Current advances related to *Clostridium difficile* infection

Yong Gil Kim & Byung Ik Jang

*Institute for Digestive Research, Digestive Disease Center, Department of Internal Medicine, Soonchunhyang University Gumi Hospital, Soonchunhyang University College of Medicine, Gumi & Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, South Korea*

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*Clostridium difficile* infection (CDI) can trigger various responses, ranging from asymptomatic carriage to fulminant colitis. Hard-to-cure CDI, such as severe CDI, multiple recurrences of CDI, refractory CDI, and hypervirulent strains of *C. difficile*, require new treatments, although antibiotics such as metronidazole and vancomycin are the treatment of choice for initial and first relapsing CDI. Active immunization with *C. difficile* toxins and faecal microbiota transplantation deserve special attention. Here we describe these strategies for difficult-to-treat CDI.

**Key words** *Clostridium difficile* infection - *Clostridium difficile* vaccine - faecal microbiota transplantation

**Introduction**

*Clostridium difficile* is an anaerobic, Gram-positive, spore-forming bacillus that is the major cause of diarrhoea and colitis associated with antibiotics. *C. difficile* infection (CDI) can trigger various responses, ranging from asymptomatic carriage to fulminant colitis and recurrent *C. difficile*-associated diarrhoea. The reasons for the variability of this disease are not clear. However, it is generally accepted that host factors are more important than bacterial virulence factors.

The initial treatment of CDI is well-established and includes withdrawing any precipitating antibiotics when possible, providing supportive care by administering fluids and electrolytes as required, and using antibiotics such as metronidazole or vancomycin. Cases of relapsing colitis are treated with either further metronidazole or vancomycin, or prolonged vancomycin treatment using ‘pulsed-tapered’ protocols. After the first post-treatment recurrence, the rate of a second recurrence is as high as 40 per cent. However, relapsing CDI and treatment failure are not associated with resistance to metronidazole or vancomycin.

Several investigators have reported increasing rates and severity of CDI. In addition, the appearance of a hypervirulent strain and treatment failure with current medication was reported. These reports reinforce the need for methods of improving host factors, such as faecal microbiota transplantation (FMT) and optimizing immune responses to *C. difficile* toxins.

**Optimizing the immune response**

*C. difficile* infection results from disruption of the normal bacterial flora of the colon, colonization with *C. difficile*, and the release of toxins that lead to
mucosal damage and inflammation. After colonization, the organism releases two protein exotoxins into the colon lumen: Toxins A and B, which cause diarrhoea and colitis. Toxin A is an enterotoxin that allows Toxin B to enter cells. The binding of the toxins to membrane receptors has toxic effects; both Toxins A and B result in mucosal inflammation and cause the secretion of a protein-rich exudate that contains neutrophils and monocytes. In addition, both toxins lead to peeling off of enterocytes and activation of cytokine release from monocytes.

In a Quebec study conducted between 1991 and 2003, vancomycin had fewer complications than metronidazole. However, between 2003 and 2006, vancomycin was not found superior to metronidazole. These results suggest that a hypervirulent strain, which produces more toxin, has spread in Quebec. The increased toxin level quickly saturates the binding sites in the colon before vancomycin can reduce the production of C. difficile toxins. Therefore, new treatment strategies that reduce the toxicity of already-bound toxin, or prevent toxin binding to the colon, are needed.

Lowy et al. examined the safety of monoclonal antibodies and their effects on the initial episode of C. difficile-associated diarrhoea (CDAD). The combined administration of monoclonal antibodies against toxin A (CDA1) and B (CDB1) significantly reduced recurrent CDAD. Active immunization with C. difficile toxins could also be a promising strategy for treating CDAD and is at present undergoing phase III trials.

Faecal microbiota transplantation (FMT)

Eiseman et al. first reported the use of FMT in CDI, in 1958. Subsequently, many case series of FMT in CDI have been reported, and many researchers have found a valid rationale for FMT in CDI. Antibiotic use disrupts the normal bacterial flora of the colon, and antibiotic damage to the normal microbiota permits invasion by C. difficile. In healthy control subjects and initial CDI patients, Fumigatus and Bacteroidetes spp. are relatively abundant in the faecal material. However, recurrent CDI patients had a different faecal microbiota. Khoruts et al. reported that the faecal bacterial composition of the recipient after FMT was similar to that of the donor and was dominated by Bacteroides spp. strains. A systemic review of FMT in CDI reported excellent cure rates (92%) and a protective effect against relapsing CDI (the relapse rate was 4%).

Finally, a recent randomized controlled trial showed that FMT was significantly more effective for treating recurrent C. difficile infection than was vancomycin. Consequently, FMT is now a recommended treatment for the third recurrence of CDI.

Generally, the donor for FMT is a member of the patient’s family. However, donor identification and work-up increases cost, which can delay FMT. Moreover, it is difficult to identify suitable donors for some patients. Hamilton et al. reported the efficacy of a frozen preparation from a universal donor. In the near future, a simplified, standardized product, such as encapsulated FMT oral therapy, will be available.

Conclusions

Antibiotics, particularly metronidazole and vancomycin, are the treatment of choice for the initial therapy and first recurrence for most patients with mild-to-moderate CDI. However, hard-to-cure CDI, such as severe CDI, multiple recurrences of CDI, refractory CDI, and hypervirulent strains of C. difficile, need new treatment options. Research on optimizing immune responses and FMT must continue, as these strategies will likely become mainstream treatments for hard-to-cure CDI.

References


*Reprint requests:* Dr Byung Ik Jang, Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, South Korea
e-mail: jbi@med.yu.ac.kr