REVIEW

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Recurrent *Clostridium difficile* Infection: Risk Factors, Treatment, and Prevention

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The most common cause of antibiotic-associated diarrhea is *Clostridium difficile* infection (CDI). Recurrent *C. difficile* infection (rCDI) often occurs after successful treatment of CDI. Due to the increased incidence and the difficulty in treating rCDI, it is becoming an important clinical issue. Identifying risk factors is helpful for early detection, treatment, and prevention of rCDI. Advanced age, use of antibiotics, gastric acid suppression, and infection with a hypervirulent strain are currently regarded as the major risk factors for rCDI. Several treatment modalities, including vancomycin, fidaxomicin, and fecal microbiota transplant (FMT), are suggested for rCDI treatment. However, there is currently no definitive treatment method with sufficient evidence for rCDI. Recent studies have focused on FMT and have shown positive results for rCDI. Prevention of rCDI by measures such as hand washing and isolation of patients is very important. However, these preventive measures are often overlooked in clinical practice. Here, we review the risk factors, treatment, and prevention of rCDI. **(Gut Liver 2019;13:16-24)**

Key Words: *Clostridium difficile*; Recurrence; Risk factors; Therapeutics; Prevention

INTRODUCTION

The most common pathogen of antibiotic-associated diarrhea is *Clostridium difficile*. Since 1978, when *C. difficile* was found to be the cause of pseudomembranous colitis,[1] occurrence of *C. difficile* infection (CDI) has increased worldwide.[2-7] Since 2003, CDI has been more frequent, virulent, refractory, and relapsing.[8] This pattern is related to the emergence of a hypervirulent strain (NAP1/BI/027).[9] The recurrence rate of CDI also continues to increase, thereby, raising important clinical concerns.[10] In a study of 845 patients treated with metronidazole, recurrence rates of CDI in 1991 to 2002 and 2003 to 2004 were 20.8% and 47.2%, respectively.[11]

Recurrent CDI (rCDI) is usually defined as an episode of CDI occurring within 8 weeks of a previous episode.[12,13] rCDI may be due to relapse of the previous CDI by the same strain or reinfection by a different strain.[14] About 15% to 30% of patients who initially respond to antimicrobial therapy experience rCDI.[15,16] After the first recurrence has improved, the risk of further recurrence significantly increases. A second recurrence rate of 40% has been reported among patients with resolved first recurrence. The subsequent recurrence rate of patients who have already recurred more than twice is approximately 45% to 65%.[17,18] The high recurrence rate of CDI contributes to increased health care costs.[19]

Identifying risk factors for rCDI is important for early detection, treatment, and prevention. For first recurrence, current treatment guidelines recommend the same regimen used in the initial episode.[12,13] However, evidence of recommended treatment for multiple rCDI is not sufficient.

Considering the increase in recurrence rate, prevention of rCDI is a very important clinical issue. Contact precautions and control of modifiable risk factors are basic preventive measures for rCDI. Other preventive measures, such as monoclonal antibodies against the *C. difficile* toxin, can also be used. Herein, we will review the risk factors, treatment, and prevention of rCDI.

RISK FACTORS FOR rCDI

1. Advanced age

The most frequently reported risk factor for rCDI is advanced age.[20-23] In a retrospective study, the probabilities of rCDI were 25.0%, 27.1%, and 58.4% among individual's aged 0 to 17, 18

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to 64, and ≥65 years, respectively.[11] In a meta-analysis of 33 studies (n=18,530) to identify risk factors for rCDI, over 65 years of age was a strong independent risk factor associated with rCDI (relative risk [RR], 1.63; 95% confidence interval [CI], 1.24 to 2.14; p=0.0005).[20] Although the reason for the recurrence in elderly people is unclear, decreased immune response to CDI and increased comorbidity may play a role.

2. Use of antibiotics

The most important modifiable risk factor for rCDI is the use of antibiotics for non-*C. difficile* after CDI diagnosis.[20-24] A meta-analysis showed that antibiotics use was an independent risk factor for rCDI (RR, 1.76; 95% CI, 1.52 to 2.05; p<0.00001).[20] Previous use of fluoroquinolones was also a remarkable risk factor (RR, 1.42; 95% CI, 1.28 to 1.57; p<0.00001).

