Review paper

Clostridioides difficile infection: a changing treatment paradigm

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Abstract

Clostridioides difficile infection (CDI) poses a persistent challenge in healthcare, with substantial morbidity and mortality implications. This comprehensive review explores current CDI management, emphasising guidelines from IDSA, SHEA, and ESCMID. Additionally, this study spotlights recent drug developments that have the potential to reshape CDI treatment paradigms. Within the current treatment landscape, fidaxomicin, vancomycin, bezlotoxumab, and faecal microbiota transplantation offer varied options, each with its unique strengths and limitations. Fidaxomicin, effective yet resource-constrained, presents a dilemma, with vancomycin emerging as a pragmatic alternative. Bezlotoxumab, though augmenting antibiotics, grapples with cost and safety concerns. Meanwhile, faecal microbiota transplantation, highly efficacious, confronts evolving safety considerations. The horizon of CDI treatment also features promising therapies such as SER-109 and Rebyota, epitomising the evolving paradigm. As CDI management advances, the critical role of standardised microbiome restoration therapies becomes evident, ensuring long-term safety and diversifying treatment strategies.

Introduction

Clostridioides difficile infection (CDI) is the most common healthcare-associated infection, causing significant morbidity and mortality [1]. In the United States (US), the Centers for Disease Control and Prevention (CDC) routinely conducts national surveillance of CDI, with most recent estimates of the national burden being 462,000 cases annually [2]. Consequently, the prevention of CDI has rightfully ascended to a position of paramount national importance [3].

The overall goal of managing CDI is two-fold: it aims to successfully treat the initial infection and prevent future recurrences, as the latter occurs in approximately 25% of those with an initial infection [4, 5]. Recent years have witnessed dynamic shifts in treatment guidelines, driven by advancements in therapeutic approaches and the emergence of new evidence related to CDI management [6–8]. As such, it is prudent to routinely evaluate the literature, to ensure ongoing alignment with the latest developments in CDI treatment. While prior reviews have examined the landscape of CDI treatment [9], this narrative review distinguishes itself by introducing contemporary treatment paradigms for CDI, incorporating recent revisions from nationally endorsed treatment guidelines and authoritative bodies such as the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA), while also casting a forward glance toward forthcoming innovations in CDI treatment and making a distinctive scholarly contribution to the field.

Methods

This narrative review employed a computer-assisted search of bibliographic databases including Google Scholar, PubMed, and Medline, using specific Boolean search terms like (((Clostridioides difficile infection) AND (recurrent)) AND (treatment)) AND (update). Inclusion criteria required studies to directly address CDI treatment without language restrictions, emphasising peer-reviewed journal articles, conference proceedings, and authoritative guidelines. Exclusion criteria excluded unrelated studies, those published before 1 January 2021,

non-research articles, studies with inaccessible full texts, duplicate publications, and non-peer-reviewed sources. The search results yielded 196 articles after the removal of duplicate studies. After titles and abstracts of search results were screened and non-related articles were excluded, full-text articles were assessed for eligibility. Additionally, a review of the reference list from relevant studies complemented other searches. Data extraction was performed using a standardised form, and multiple reviewers were involved to ensure robustness and minimise bias. A total of 22 articles have been included in this review.

Results

Clinical guideline recommendations

The leading guidelines for the management of CDI are provided by the IDS/SHEA as well as the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [6–8]. Notably, in 2021, the IDSA/SHEA released a focused update to their CDI management guidelines, revising their earlier recommendations from 2017 [7]. Concurrently, in October 2021, the ESCMID published an updated edition of their CDI treatment guidelines, building upon their prior guidance issued in 2014 [8]. Throughout the ensuing discussion, we delve into key insights gleaned from these recent guideline updates.

The current mainstays of therapy for CDI treatment include fidaxomicin, vancomycin, bezlotoxumab, and faecal microbiota transplantation (FMT). The IDSA/SHEA and ESCMID updated guidelines both designate fidaxomicin as the preferred choice for initial, non-severe CDI, as well as for the first recurrence. Subsequently, for recurrent cases, FMT is recommended by both guidelines. Additionally, bezlotoxumab is endorsed in these guidelines for its crucial role in preventing CDI recurrences [6–9].

