REVIEW ARTICLE

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Current treatments for recurrent Clostridium difficile infection

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Abstract

Introduction. Clostridium difficile infection most commonly manifests in patients with antibiotic-associated diarrhea, ranging from very mild to severe pseudomembranous colitis. Recurrent C. difficile infections remain a serious clinical problem, occurring in approximately one in five patients. Recurrence of infection despite antibiotic therapy is often due to disruption of the intestinal microbiota.

Objective The aim of this review is to summarize knowledge of current treatments and explore new therapies for Clostridium difficile infection, excluding vaccines under development and bacteriophage therapy, with a particular focus on patients with recurrent infections.

Review Methods. The review is based on 59 articles on the pathophysiology, epidemiology and treatment of clostridium difficile infections found in PubMed databases published between 2009–2024.

Brief description of the state of knowledge. Current treatments are mainly based on antibiotic therapy, or, for severe antibiotic-resistant forms, the faecal microbiota transplantation (FMT) method. In patients with recurrent infections, prolonged antibiotic therapy or sequential therapy with vancomycin and rifaximin is used. FMT is suggested for second or subsequent recurrent infections. Hopes are pinned on oral microbiome preparations, antibodies, new antibiotics, non-toxic strains or antibiotic degraders.

Summary. The treatment of recurrent infections is a difficult problem that requires a broader view. Emerging therapies with promising results focus both on antibiotic therapy that eliminates toxin-producing bacteria, and on modifying the microbiota and reducing the conversion of spore forms of these bacteria into toxin-producing forms.

Key words

treatment, microbiota, Clostridium difficile, toxins, recurrent infections, microbiome modulators.

INTRODUCTION

Pathophysiology of clostridium difficile infection. Clostridium difficile is a gram-positive bacillus that produces toxins A and B. The bacterium is transmitted via foodborne spores found in the environment or on carriers [1]. The normal intestinal microflora protects against infection, but when this is disturbed, Clostridium difficile begins to overgrow in the intestine. Bile acids play an important role in inducing the maturation of Clostridium spores, and primary bile acids induce the maturation of Clostridium spores into a toxigenic form. In contrast, secondary bile acids, which are formed in the intestinal lumen by the action of intestinal bacteria, inhibit the maturation of spores [2]. A higher concentration of primary bile acids compared to the first episode of infection is particularly notable in patients with recurrent infections, but the process is more complex than this relationship alone [3]. Infection may be symptomatic or asymptomatic. The most common symptoms of infection are diarrhea, usually mild to moderate, abdominal pain, nausea, vomiting, weakness and fever. Less commonly, the infection may progress to severe pseudomembranous colitis or life-threatening symptoms, such as shock, severe dehydration, colonic distension, signs of renal failure, or ultimately, death [4].

Recurrent clostridium difficile infection. According to the Guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) for Clostridium Difficile infection, recurrent infection occurs when symptoms recur within eight weeks of a previous episode, only if the symptoms of the previous episode have resolved after treatment [5].

Recurrent infection occurs in up to 20–25% of initially infected patients, most commonly in the first week after

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treatment for the original infection. The risk of recurrence in patients with one recurrence is between 45%-65%[6].

Risk factors for primary and secondary infections. The main risk factors for developing a primary Clostridium difficile infection are antibiotic therapy (highest risk is with lincosamides, fluoroquinolones, penicillins, cephalosporins and carbapenems) (Tab. 1), hospitalization (risk increases with length of stay), age over 65 years, immunosuppression, presence of cancer, abdominal surgery, inflammatory bowel disease, and chronic kidney disease [5, 7].

Table 1. Degrees of risk of Clostridium difficile infection with antibiotic use

Risk of infection	Group of antibiotics
High risk	Lincosamides, Fluoroquinolones, 2nd and 3rd generation Cephalosporins, Carbapenems
Moderate risk	penicillins, Vancomycin, Metronidazole
Low risk	Aminoglycosides, Tetracyclines, sulphonamides, Rifampicin, Trimethoprim, macrolides

Risk factors for recurrent infections include age over 65 years, previous infections, hospitalization within the last three months, severe underlying disease, use of antibiotics (as above) or proton pump inhibitors [5, 7].

Treatment of primary clostridium difficile infection. The 2021 ESCMID Guidelines for the Treatment of Primary Clostridium Difficile Infection [5] recommend stopping antibiotics and observing the patient in the case of a mild infection. ESCMID recommends fidaxomicin 200 mg twice daily for 10 days for a first infection requiring antibiotic administration, especially in patients with a risk factor for recurrent infection, as it significantly reduces the risk of recurrence compared with vancomycin treatment [8].

