Johnson S, Schriever C, Galang M, et al. Interruption of recurrent *Clostridium difficile*-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. Clin Infect Dis 2007;44:846–8.
[53] Ackermann G, Loffler B, Adler D, et al. In vitro activity of OPT-80 against *Clostridium difficile*. Antimicrob Agents Chemother 2004;48:2280–2.
[54] Bartlett JG, Chang TW, Onderdonk AB. Comparison of five regimens for treatment of experimental clindamycin-associated colitis. J Infect Dis 1978;138:81–6.
[55] Mogg GA, Arabi Y, Youngs D, et al. Therapeutic trials of antibiotic associated colitis. Scand J Infect Dis 1980;(Suppl 22):41–5.
[56] Mogg GA, George RH, Youngs D, et al. Randomized controlled trial of colestipol in antibiotic-associated colitis. Br J Surg 1982;69:137–9.
[57] Taylor NS, Bartlett JG. Binding of *Clostridium difficile* cytotoxin and vancomycin by anion-exchange resins. J Infect Dis 1980;141:92–7.
[58] Kelly CP, Pothoulakis C, Vavva F, et al. Anti-*Clostridium difficile* bovine immunoglobulin concentrate inhibits cytotoxicity and enterotoxicity of *C. difficile* toxins. Antimicrob Agents Chemother 1996;40:373–9.
[59] Lyerly DM, Bostwick EF, Binion SB, et al. Passive immunization of hamsters against disease caused by *Clostridium difficile* by use of bovine immunoglobulin G concentrate. Infect Immun 1991;59:2215–8.
[60] Babcock GJ, Broering TJ, Hernandez HJ, et al. Human monoclonal antibodies directed against toxins A and B prevent *Clostridium difficile*–induced mortality in hamsters. Infect Immun 2006;74:6339–47.
[61] Beales IL. Intravenous immunoglobulin for recurrent *Clostridium difficile* diarrhoea. Gut 2002;51:456.
[62] Salcedo J, Keates S, Pothoulakis C, et al. Intravenous immunoglobulin therapy for severe *Clostridium difficile* colitis. Gut 1997;41:366–70.
[63] Wilcox MH. Descriptive study of intravenous immunoglobulin for the treatment of recurrent *Clostridium difficile* diarrhoea. J Antimicrob Chemother 2004;53:882–4.
[64] Juang P, Skledar SJ, Zgheib NK, et al. Clinical outcomes of intravenous immune globulin in severe *Clostridium difficile*-associated diarrhea. Am J Infect Control 2007;35:131–7.
[65] Cavagnaro C, Berezin S, Medow MS. Corticosteroid treatment of severe, non-responsive *Clostridium difficile* induced colitis. Arch Dis Child 2003;88:342–4.
[66] Durai R. Epidemiology, pathogenesis, and management of *Clostridium difficile* infection. Dig Dis Sci 2007.
[67] Schwan A, Sjolin S, Trottestam U, et al. Relapsing *Clostridium difficile* enterocolitis cured by rectal infusion of normal faeces. Scand J Infect Dis 1984;16:211–5.
[68] Nathanson DR, Sheahan M, Chao L, et al. Intracolonic use of vancomycin for treatment of *Clostridium difficile* colitis in a patient with a diverted colon: report of a case. Dis Colon Rectum 2001;44:1871–2.
[69] Persky SE, Brandt LJ. Treatment of recurrent *Clostridium difficile*-associated diarrhea by administration of donated stool directly through a colonoscope. Am J Gastroenterol 2000;95:3283–5.
[70] Aas J, Gessert CE, Bakken JS. Recurrent *Clostridium difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. Clin Infect Dis 2003; 36:580–5.

[71] Musher DM, Manhas A, Jain P, et al. Detection of *Clostridium difficile* toxin: comparison of enzyme immunoassay results with results obtained by cytotoxicity assay. J Clin Microbiol 2007;45:2737–9.
[72] Dallal RM, Harbrecht BG, Boujoukas AJ, et al. Fulminant *Clostridium difficile*: an underappreciated and increasing cause of death and complications. Ann Surg 2002;235:363–72.
[73] Longo WE, Mazuski JE, Virgo KS, et al. Outcome after colectomy for *Clostridium difficile* colitis. Dis Colon Rectum 2004;47:1620–6.
[74] Pepin J, Valiquette L, Alary ME, et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ 2004;171:466–72.
[75] Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Engl J Med 2005;353:2442–9.
[76] Warny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. Lancet 2005;366:1079–84.
[77] Lipsett PA, Samantaray DK, Tam ML, et al. Pseudomembranous colitis: a surgical disease? Surgery 1994;116:491–6.
[78] Klipfel AA, Schein M, Fahoum B, et al. Acute abdomen and *Clostridium difficile* colitis: still a lethal combination. Dig Surg 2000;17:160–3.
[79] Synnott K, Mealy K, Merry C, et al. Timing of surgery for fulminating pseudomembranous colitis. Br J Surg 1998;85:229–31.
[80] Koss K, Clark MA, Sanders DS, et al. The outcome of surgery in fulminant *Clostridium difficile* colitis. Colorectal Dis 2006;8:149–54.
[81] Wanahita A, Goldsmith EA, Marino BJ, et al. *Clostridium difficile* infection in patients with unexplained leukocytosis. Am J Med 2003;115:543–6.
[82] Kyne L, Sougioultzis S, McFarland LV, et al. Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea. Infect Control Hosp Epidemiol 2002;23:653–9.
[83] Buggy BP, Fekety R, Silva J Jr. Therapy of relapsing *Clostridium difficile*-associated diarrhea and colitis with the combination of vancomycin and rifampin. J Clin Gastroenterol 1987;9:155–9.
[84] Zar FA, Davis MB. Reply to Bishara et al, Huggan et al, and Lawrence et al. Clin Infect Dis 2007;45:1649–51.