Fidaxomicin and vancomycin

Fidaxomicin received approval from the US Food and Drug Administration (FDA) in 2011, marking a pivotal development in CDI treatment [10]. In the IDSA/SHEA guideline updates, a significant consideration is introduced regarding the recommendation of fidaxomicin over a standard course of vancomycin for initial CDI treatment – specifically, the choice of fidaxomicin hinges on resource availability [7]. The considerable cost associated with fidaxomicin has indeed posed a barrier to its widespread adoption [5, 11]. Consequently, the IDSA/SHEA guidelines deem vancomycin as an acceptable alternative to fidaxomicin for patients with an initial CDI [7].

Fidaxomicin's designation as first-line therapy is geared toward attaining a sustained clinical response, characterised by the successful resolution of initial CDI symptoms and the prevention of recurrence [4, 7]. Furthermore, for patients grappling with recurrent CDI, the IDSA/SHEA guidelines advocate fidaxomicin use, either as a standard or extended-pulsed regimen, in preference to a standard course of vancomycin [7].

Bezlotoxumab

In 2016, the FDA granted approval to bezlotoxumab, marking a milestone as the first monoclonal antibody introduced into the CDI treatment repertoire, specifically designed to prevent CDI recurrence [10]. Bezlotoxumab's mechanism of action centres on targeting toxin B, a product of *C. difficile* [4]. It is recommended as an adjunct to standard-of-care antibiotics rather than as a standalone treatment, particularly for patients who have experienced a CDI recurrence within the past 6 months [7]. Administration of bezlotoxumab involves intravenous infusion, and akin to fidaxomicin, it is associated with substantial costs, which has limited its widespread use. Furthermore, the FDA advises caution in administering bezlotoxumab, emphasising that it should be considered only when the benefits outweigh the risks in patients with a history of congestive heart failure [7]. Additionally, there remains limited knowledge regarding the efficacy of fidaxomicin in combination with bezlotoxumab for preventing recurrent CDI [5].

Faecal microbiota transplantation

The therapeutic approach of FMT involves introducing processed stool from a healthy donor with diverse intestinal microbiota into the intestinal tract of individuals with recurrent CDI to restore their dysbiotic microbiota [12, 13]. A systematic review and meta-analysis found that repeat FMT and single FMT achieved sustained resolution in 91% and 84% of individuals, respectively, defined as either clinical resolution of diarrhoea or persistent diarrhoea with a negative *C. difficile* test [14]. Furthermore, the review highlighted that administration via lower gastrointestinal endoscopy outperformed other delivery methods (e.g. upper gastrointestinal, enema, capsules) in terms of sustained resolution [14]. However, it is important to note that despite the high rates of effectiveness, FMT failure can still occur. Another meta-analysis reported FMT failure in 16.3% of patients with recurrent or refractory CDI, typically manifesting within 2 to 3 months [15].

FMT is generally well-tolerated, with serious adverse events being rare. In a comprehensive review of 5099 patients across 61 studies, serious adverse events occurred in less than 1% of cases [16]. However, concerns

about potential pathogen transmission via FMT have prompted safety alerts. These alerts have highlighted risks like monkeypox virus transmission [17], infections from enteropathogenic *Escherichia coli* and Shigatoxin-producing *Escherichia coli* [18], SARS-CoV-2 transmission [19], and infections from multi-drug resistant organisms (MDROs) [20]. To address these concerns, additional donor stool screening and informed consent updates have been implemented. In a study involving 66 individuals with donor screening for MDROs and quarantine measures, 19 cases of MDROs were detected, confirming their effectiveness in preventing MDROs transmission via FMT [21].