An alternative when fidaxomicin is not available is vancomycin at a dose of 125 mg four times daily for 10 days. Metronidazole can only be used if vancomycin or fidaxomicin is not available, at a dose of 500 mg three times a day for 10 days [5]. Trials comparing treatment with metronidazole and vancomycin have found vancomycin to be more effective, regardless of the severity of the primary infection (Tab. 2) [9].

Table 2. Current treatments for primary uncomplicated Clostridium difficile infection

First choice treatment	Fidaxomicin 200 mg twice daily for 10 days
	Vancomycin 125 mg four times daily for 10 days
Second choice treatment	Metronidazole 500 mg three times a day for 10 days

A study in a group of patients with a severe course of infection showed no significant advantage in cure with fidaxomicin compared with vancomycin [10]. Tigecycline 50 mg intravenously twice daily may be considered for complicated infection, but there is insufficient evidence for this therapy to be included in standard treatment [11].

Ridinilazole may become an antibiotic alternative in the future due to its 10% higher rate of sustained cure than vancomycin [12]; however, due to the paucity of data and ongoing research comparing ridinilazole's effect with other therapeutic options, it has not found a place in strict treatment algorithms.

The ESCMID guidelines also suggest that urgent surgical consultation should be sought whenever a patient is in a severe clinical condition, or has a complicated course of infection [5].

STANDARD TREATMENT FOR RECURRENT AND SEVERE CLOSTRIDIUM DIFFICILE INFECTIONS

Fidaxomicin. Fidaxomicin is a macrocyclic antibiotic which is bactericidal against Clostridium difficile by inhibiting bacterial RNA synthesis. It has a narrow spectrum of activity which limits the negative impact on the intestinal microbiome. This is important for the pathophysiology of recurrent infections, in which disruption of the intestinal microflora plays a key role [13].

For the first recurrence of infection, it is recommended to use fidaxomicin 200 mg twice daily for 10 days if the first episode was treated with vancomycin/metronidazole [5], or to prolong therapy by administering 200 mg twice daily for the first five days of therapy, and then 200 mg once daily for a further 20 days (Tab. 3) [8]. Analysis of a trial comparing the rate of recurrence after treatment of the first recurrence showed that the use of fidaxomicin was more favourable than vancomycin [14]. Monitoring the effectiveness of fidaxomicin treatment showed that the higher the number of previous episodes of Clostridium difficile infection, the higher the risk of recurrent infection after treatment [15].

Table 3. Current treatments for recurrent Clostridium Difficile infections

First recurrence	Fidaxomicin 200 mg twice daily for 10 days, or prolong therapy by giving 200 mg twice daily for the first five days of therapy, and then 200 mg once daily for a further 20 days
	Vancomycin 125 mg orally four times a day for two weeks, then one week at 125 mg twice a day, then one week 125 mg daily, then one week 125 mg every other day, and finally, 125 mg orally every third day for one week
	Bezlotoxumab is recommended in addition to standard antibiotic therapy
second and subsequent recurrence	Fidaxomicin 200 mg twice daily for 10 days, or prolong therapy by giving 200 mg twice daily for the first five days of therapy and then 200 mg once daily for a further 20 days
	Vancomycin 125 mg orally four times a day for two weeks, then one week 125 mg twice a day, then one week 125 mg daily, then one week 125 mg every other day, and finally, 125 mg orally every third day for one week
	Sequential therapy with a regimen of vancomycin 125 mg four times a day for 10 days, followed by rifaximin 400 mg three times a day for 20 days
	Faecal microbiota transplantation after initial antibiotic treatment with standard therapy

Vancomycin. Vancomycin is a glycopeptide antibiotic used mainly to treat serious gram-positive bacterial infections. It is bactericidal by blocking the synthesis of the bacterial cell wall [16]. For recurrent Clostridium difficile infections in the absence of fidaxomicin or bezlotoxumab, vancomycin can be used in a gradually decreasing dose regimen (two weeks vancomycin 125 mg orally four times a day, then one week administration of 125 mg twice a day, then one week administration of 125 mg daily, then another week with 125 mg every other day, and finally, 125 mg orally every third

day for one week), or a pulse regimen. Both regimens are associated with a lower risk of recurrent infection compared with 10 days of standard therapy [5,8].

