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General review

Existing and investigational therapies for the treatment of *Clostridium difficile* infection: A focus on narrow spectrum, microbiota-sparing agents

Traitements actuels et expérimentaux dans la prise en charge des infections à Clostridium difficile : agents à spectre étroit épargnant le microbiome

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Abstract

Despite intense international attention and efforts to reduce its incidence, *Clostridium difficile* infection (CDI) remains a significant concern for patients, clinicians, and healthcare organizations. It is costly for payers and disabling for patients. Furthermore, recurrent CDI is particularly difficult to manage, resulting in excess mortality, hospital length of stay, and other healthcare resource use. A greater understanding of the role of the gut microbiome has emphasized the importance of this diverse community in providing colonization resistance against CDI. The introduction of fidaxomicin, which has limited effect on the microflora has improved clinical outcomes in relation to disease recurrence. There are a number of other new agents in development, which appear to have a narrow spectrum of activity whilst exerting minimal effect on the microflora. Whilst the role of these emerging agents in the treatment of CDI is presently unclear, they appear to be promising candidates.

Keywords: *Clostridium difficile*; Metronidazole; Vancomycin; Fidaxomicin; Cadazolid; Ridinilazole; CRS3123; LFF517

Résumé

Malgré l'attention internationale et les efforts entrepris pour réduire leur incidence, les infections à *Clostridium difficile* (ICD) restent une préoccupation majeure pour les patients, les médecins et les organismes de santé. Les ICD coûtent cher et sont invalidantes pour les patients. De plus, les ICD récurrentes sont particulièrement difficiles à traiter, entraînant une augmentation de la mortalité, de la durée du séjour hospitalier et du recours à d'autres ressources de soin. Une meilleure compréhension du rôle du microbiome intestinal a mis en évidence l'importance de cette communauté variée dans le développement d'une résistance à la colonisation contre les ICD. La mise sur le marché de la fidaxomicine, dont les effets sur la microflore sont limités, a permis d'améliorer les résultats cliniques relatifs à la récidive de l'infection. De nombreux autres agents sont actuellement en développement ; ces derniers semblent avoir un spectre étroit et leurs effets sur la microflore semblent être très limités. Bien que le rôle de ces nouveaux agents dans le traitement des ICD reste incertain, ils semblent tout de même prometteurs.

Mots clés : *Clostridium difficile* ; Métronidazole ; Vancomycine ; Fidaxomicine ; Cadazolide ; Ridinilazole ; CRS3123 ; LFF517

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1. Introduction

The incidence of *Clostridium difficile* infection (CDI) has risen significantly during the last 15 years, resulting in substantial morbidity, mortality, and economic burden. Recurrent CDI (rCDI) is especially challenging to prevent and manage, often requiring repeated and prolonged courses of treatment. Uniform consensus on how to effectively manage these patients is lacking. Novel therapeutic strategies are urgently needed to treat patients presenting with or at risk of rCDI.

"Dysbiosis" of the gut microflora and a failure for it to be reconstituted (usually caused by administration of antibiotics) is a significant risk factor for initial CDI and rCDI. Improved antimicrobial stewardship strategies may help to address this problem as well as use of anti-CDI agents that have minimal effect on the microflora, allowing it to recover rapidly. Fecal microbiota transplantation is increasingly being used to prevent further recurrence in patients who have had three or more episodes of infection. Although this approach is efficacious, long-term safety data is lacking and there is little consensus about optimal methods and procedures [1]. In this review current management strategies for CDI are explored together with novel and emerging therapies with a focus on narrow spectrum, microbiota-sparing antibiotics. Other treatment and prevention modalities including fecal microbiota transplantation and augmentation, non-toxigenic *C. difficile*, antitoxin antibodies (bezlotoxumab), beta-lactamase enzymes (ribaxamase) and toxin-binding agents are beyond the scope of this review.

2. Recurrent Clostridium difficile infection

The major underlying risk factor for CDI is an alteration in intestinal microbiota, mainly caused by the administration of antimicrobials. Virtually all classes of antimicrobials have been implicated in precipitating CDI. Persistence of spores that are able to germinate after completion of anti-CDI therapy, continuing suppression of protective intestinal bacteria, and failure to establish an adequate host immune response create the conditions that lead to rCDI.

Up to 25 % of patients treated with metronidazole or vancomycin will present with a recurrent episode within 30 days [2–4], and approximately 45–65 % of these will have a further recurrence [5–7].

Rates of recurrence appear to have increased over the past decades, potentially related to the spread of the epidemic BI/NAP1 027 strain.

With each recurrent episode comes an increased risk of serious complications including death. In one study rCDI was associated with a six-month mortality rate of 36 %, compared with 26 % in patients without recurrence [8].

A number of risk factors have been identified in patients at increased risk of rCDI: those aged 65 years and older [6,9], those taking proton pump inhibitors (PPIs) and other gastric acid suppressing agents [6], those taking concomitant antimicrobials [6,9], those with renal impairment [6], and those with inflammatory bowel disease [10].

3. Currently available agents to treat *Clostridium difficile* infection

In addition to general supportive measures including discontinuing the inciting antimicrobial(s) and fluid and electrolyte replacement, there are a limited number of anti-CDI agents currently available, each of which will be discussed.

An ideal drug for the treatment of CDI should have low systemic absorption, achieve high intraluminal concentrations, preserve the normal microflora, result in high clinical cure rate with low recurrence rate, have low risk for developing resistance, be well tolerated, and be low cost. Currently available agents are assessed against these ideal attributes in Table 1.

4. Metronidazole

Metronidazole is a nitroimidazole compound with broad-spectrum activity against anaerobic bacteria including *C. difficile*. However, due to the relatively poor pharmacokinetic properties of oral metronidazole, only low drug levels can be realistically achieved in the lumen of the colon [11]. Additionally, there are concerns over the emergence of reduced susceptibility [12] and at least one documented case of resistance to metronidazole [13].

As it is systemically absorbed and has a number of adverse effects such as nausea and vomiting, taste disturbance, peripheral neuropathy, and a disulfiram-like reaction with alcohol, its use is limited.

Several authors have reported relatively poor outcomes and treatment failures with metronidazole [14–16].

The concerns and disadvantages of this agent mean that metronidazole is usually used only for mild, uncomplicated CDI [17–20].

5. Vancomycin

Vancomycin is a glycopeptide, which exerts its effect by inhibition of bacterial cell wall synthesis. When administered orally it is not systemically absorbed.

In a study stratifying patients into mild or severe infection and randomizing to receive either metronidazole or vancomycin for 10 days, there was no difference in cure rates between the two drugs (90 % for metronidazole vs. 98 % for vancomycin) in the non-severe cohort. However, in the severe infection group the cure rates were 76 % for metronidazole and 97 % for vancomycin ($P = 0.02$) [2].

This finding has led to the recommendation to use vancomycin in patients presenting with severe infection in a number of international guidelines [17–20].

However, there is additional (and often overlooked) evidence from a large phase III multicenter randomized controlled trial of tolevamer, a toxin-binding agent, metronidazole and vancomycin, which showed vancomycin to be superior to metronidazole for clinical success (defined as resolution of diarrhea and absence of severe abdominal discomfort due to CDI for more than two consecutive days including Day 10) [21,22].

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