Despite evolving strategies for recurrent CDI management, significant research gaps persist. Long-term safety following FMT is a crucial area of study [13]. Furthermore, healthcare providers lack knowledge about FMT, necessitating ongoing education [22]. FMT is also being investigated for treating non-communicable conditions like obesity, diabetes, neuropsychiatric disorders, and more [23], suggesting its expanding use. In summary, FMT integration into CDI management has transformed treatment and spurred innovation in live bacterial products [13].

Novel treatment strategies

Recent advancements in recurring CDI treatment have spurred the exploration of new therapies, given the uncertainty about the long-term safety of FMT. Standardisation, including donor screening, manufacturing, and consistent product ingredients, is crucial [24]. The FDA recently approved Rebyota, the first faecal microbiota product [25]. It is set to be available in Q1 2023, specifically for preventing recurrent CDI in adults after antibiotic treatment [25]. It is administered rectally with a provided gravity flow set [25]. Several capsule-based therapies (SER-109, CP101, RBX7455, VE303) are also in clinical trials for recurrent CDI management.

SER-109, an oral microbiome therapy composed of purified Firmicutes spores, has demonstrated positive safety and efficacy results in phase 3 clinical trials [26]. In this trial, 182 patients with 3 or more episodes of CDI were enrolled. The occurrence of CDI was 12% in the SER-109 arm and 40% in the placebo arm 8 weeks after treatment [26]. The safety profile of SER-109 was similar to that of a placebo, although its long-term safety needs to be further investigated.

CP101 is an orally administered microbiome therapeutic with purified bacterial spores, which aims to restore a robust gut microbiota that can outcompete CDI [24]. Phase 2 trial data indicate an 80.3% sustained clinical cure rate at 8 and at 24 weeks, with a consistent safety profile [27]. In a post-hoc analysis, an aggregated 88.2% sustained clinical cure rate was observed at 8 weeks post the last dose [27]. However, a phase 3 trial of CP101 was discontinued due to funding challenges, slow enrolment, and intellectual property issues [27].

RBX7455 represents a single-dose oral microbiome therapeutic consisting of a consortium of bacterial strains isolated from the microbiota of healthy human donors. This innovative therapy seeks to reinstate a diverse and resilient microbiota capable of resisting *C. difficile* colonisation and infection. Promisingly, phase 1 clinical trials, incorporating 3 distinct dosing regimens, have yielded favourable safety outcomes, with participants remaining free from recurrence during an 8-week evaluation period [28].

VE303 is an orally administered microbiome therapeutic also sourced from healthy human donors with the aim of restoring protective microbiota against CDI. Phase 2 results show that a high dose of VE303 significantly decreased CDI recurrence rates (13.8%) compared with placebo (45.5%) [29].

These capsule-based therapies have the potential to provide a safe and effective alternative to FMT for the treatment of recurrent CDI. Further clinical trials are needed to confirm their safety and efficacy. The standardisation of microbiome therapies, including donor screening, manufacturing, and ensuring consistent ingredients, remains critical for advancing these treatments toward regulatory approval and widespread clinical use.

Limitations

This narrative review has limitations, including the absence of a formal meta-analysis, which precluded quantitative synthesis of evidence. Generalisability may be limited as the findings are based on available literature and may not universally apply across diverse healthcare settings and populations. The focus on studies published from 1 January 2021 may not fully capture the evaluation of recently endorsed guidelines, given that emerging evidence continues to evolve. Additionally, a formal quality assessment of included studies was not conducted, which could have provided insights into methodological rigor and biases. These limitations underscore the need for ongoing research to refine the understanding of CDI treatment.

Conclusions

CDI management has evolved with new treatments and updated guidelines, improving patient outcomes through higher cure rates and reduced recurrence. Greater focus on prevention strategies and appropriate antibiotic use underscores the need for ongoing research in this evolving field. Future research should

evaluate guideline effectiveness, considering cultural and geographic variations. Assessing real-world impacts and improving patient outcomes will refine CDI management strategies across diverse healthcare settings. This ongoing research is essential for better understanding and effectively addressing CDI challenges.

Conflict of interest

The authors declare no conflict of interest.

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