Antibiotic use alters the indigenous intestinal microbiota and subsequently produces an environment where CDI is easily induced in patients.[25] The altered intestinal microbiota by antibiotics also influences bile acid composition in the colon, thereby promoting the growth of *C. difficile*.[25] In a retrospective case-control study of 60 rCDI patients and 180 non-rCDI patients, previous antibiotic exposure increased the risk of rCDI (odds ratio [OR], 2.23; 95% CI, 1.0 to 4.9; p=0.04).[26] Among the rCDI group, patients with relapse had greater previous antibiotic exposure than those with reinfection (91.3% vs 61.5%: OR, 0.1; 95% CI, 0.0 to 0.9; p=0.03).

3. Gastric acid suppression

Gastric acid suppression has been reported to be associated with rCDI development.[20,21,23] Gastric acid suppressive agents are widely used to prevent stress ulcers or treat acid-related diseases. Loss of gastric acidity caused by these agents may weaken defenses against *C. difficile* and increase the risk of CDI. In a recent meta-analysis that included 16 observational studies of 7,703 CDI patients, the rate of rCDI in patients with gastric acid suppression was higher, compared with patients without gastric acid suppression (22.1% vs 17.3%: OR, 1.52; 95% CI, 1.20 to 1.94; p<0.001).[27] Therefore, gastric acid suppressors, especially proton pump inhibitors, should be used cautiously in patients with critical underlying disease.[28]

4. Hypervirulent strains

Increased recurrence rates have been observed among patients infected with the hypervirulent *C. difficile* strain (NAP1/BI/027).[21,29,30] This strain produces comparatively larger amount of toxins A and B than other *C. difficile* strains and additionally produces binary toxin.[31] Binary toxin induces depolymerization of the actin cytoskeleton in the epithelial cells and formation of protrusions on epithelial cell surfaces, resulting in enhanced adherence and colonization by *C. difficile*.[32] Strain NAP1/BI/027 is highly resistant to fluoroquinolone, which is known to be associated with geographically dispersed outbreaks of CDI.[6] In a clinical trial of 719 CDI patients, patients with strain NAP1/BI/027 had higher recurrence rate than patients with non-hypervirulent strains (27.4% vs 16.6%, p=0.002).[29]

Table 1. Risk Factors for Recurrent *Clostridium difficile* Infection

Advanced age
Antibiotics use for non-*C. difficile* after CDI diagnosis
Gastric acid suppression
Hypervirulent strain, NAP1/BI/027
Severe underlying disease and/or renal insufficiency
History of previous CDI
Previous CDI severity
Prolonged hospital stays
Lack of adaptive immune responses to toxins A and B

CDI, *C. difficile* infection.

5. Other risk factors

Other reported risk factors for rCDI include severe underlying disease and/or renal insufficiency, a history of previous CDI, previous CDI severity, prolonged hospital stays, and lack of adaptive immune responses to toxins A and B (Table 1).[12,17,20,22,33-36]

It is important for clinicians to predict the occurrence of rCDI using the known risk factors. Some studies have provided prediction models for rCDI.[17,36,37] One study suggested a prediction model for rCDI based on the following predictors: age over 65, severe illness by the Horn index, and antibiotic use after CDI therapy.[36] In this study, each predictor was assigned 1-point and high-risk score was associated with high risk of rCDI. The area under the curve of the receiver-operating-characteristic curve was 0.83 (95% CI, 0.70 to 0.95) in the derivation cohort and 0.80 (95% CI, 0.67 to 0.92) in the validation cohort.

