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Review

Use of alternative or adjuvant pharmacologic treatment strategies in the prevention and treatment of *Clostridium difficile* infection

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SUMMARY

Infection with *Clostridium difficile* is currently the leading cause of infectious diarrhea in hospitalized patients, and recent surveillance data indicate that *C. difficile* has surpassed methicillin-resistant *Staphylococcus aureus* as the number one cause of hospital-acquired infections in some areas of the USA. In addition, concern over *C. difficile* has increased over the past decade due to the appearance of new hypervirulent strains. Metronidazole and vancomycin have remained the treatments of choice for initial therapy of primary infection with *C. difficile* for the past 25 years, but the persistence of spores leads to a recurrence of infection in an estimated 20–25% of patients. Patients who have one recurrent episode have up to a 65% chance of having additional recurrence. While the judicious use of antimicrobials in accordance with antibiotic stewardship guidelines remains the most effective method for the control of *C. difficile*, the high recurrence rate, increasing incidence, and changing epidemiology of *C. difficile* has led to an increased interest in the study of alternative strategies for the prevention and treatment of *C. difficile* disease. These alternative strategies attempt to eliminate *C. difficile* spores, replenish the normal gut flora, reduce the *C. difficile* toxin load in the bowel, or bolster the patient's own immune response to the *C. difficile* toxins. To evaluate the available evidence on these alternative strategies, we conducted a literature search of MEDLINE (1966–March 2011) and International Pharmaceutical Abstracts (1970–March 2011). Available citations from these articles were also utilized. The aim of this review is to summarize the available evidence for alternative treatment strategies for *C. difficile* disease and to make recommendations for their place in therapy.

1. Introduction

Clostridium difficile is a Gram-positive, anaerobic, spore-forming, cytotoxin-producing bacillus transmitted via the fecal–oral route.[1] *C. difficile* was first linked to human disease in 1977 and has increased in incidence to become the leading cause of infectious diarrhea in hospitalized patients.[2,3] The Centers for Disease Control and Prevention (CDC) estimates the annual incidence of hospitalized cases of *C. difficile* infection (CDI) to exceed 250 000, with a mortality rate of 1–2.5% in infected persons and an estimated cost to the health care system of over 3 billion dollars per year.[1,4,5] Recent surveillance data indicate that *C. difficile* has surpassed methicillin-resistant *Staphylococcus aureus* (MRSA) as the number one cause of hospital-acquired infections in some areas of the USA.[6]

The increasing concern with *C. difficile* seen over the past decade has primarily been due to changing epidemiology. North America has seen CDI incidence increase five-fold in the community dwelling populations. Incidence has also increased in Europe, most noticeably the UK, the Netherlands, and France.[7] In addition to the increased number of cases, the severity has also increased. Between 1997 and 2005, a nearly four-fold increase in *C. difficile*-associated mortality was observed in Canada.[8] These epidemiologic changes appear to be due in part to a new hypervirulent, epidemic strain of *C. difficile*, referred to as BI/NAP1/027, which produces higher concentrations of toxins and appears more resistant to treatment.[7]

The heightened interest in *C. difficile* treatment is also related to the high risk of *C. difficile* infection in severely immunocompromised HIV and cancer patients, as well as the appearance of *C. difficile* in patients treated with short courses of antibiotics for traveler's diarrhea or surgical prophylaxis.[9,10] Therefore, the best practice in all patients—high or low risk—is the judicious use of antimicrobials for the prevention of CDI. Despite efforts to prevent CDI, changing epidemiology and high rates of recurrence of CDI demand an understanding of not only traditional treatment options for infection, but also the evidence for alternative

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treatments. To evaluate the available evidence of alternative treatments, we conducted a literature search of MEDLINE (1966–March 2011) and International Pharmaceutical Abstracts (1970–March 2011) and available citations from the reviewed literature.

2. Standard treatment of *Clostridium difficile* infection

Initial treatment of CDI involves the discontinuation of causative antimicrobial therapies.[1,5] After discontinuation of inciting antibiotics, current practice guidelines from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America (SHEA/IDSA) recommend either metronidazole or oral vancomycin as the treatments of choice.[5] Oral metronidazole is recommended for initial episodes of mild-to-moderate CDI (500 mg orally three times daily for 10–14 days) and oral vancomycin (125 mg four times daily for 10–14 days) is recommended for initial treatment of severe disease.[5]

The European Society of Clinical Microbiology and Infectious Diseases treatment guidance document for CDI recommends teicoplanin, a glycopeptide with similar activity to vancomycin, at a dose of 100 mg twice daily as an additional oral treatment option.[11] Oral bacitracin (20 000–25 000 U four times daily for 7–10 days) and fusidic acid (250–500 mg three times daily for 7–10 days) are considered less effective than the glycopeptides and metronidazole and are therefore not recommended for use. Teicoplanin, fusidic acid, and oral bacitracin are not available in the USA.[11,12]