Rifaximin. Rifaximin is a non-absorbable antibiotic with uncertain effects on the intestinal microbiota [17]. A placebo-controlled trial analyzing the administration of rifaximin at a dose of 400 mg three times daily for two weeks, reduced to 200 mg three times daily for a further two weeks. In patients after treatment of a primary episode of infection with vancomycin or metronidazole showed that rifaximin reduced the recurrence rate by half [6].

Sequential therapy with a regimen of vancomycin 125 mg four times a day for 10 days, followed by rifaximin 400 mg three times a day for 20 days, can be used in the case of a subsequent recurrence of Clostridium difficile [8]. However, further studies are needed to confirm the efficacy of rifaximin and to clarify the development of drug resistance in Clostridium, particularly ribotype 001 [18].

Metronidazole. Metronidazole is not included in treatment guidelines for recurrent Clostridium difficile infections [5,8]. The use of intravenous metronidazole as a dual therapy with oral vancomycin in severe infections is also questionable because of the lack of improved outcomes compared with vancomycin monotherapy [19]. A retrospective study suggests that dual therapy may be associated with better treatment outcomes than monotherapy, as it was associated with a 20% lower mortality rate; however, there were more patients with oncological and haematological burden in the vancomycin-only group [20].

NEW DRUGS UNDER INVESTIGATION FOR POSSIBLE FUTURE TREATMENT OF RECURRENT INFECTIONS

Probiotics. Probiotics containing Lactobacillus, Bifidobacterium, or Saccharomyces are used as adjunctive therapy after antibiotic therapy, or as prophylaxis during vancomycin therapy [21].

Probiotics can inhibit the production of the cytokine IL-8, increase the production of antitoxins and proteases that eliminate the activity of toxins [22]. However, more research is needed to select and standardize the best available probiotic preparation to help in the treatment and prevention of Clostridium difficile infections.

Cadazolid. Cadazolid is an oxazolidinone antibiotic with low absorption and little effect on the microbiome. It has bactericidal activity against Clostridium difficile and inhibits bacterial DNA synthesis [23]. In a Phase 2 study comparing treatment with cadazolid and vancomycin [24], the percentage of durable cures was significantly higher in patients treated with cadazolid. However, it did not have better cure rates than vancomycin in a phase 3 trial [25]. Further comparative studies, extended to include fidaxomicin, are needed.

Ridinilazole. Ridinilazole is another very narrow-spectrum, non-absorbable antibiotic that is effective against Clostridium Difficile with trace effects on other bacteria in the microbiome. A phase 2 study comparing cure rates and recurrence rates after treatment with ridinilazole and Vancomycin found a significantly better effect of ridinilazole therapy [12].

In the most recent phase 3 study, the use of Ridinilazole at a dose of 200 mg twice daily resulted in a significant 53% reduction in recurrence rates compared with Vancomycin at a dose of 125 mg four times daily. Ridinilazole, unlike Vancomycin, did not disrupt the microbiota, did not affect resistance, and increased the levels of secondary bile acids, the deficiency of which plays an important role in the pathogenesis [26]. Further comparative studies should be extended to include fidaxomicin.

Tigecycline. Tigecycline is a glycylcycline antibiotic with broad-spectrum bacteriostatic activity. A retrospective study showed that patients receiving tigecycline had a higher cure rate and fewer complications than standard antibiotic therapy [27], but more recent studies have shown no significant difference in treatment response [28]. It has been suggested that Tigecycline may be used for severe Clostridium difficile infections, but further studies are needed [5].

CRS3123. CRS3123 is a protein translation inhibitor that interferes with toxin production and growth of Clostridium difficile. Phase 1 studies have confirmed the drug's safety, tolerability, low absorption in the gastrointestinal tract and minimal effect on intestinal microflora [29]. Phase 2 studies are ongoing.

MGB-BP-3. MGB-BP-3 is a genetic transcription inhibitor of bacterial DNA, and has potent bactericidal activity against strains of Clostridium difficile. It has very limited activity against gram-negative bacteria [30]. It is currently in Phase 3 trials.

Ibezapolstat. Ibezapolstat is a DNA polymerase inhibitor with bactericidal activity against Clostridium difficile. It helps restore the disturbed microbiota in the intestine, which can have a major impact on the treatment of recurrent infections. Ibezapolstat also had less impact on the microbiota and a favourable secondary bile acid ratio compared to vancomycin [31]. A recent study shows the potential of Ibezapolstat against multidrug-resistant strains [32].