TREATMENT OF rCDI

1. Standard antibiotics

Withdrawing the implicated antibiotics is very important in the treatment of rCDI. Supportive care, such as correcting fluid loss and electrolyte imbalance, are also important in treatment. In the case of the first recurrence, the antibiotics used for the initial episode can be used again (Table 2). Non-severe initial rCDI can be treated using oral metronidazole. However, oral vancomycin should be used in severe cases.[12,13] If recurrence happens after the use of vancomycin in the initial episode, a tapered and/or pulsed regimen of vancomycin may be considered.[13] In studies comparing the efficacy and safety of fidaxomicin with those of vancomycin for treating CDI, clinical cure rates were similar between the fidaxomicin and vancomycin groups.[38,39] The recurrence rate in CDI patients with non-NAP1 strains was lower in the fidaxomicin group than the vanco-

Table 2. Treatment of Recurrent *Clostridium difficile* Infection[12,13]

Episode	Therapy
First recurrence	Mild to moderate CDI:
	metronidazole 500 mg orally 3 times a day for 10 days
	vancomycin 125 mg orally 4 times a day for 10 days
	fidaxomicin 200 mg orally 2 times a day for 10 days
	Severe CDI:
	vancomycin 125 mg orally 4 times a day for 10 days
	fidaxomicin 200 mg orally 2 times a day for 10 days
Second recurrence	Tapered and/or pulsed vancomycin regimen
	Fidaxomicin 200 mg orally 2 times a day for 10 days
Third or more recurrence	Fecal microbiota transplant
	Fidaxomicin 200 mg orally 2 times a day for 10 days

CDI, *C. difficile* infection.

mycin group, but the recurrence rate of the NAP1 strain was similar in both groups.[38] In another study of patients with first recurrence, the treatment response was similar for fidaxomicin and vancomycin, but the second recurrence rate within 28 days was lower when fidaxomicin was used.[40] Therefore, fidaxomicin can be an alternative therapy for first recurrence of CDI, especially in patients with non-NAP1 strains. While metronidazole and vancomycin are bacteriostatic to *C. difficile*, fidaxomicin is a non-absorbed macrocyclic antibiotic that is bactericidal to it.[41] Fidaxomicin also has less effect on the change of bowel microbiota than vancomycin.[42] This finding is associated with a lower relapse rate of fidaxomicin compared to vancomycin.

The second recurrence of CDI can be treated with a tapered and/or pulsed vancomycin regimen.[12,13,43] A pulsed regimen involves administering the drug every few days. It may allow the spores to germinate while antibiotics are not administered. Once the spores germinated, they are susceptible to antibiotics. An example of tapered and/or pulsed vancomycin regimen is as follows: 125 mg 4 times a day for 10 to 14 days, 125 mg 2 times a day for a week, 125 mg once a day for a week, and then 125 mg every 2 or 3 days for 2 to 8 weeks.[44] Use of metronidazole is not recommended for repeated recurrences due to the risk of neuropathy.[44]

2. Fecal microbiota transplant

In cases of multiple recurrences or refractoriness though proper use of standard antibiotics, fecal microbiota transplant (FMT) should be considered.[13,45] The human gut microbiota is a highly complex community of microorganisms. However, antibiotics reduce the diversity of the intestinal microbiota.[46] Compared with the fecal microbiota of patients without CDI, the fecal microbiota of patients with rCDI is more variable in bacterial composition and is characterized by a marked decrease in ecological diversity and lower species richness.[47] FMT restores these changes in bacterial composition and improves rCDI symptoms.[48] Studies have shown that FMT produced a primary cure rate of approximately 90% in patients with rCDI.[49-52] As a result, FMT is acknowledged as a treatment modality for rCDI patients who have failed standard antibiotics treatment.[13]

After introducing FMT as a treatment modality for CDI, its safety and usefulness have been studied. FMT via enema is the first introduced FMT method and many case studies have shown its efficacy and safety. In a case series of 27 patients with refractory or recurrent CDI, 25 of 27 patients (93%) experienced clinical resolution following FMT via retention enema using stool from two healthy donors.[53] There were no relapses or adverse events in these patients, with a mean follow up time of 427.3 days. Owing to the facile nature of this method, self-administered FMT via enema is available for rCDI patients at home. In a case series of 7 rCDI patients using home FMT, all of them were cured after the procedure.[54]

While enemas can generally reach the splenic flexure, FMT via colonoscopy allows for administration throughout the colon. Therefore, colonoscopy has been proposed as the preferred route for FMT. However, colonoscopy must be performed cautiously in patients with severe colitis and ileus due to a risk of perforation. In an open-label randomized controlled clinical trial, 39 patients with rCDI were assigned to FMT via colonoscopy or vancomycin pulsed regimen.[55] Patients receiving FMT achieved significantly higher cure rates compared with the vancomycin group (18/20 vs 5/19).