Because optimal treatment of CDI involves oral antibiotic administration, treatment of a patient without oral access can be challenging. Intravenous (IV) administration of metronidazole diffuses from the serum of inflamed colon into the lumen and undergoes hepatic recirculation, providing comparable concentrations to oral administration.[1] Vancomycin can also be administered per rectum in the form of a retention enema or intracolonically.[13] Combination therapy with oral vancomycin and IV metronidazole has also been suggested as initial therapy in severe disease.[5]

3. Alternative agents and therapies

3.1. Assessing the need for alternative/adjuvant treatment strategies

Vancomycin and metronidazole have been used as effective treatments for CDI for over 25 years, but they may further disrupt and suppress the return of the healthy intestinal flora and do not reduce exposure to spores in the environment or positively alter host risk factors. For these reasons, it is estimated that 20–25% of patients who respond to initial treatment with metronidazole or vancomycin will experience recurrence of *C. difficile*, or reappearance of clinical symptoms, typically within 2 weeks of completed therapy.[14,15]

Approximately half of recurrences are due to relapse, while the other half are due to reinfection. A relapse involves the same strain of *C. difficile* as the original infection and occurs when *C. difficile* spores remain in the intestine after CDI treatment.[14,15] These spores can easily proliferate and begin producing toxins again, because the normal flora of the intestine is not reestablished for approximately 3 months.[16]

The SHEA/IDSA guidelines recommend that a patient experiencing their first recurrence of *C. difficile* be treated with the same antibiotic as was used for the initial episode; however, patients who have a single recurrence have up to a 24% chance of having repeat recurrence, and risk increases up to 65% when a patient has had more than two prior episodes of CDI. Treatment with vancomycin instead of metronidazole or vice versa does not reduce this likelihood.[16,17]

Due to the high recurrence rate, as well as increasing incidence and fatality rate of CDI since the year 2000, there has been increased interest in the study of alternative and adjuvant strategies for the prevention and treatment of CDI.[4] These strategies attempt to eliminate *C. difficile* spores, replenish normal gut flora, reduce *C. difficile* toxin load in the bowel, or bolster the patient's own immune response to *C. difficile* toxins. Table 1 provides a summary of pharmacologic agents discussed in this review.

3.2. Alternative vancomycin dosing strategies

Alternative dosing strategies that have been successfully used in the treatment of chronically recurring CDI are tapered dose vancomycin, which involves a gradual lowering of the vancomycin dose over time, and pulsed dose vancomycin, which involves short, intermittent courses. In addition, the use of adjunctive intracolonic vancomycin has been studied for the treatment of severe CDI.

In 1985, Tedesco et al. reported a case series of 22 patients whose recurrent CDI was treated using these strategies: patients were first treated with a 6-week tapered regimen of vancomycin (125 mg every 6 h for 1 week, then 125 mg every 12 h for 1 week, then 125 mg daily for 1 week), followed by a pulsed dose regimen (125 mg every other day for 1 week, then 125 mg every 3 days for 2 weeks). No recurrences were reported after 6 months.[18]

In 2002, McFarland et al. reported a case series of 163 patients with recurrent CDI who were treated with various dosing regimens of vancomycin. Vancomycin tapered dosing (doses decreased stepwise from 500 mg–3 g per day down to 125–750 mg per day over approximately 21 days) resulted in a 31% recurrence rate, and pulsed dosing of vancomycin (125–500 mg as a single daily dose every 2–3 days over approximately 27 days) resulted in a 14% recurrence rate, compared to 43–54% recurrence rates with standard vancomycin 10-day regimens.[17]

Targeted antibiotic therapy eradicates *C. difficile* colonies but has no effect on spores, leading to recurrence of infection. It is hypothesized that pulsed and tapered dosing regimens allow *C. difficile* spores to germinate and then eliminate the cells, while also supporting re-establishment of normal flora in the intestines.[17] One major concern with pulsed and tapered regimens is the development of vancomycin-resistant Enterococcus (VRE), given the protracted exposure to vancomycin.[15]

Though there are no randomized controlled trials evaluating these dosing regimens, 2010 SHEA/IDSA guidelines recommend for second recurrence of CDI a usual dosage of 125 mg four times daily for 10–14 days followed by 125 mg twice daily for 1 week, 125 mg once daily for 1 week, and then 125 mg every 2 or 3 days for 2 to 8 weeks.[5] At this time, the use of tapered or pulsed dose vancomycin should be considered for treatment of second or later recurrences of CDI.

The adjunctive intracolonic administration of vancomycin to patients with *C. difficile* colitis has been studied in an attempt to achieve higher concentrations of drug within the colon than may be achieved by oral administration of vancomycin or metronidazole alone.[13] Intracolonic vancomycin therapy involves administration of an IV solution of vancomycin via intracolonic bolus (for example, a 2 g bolus followed by 100 mg after each watery stool in addition to 125 mg of oral vancomycin four times daily) or via rectal retention enema (for example, individual doses of 500 mg in 1 l of normal saline).[19] Administration via retention enema may be a more desirable option due to the risk of perforation with the insertion of catheters into the colon for intracolonic bolus. A literature review by Apisarnthanarak et al. estimates a success rate for intracolonic vancomycin of 57–75%. Patients receiving intracolonic vancomycin in case reports or case series have not experienced recurrent disease, required surgical intervention, or