Auranofin. Auranofin is an anti-rheumatic drug with bactericidal properties against Clostridium

difficile. It reduces the amount of toxins and spores produced. Auranofin had comparable efficacy to Vancomycin for recurrent infections in hamsters [33]. Because of the promising results, this drug is being investigated further.

OTHER NEW TREATMENTS IN EARLY-STAGE TRIALS

ADS-024, RBX7455, MET-2. These are the latest compounds in the early stages of research based on modulation of the microbiome. Initial safety results for these formulations have been positive. Further studies of these formulations are ongoing.

Bezlotoxumab. Bezlotoxumab is a human monoclonal antibody that binds to the B toxin produced by Clostridium difficile and neutralizes its activity [34]. Bezlotoxumab is recommended as an adjunct to standard antibiotic therapy for recurrent infections [5, 8]. The greatest efficacy

of Bezlotoxumab therapy was observed in patients with recurrent infection and risk factors for recurrence [34]. There is an increased risk of heart failure with the use of Bezlotoxumab, therefore the balance of benefits and harm should be assessed before including this treatment in patients with pre-existing heart failure [35]. In patients with recurrent infections who were eligible for FMT and awaiting this therapy, the use of Bezlotoxumab resulted in some patients no longer needing FMT due to lack of recurrence [36]. The sustained cure rate after standard antibiotic therapy and Bezlotoxumab in patients with a single recurrence was higher than in the group of patients with at least two recurrences [35].

LMN-201. LMN-201 is a formulation containing three proteins similar in structure to antibodies against toxins produced by Clostridium difficile, and proteins that degrade the bacterial cell wall. It is thought to be more effective than single antibody therapy and may be a better alternative to current treatment in the future [37]. Phase 2 and 3 trials are currently investigating the potential of the formulation in recurrent infections.

SER-109. In 2022, a study was published [38] in which patients with at least three episodes of infection were treated with a SER-109 preparation consisting of purified Firmicutes bacterial spores or placebo, after completing a standard course of antibiotic therapy. The authors of this study highlighted the pathophysiology of recurrent infections and identified microbiota dysbiosis as the cause of the transformation of spore forms into toxigenic bacteria. They emphasize that antibiotic therapy is only effective against toxigenic bacteria, while spore forms persist due to microbiome perturbation. Patients treated with SER-109 were significantly less likely to have a recurrent infection within eight weeks (12% with SER-109, 40% with placebo). Firmicutes bacterial spores also increased secondary bile acids, which inhibit the maturation of Clostridium difficile spores. A Phase 3 study reported a significantly lower recurrence rate in all age groups and fewer recurrences, regardless of the number of episodes of infection, suggesting a positive effect of this formulation and further work on its widespread use in Clostridium difficile [39].

RBX2660. RBX2660 is an enema preparation in the form of a suspension. It consists of human donor faeces with diverse microbiota, Glycol and other ingredients. The beneficial effect on the microbiota offers hope of reducing the rate of recurrent infections. A Phase 3 trial confirmed the efficacy of the treatment after standard antibiotic therapy, a reduction in recurrences at six months, safety of use, and few adverse events [40].

CP101. CP101 is an oral formulation released at the site of infection. It contains a diverse composition of natural microbiota to restore the perturbed microbiota [41]. It has the potential to reduce the number of relapses. Phase 3 studies are ongoing.

NTCD-M3 spores. NTCD-M3 spores are non-toxic strains of Clostridium difficile that do not produce toxins because they lack the genes required for toxin production. In Phase 2 trials, NTCD-M3 administered after vancomycin therapy resulted in transient colonization of the intestinal tract, allowing the restoration of normal intestinal microflora without the presence of clinical signs of infection. This significantly protected the patient from recurrent infection [42, 43]. Phase 3 trials are currently underway to compare the efficacy of this therapy after Fidaxomicin administration.

Ribaxamase. Ribaxamase is an enzyme that breaks down beta-lactam antibiotics. When taken during intravenous beta-lactam antibiotic therapy, it helps to reduce the amount of antibiotics in the gastrointestinal tract that negatively affect the intestinal microflora. This helps to protect the patient from colonization by Clostridium difficile. Ribaxamase is released in the proximal part of the small intestine where it degrades the excreted antibiotics. It is noteworthy that ribaxamase does not reduce the efficacy of antibiotic treatment [44]. A phase 2b study confirmed a significant reduction in the incidence of Clostridium difficile after intravenous antibiotic therapy [45]. Further studies are underway to determine whether Ribaxamase will find its place in standard of care.