FMT via the upper gastrointestinal (GI) route, such as nasogastric/jejunal tube or gastroduodenoscopy, is easy to perform. However, it has some risk of aspiration or small bowel bacterial overgrowth. In addition, donor stool may not reach to the distal colon and the cure rate of FMT via the upper GI route is lower compared with that of the lower GI route.[56] In an open-label randomized controlled clinical trial, 43 patients with rCDI received one of three treatments: (1) a vancomycin regimen followed by bowel lavage and subsequent FMT through a nasoduodenal tube; (2) a vancomycin regimen alone; or (3) a vancomycin regimen with bowel lavage.[57] The cure rate for the FMT group, the vancomycin group, and the vancomycin with bowel lavage group were 81%, 31%, and 23%, respectively.

In FMT, fresh stool suspension from prescreened suitable donor is usually used. This can be a practical barrier to FMT because it takes time to prepare a stool suspension and the stool product must be used within a short period of time. Therefore, there has been research on stool product that can be stored for a long time and can be used immediately if necessary. In a randomized clinical trial, clinical response and improvement of colonic microbiota diversity were studied in subjects with rCDI using different donor product (fresh, frozen, or lyophilized FMT product via colonoscopy).[58] Cure rates were comparative in fresh or frozen product (100% and 83%, respectively, p=0.233). However, the cure rate of lyophilized product was lower than that of fresh product (78%, p=0.022). Microbial diversity was recon-

stituted at a similar speed in the subjects receiving either fresh or frozen product. In a recently reported systematic review with meta-analysis that evaluated the efficacy of FMT in treating rCDI, there was no difference between fresh and frozen FMT (92% and 93%, respectively) and re-treatment with FMT following failure of the first FMT resulted in an incremental effect.[56] These results suggest ways to develop more convenient therapies for treating rCDI using FMT. In a preliminary feasibility study, 20 patients with rCDI were treated with frozen FMT oral capsules.[59] Fourteen patients (70%) were cured after initial treatment. All six non-responders were re-treated and four of them had improved diarrhea, resulting in an overall 90% clinical resolution rate. No serious FMT-attributable adverse events were observed.

Gut dysbiosis is associated with inflammatory bowel disease (IBD) as well as CDI. FMT has been studied as a new option in the treatment of IBD.[60-62] Occurrence of CDI in patients with IBD leads to an exacerbation of IBD and a poor prognosis. Therefore, although evidence for the efficacy of FMT in the treatment of IBD is still insufficient and some adverse events are reported after FMT in CDI patient with IBD,[63] FMT should be considered in rCDI patients with IBD.[64-66]

Adverse events associated with FMT have not been well evaluated. According to a systematic review, the most common FMT-attributable adverse event was abdominal discomfort.[67] Abdominal discomfort occurred more frequently in the FMT via upper GI routes than via lower GI routes (43.6% and 17.7%, respectively). The second common FMT-attributable adverse event was transient fever, which was also more frequent in the FMT via upper GI routes (3.4% and 2.8% for upper and lower GI routes, respectively). Other mild to moderate adverse events included diarrhea, constipation, vomiting, belching, and transient increase of C-reactive protein. FMT-attributable severe adverse events included death, pathogen infections, IBD flare, autoimmune disease, and FMT procedure related injury. Among the severe adverse events, the incidence of FMT-attributable death was 0.28%. Donor screening protocols generally includes history taking and stool and serologic testing for infectious agents.[60] However, FMT has the potential for transmitting infectious disease despite strict donor screening. Another potential problem of FMT is that changes in gut microbiota can affect various extraintestinal disorders, such as metabolic, neuropsychiatric, autoimmune, and tumorous disorders.[68]

3. Rifaximin

Rifaximin is a poorly absorbed rifamycin derivative that has broad spectrum bactericidal activity against gram-positive, gram-negative, aerobic, and anaerobic bacteria.[69] Despite its broad spectrum activity, including *C. difficile*, rifaximin produces minimal alterations in the intestinal microflora.[69] This is the basis for considering rifaximin as a treatment option for rCDI. In a study including eight patients with multiple recurrent CDI, seven patients were cured after a 2-week course of rifaximin therapy following vancomycin.[70] In a randomized, double-blinded, placebo-controlled study including 68 CDI patients, however, the rifaximin chaser regimen did not show a statistical decrease in rCDI.[71] Rifaximin resistant *C. difficile* can be a clinical problem, especially in patients with prior exposure to rifaximin.[72]

4. Probiotics and intravenous gamma globulin

There have been several studies on the efficacy of probiotics for rCDI treatment. In one study, the addition of *Saccharomyces boulardii* to standard antibiotics in rCDI patients resulted in a lower recurrence rate compared with only the standard antibiotics group (34.6% vs 64.7%).[73] A meta-analysis of probiotics (*S. boulardii*, *Lactobacillus rhamnosus* GG, *Lactobacillus plantarum* 299v, and a mixture of *Lactobacillus acidophilus* and *Bifidobacterium bifidum*) for the treatment of CDI revealed that *S. boulardii* alone had a significant decrease in rCDI.[74] However, a Cochrane review concluded that probiotics as an adjunct to antibiotic therapy did not have sufficient evidence and probiotics alone had no evidence for the treatment of CDI.[75]

Some case reports have shown that intravenous gamma globulin is effective for rCDI.[76,77] However, additional large-scale studies are needed to confirm these results.

PREVENTION OF rCDI

1. General measures

rCDI may be due to relapse of the same strain as the first infection or reinfection by a different strain.[14] Thus, two important goals in rCDI prevention are reducing patient susceptibility and preventing organism transmission.[78]

The first step in the prevention of rCDI is to control modifiable risk factors. Minimizing antibiotic use is important for prevention of rCDI. Antimicrobial stewardship is recommended.[13,79] Avoidance of gastric acid suppressants also helps prevent rCDI.

In a study comparing colitis patients in long-term care facilities (LTCFs) with colitis patients in local communities, patients in LTCFs had a higher proportion of CDI than patients in local communities (55% vs 4.5%).[80] Among the possible reasons for this, environmental factors that facilitate transmission of *C. difficile* are an important cause. To prevent *C. difficile* transmission, it is important to implement contact precautions, hand hygiene, and environmental cleaning and disinfection. Contact precautions for CDI patients should be continued, at least until diarrhea is resolved.[13] In a prospective study of 27 patients with CDI, skin contamination with *C. difficile* often persisted after resolution of diarrhea.[81] The median time from diarrhea relief to detection of negative skin cultures was 7 days, which suggests that contact precautions should be maintain after the diarrhea has improved. All health-care workers should perform hand hygiene and barrier precautions, including wearing gloves and gowns.[13] None of the agents used in antiseptic hand-rub

preparations including alcohol-based hand rub are reliably sporicidal against *C. difficile*.[82] It is more effective to wash hands with soap and water than alcohol-based hand rub to remove *C. difficile*.[83] Environmental disinfection is recommended using a sporicidal agent such as a dilution of sodium hypochlorite (household bleach) or other product with *C. difficile*-sporicidal label claim.[13,78]

Rapid diagnosis of CDI patients is also important to prevent CDI transmission. In our study, use of the real-time polymerase chain reaction (PCR) to detect toxin genes could diagnose CDI more quickly than *C. difficile* toxin assay and culture for *C. difficile* (2.27 hours for real-time PCR, 83.67 hours for toxin assay, and 105.79 hours for culture).[84] Furthermore, real-time PCR was more sensitive than the other tests (87.2% for real-time PCR, 48.7% for toxin assay, and 65.0% for culture). Therefore, it is recommended to use real-time PCR for diagnosing CDI.