DAV132. DAV132 is a formulation that binds antibiotic residues in the colon without interfering with their absorption in the proximal small intestine. A study of co-administration of DAV132 with antibiotics has shown that it preserves the diversity of the microbiome with the standard bactericidal effect of the antibiotic [46]. Further studies of this formulation are ongoing.

Faecal microbiota transplantation (FMT). Faecal microbiota transplantation is a method that can be used in primary severe complicated infections resistant to antibiotic therapy. For recurrent infections, FMT is recommended for the second and subsequent recurrences of infection after initial antibiotic treatment with standard therapy.

Each time FMT therapy is considered for a patient, the risk of its use should be assessed by a multidisciplinary team [5]. FMT therapy restores the diversity of the intestinal microflora, protects the intestines from recolonisation and increases the synthesis of secondary acids, which are important in the pathophysiology of recurrent infections [47]. FMT can be administered in a variety of ways, including by gavage into the stomach or duodenum through colonoscopy, as a swallowable capsule, or as an enema [48].

The efficacy of FMT has been the subject of many studies, varying by route of administration, number of administrations or prior antibiotic therapy. FMT has been positively evaluated for the treatment of severe and severe complicated primary infections. In severe antibiotic-resistant infections, the response rate to FMT therapy has been shown to be as high as 91% [49]. The number of infusions for severe infections has also been shown to be important.

Many studies have been performed on the treatment of recurrent infections with FMT therapy, but only a few have had a control group using Vancomycin or Fidaxomicin and multiple therapeutic administrations. Cure rates after a single course of FMT in these trials ranged from 65% -95%, and 90% after multiple courses [50, 51]. The most common adverse effects of FMT therapy are flatulence, diarrhea, constipation, nausea or mild abdominal cramping. One of the most serious adverse effects of FMT therapy is the transmission of pathogens of unknown potential – both carcinogenic and infectious [52]. Therefore, it is very important to standardize the inclusion of stool donors in FMT therapy [53].

CONCLUSIONS

Recurrent Clostridium difficile infection remains a major clinical problem, with-one-in five initially infected patients still experiencing a recurrence. The recurrence of infection is mainly related to a dysbiosis of the intestinal microflora, which has led to metronidazole being currently recommended only when other standard antibiotics, such as Vancomycin or Fidaxomicin, are unavailable, due to its large effect on the entire microbiome. The very limited effect on the microflora has given Fidaxomicin an advantage over Vancomycin as a first-line treatment in patients with risk factors for relapse. For recurrent infections, the use of Bezlotoxumab, which is now the standard of care, is becoming more common. However, the use of new antibodies needs to be supported by their safety in terms of secondary antibody production. More and more immunotherapies are targeting not only toxins A and B, but also bacterial proteins. The use of faecal microbiota transplantation is already the norm for patients with severe antibiotic resistance and multiple relapses.

New antibiotics, such as Ridinilazole and Tigecycline may become alternative treatments, but more research is needed. Inhibitors, such as CRS3123, MGB-BP-3 or Ibezapolstat, and other formulations in development that act by modulating the microbiome are promising treatment options, especially in patients with recurrent infections.

Probiotics are increasingly being used to prevent recurrent infections in combination with standard treatment. Other compounds, such as SER-109, RBX2660 and CP101, may become the treatment of choice for recurrent infections in the near future due to their beneficial effects on dysbiosis and secondary bile acid metabolism. Further progress is being made with the use of NTCD-M3 non-toxigenic spores, which allow the restoration of normal microbiota by temporarily colonizing the intestines. Ribaxamase, on the other hand, protects the intestinal microflora by degrading antibiotics that are excreted through the gastrointestinal tract and allows a reduction in the relapse rate, but more research is needed focused on Clostridium difficile. Many new studies are emerging on both vaccines and bacteriophage therapy, but due to the breadth of these topics, they are beyond the scope of this article.

In summary, the latest treatments for recurrent infections focus primarily on the pathophysiological causes. This is the correct way to reduce recurrent infections in the future by favourably affecting the microbiota, reducing Clostridium difficile colonization, secondary bile acid synthesis, and directly targeting toxins A and B produced by Clostridium difficile strains. The current state-of-the-art formulations under investigation have the potential to change future standards of practice and revolutionize the treatment and prevention of Clostridium difficile.

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