Oral vancomycin for secondary prevention may reduce the risk of recurrence following antibiotic exposure in patients with a recent CDI history.[85,86] In a retrospective cohort study, an oral vancomycin prophylaxis group (41% at a dose of 125 mg and 59% at a dose of 250 mg twice daily) had a lower recurrence rate compared with a no prophylaxis group (4.2% vs 26.6%).[85]

2. Monoclonal antibodies

The level of antibodies against toxin A or toxin B has been correlated with protection against rCDI.[33-35] Actoxumab and bezlotoxumab are fully human monoclonal antibodies for *C. difficile* toxin A and B, respectively. In a randomized clinical trial, actoxumab and bezlotoxumab were administered to patients with CDI who received metronidazole or vancomycin.[87] The recurrence rate of CDI was lower in patients treated with actoxumab and bezlotoxumab than in those treated with placebo (7% vs 25%). In other randomized trials, however, there was no significant difference in the recurrence rate of CDI between the bezlotoxumab alone group and the actoxumab-bezlotoxumab combination group (17% and 15%, respectively).[88] Additionally, the recurrence rate in the actoxumab alone group was similar to the placebo group (26% and 28%, respectively). Among the participants with a high risk of rCDI (age ≥65 years, history of CDI, compromised immunity, clinically severe CDI, and infection with a hypervirulent strain), rates of rCDI were lower in the bezlotoxumab group and in the actoxumab-bezlotoxumab group than in the placebo group. Therefore, bezlotoxumab is considered to be useful as secondary prophylaxis for CDI.

3. Non-toxigenic *C. difficile*

Studies in hamsters have shown that colonization with non-toxigenic *C. difficile* could prevent CDI caused by toxigenic strains.[89-92] In a human study, a symptomless colonization by *C. difficile* was associated with decreased risk of *C. difficile* associated diarrhea (1.0% of symptom-free *C. difficile* carriers vs 3.6% of non-colonized patients).[93] These results suggest that administration of non-toxigenic *C. difficile* may reduce risk of CDI. In a phase 2 randomized clinical trial of patients who recovered from CDI, oral administration of non-toxigenic *C. difficile* strain M3 spores reduced CDI recurrence rates (11% of M3 patients vs 30% of placebo patients).[94]

4. Vaccines

Some vaccines for CDI are currently under clinical trials.[95,96] These vaccines have altered toxin structures and produce antitoxin A and B antibodies. These toxoid vaccines are generally well tolerated and common adverse events are pain at injection site and flu-like symptoms.[95] However, all of these studies are in phase II or phase III and efficacy data is not yet available.

CONCLUSIONS

Risk factors for rCDI, including advanced age, use of antibiotics for non-*C. difficile* after CDI diagnosis, gastric acid suppression, and infection with the hypervirulent *C. difficile* strains, are well documented by meta-analysis. In addition, severe underlying disease and/or renal insufficiency, a history of previous CDI, previous CDI severity, prolonged hospital stays, and lack of adaptive immune responses to toxins A and B are also acknowledged as risk factors for rCDI. The first recurrence of CDI can be managed with oral metronidazole, vancomycin, or fidaxomicin. The second recurrence of CDI can be managed with a tapered and/or pulsed vancomycin regimen. For third recurrence, FMT should be considered. Although FMT has beneficial effects for multiple rCDI, there are unresolved problems with potential long term adverse events. Fidaxomicin and rifaximin chaser regimen can be treatment options for multiple rCDI. The first step in the prevention of rCDI is to control modifiable risk factors. Oral vancomycin usage in patients with a recent CDI history who undergo subsequent antibiotic exposure can be an option as secondary prophylaxis. Bezlotoxumab, a fully human monoclonal antibody for *C. difficile* toxin B, received U.S. Food and Drug Administration approval for secondary prevention of CDI in patients with high recurrence risk. Some vaccines for CDI are currently under clinical trials. It is important to implement contact precautions, hand hygiene, and environmental cleaning and disinfection for prevention of *C. difficile* transmission.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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