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Therapeutics involved in managing initial and recurrent Clostridium difficile infection, an updated literature review

Updated review on C difficile

Abstract

Clostridium difficile infection (CDI) infections have been increasing due to the effect of recurrent hospitalizations. The use of antibiotics has been shown to alter the gut microbiome and lead to CDIs. The treatment is limited to three major antibiotics, however, the incidence of recurrent CDIs has been increasing and drug resistance is a major concern. This aspect is a growing concern in modern medicine especially in the elderly population, critical care patients, immunocompromised individuals who are at high risk of developing CDIs. *C difficile* can lead to various complications including septic shock and fulminant colitis that could prove to be lethal in these patients. Newer modalities of treatment have been developed including bezlotoxumab, a monoclonal antibody and fecal microbiota transplant(FMT). There have been studies showing asymptomatic carriers and drug resistance posing a major threat to the healthcare system. Newer treatment options are being studied to treat and prevent CDIs. This review will provide an insight into the current treatment modalities,prevention and newer modalities of treatment and challenges faced in the treatment of CDIs.

Key Words: C difficile; antibiotics; vancomycin; fidaxomicin; prevention; bezlotoxumab; FMT

Core Tip: Clostridium difficile infections(CDIs) are one of the most common hospital acquired infections and are caused by use of antibiotics. The treatment is limited to 3 antibiotics currently. There has been a rise in recurrent CDIs. Our review aims to provide an overview of current testing and treatment modalities, prevention, new treatment options,challenges and current studies in the aspect of CDIs, which has become a growing concern to global health.

INTRODUCTION

Clostridium difficile infection (CDI) remains a significant healthcare challenge globally, characterized by its substantial morbidity, mortality, and propensity for recurrence. Managing both initial and recurrent CDI necessitates a multifaceted approach, encompassing prevention, diagnosis, and treatment strategies. In this comprehensive review, we aim to provide an updated synthesis of the literature focusing on the therapeutics involved in managing CDI, with particular emphasis on recurrent infections.

As highlighted by Song and Kim (2019), recurrent CDI poses a formidable clinical challenge, requiring a nuanced understanding of risk factors, treatment modalities, and preventative measures[1]. Madoff *et al*. (2020) further underscore the importance of preventative strategies through their systematic review of randomized controlled trials, offering insights into interventions aimed at reducing CDI recurrence rates[2]. The advent of monoclonal antibodies, such as bezlotoxumab, has introduced new avenues for preventing recurrent CDI in high-risk patient populations[3]. Moreover, microbiologic factors elucidated by Chilton *et al*. (2018) shed light on disease persistence dynamics, informing targeted therapeutic approaches[4].

Fecal microbiota transplantation (FMT) has emerged as a promising intervention in recurrent CDI management. Rokkas *et al*. (2019) conducted a network meta-analysis, demonstrating the efficacy of FMT in reducing CDI recurrence rates[5]. Conversely, Knudsen *et al*. (2023) systematically reviewed the clinical efficacy and safety of vancomycin, a cornerstone antibiotic in CDI management, particularly in recurrent

scenarios[6]. The impact of FMT on patient quality of life is explored by Hammeken *et al*. (2022), emphasizing the multifaceted nature of CDI management[7].

The emergence of novel therapeutic modalities continues to shape the landscape of CDI management. Fein *et al*. (2022) investigated the use of bezlotoxumab therapy in an ulcerative colitis patient with recurrent CDI, highlighting its potential in unique clinical scenarios[8]. Innovative microbiome therapeutics, as discussed by Bloom and Young (2023), represent a paradigm shift in CDI management, showcasing the evolving landscape of therapeutic innovation[9].

Furthermore, Sandhu and Chopra (2021) provide insights into the safety and pitfalls of FMT, offering valuable considerations for its clinical implementation[10]. Microbiologic factors affecting CDI recurrence are further explored by Okafor *et al*. (2023), emphasizing the multifaceted interplay between microbial ecology and disease dynamics[11].

By synthesizing diverse perspectives and empirical evidence, this review aims to inform clinical decision-making and advance patient care in the realm of CDI management.

RISK FACTORS

Clostridium difficile (C. diff) infection poses a significant threat to healthcare settings worldwide, with a complex interplay of risk factors contributing to its prevalence.[12] Understanding these factors is crucial for effective prevention and management strategies. C diff infection can be divided into three types based off on epidemiology: Community-onset healthcare facility–associated (CO-HCFA), community-associated (CA) CDI and healthcare facility–onset (HCFO) provides a framework for understanding its transmission and guiding intervention strategies[12,13].

Clostridium difficile infection represents a predominant cause of hospital-acquired antibiotic-associated diarrhea, leading to a range of conditions marked by significant recurrence, morbidity, and mortality rates[14]. The exact mechanism by which the gut microbiota confers colonization resistance remains unclear, but it mainly involves the

release of antimicrobial substances, gut barrier integrity maintenance, and utilization of bacteriophages[15]. Broad-spectrum antibiotics that include penicillins, cephalosporins and Clindamycin are very well known to cause C. diff infections more often than the other antibiotics[16]. A 2022 meta-analysis of studies on C. diff infection risk factors found that prior antibiotic exposure significantly increased the likelihood of developing CDI (OR 1.93) compared to those without such exposure. The meta-analysis also showed that the risk for CID was greatest with clindamycin and lower with fluoroquinolones.[17].

Gastric acid inhibitors like proton pump inhibitors (PPIs) and H2 receptor antagonists are other causes that have been linked to a higher risk of causing CDI. However, some studies have not found a correlation between these two factors[18], thereby casting doubt on this association. Another dimension of the research focused on pediatric populations. A 2018 study analyzing risk factors for Clostridium difficile-associated diarrhea in hospitalized children older than one year found that a hospital stay of 10 days or more before the onset of diarrhea was an independent risk factor for CDAD in children with antibiotic-associated diarrhea[19].

In 2022, a study aimed to identify risk factors for the first recurrence of C. diff infection, given the high incidence of recurrence in these infections. This retrospective analysis examined patient backgrounds and treatment-related factors, employing both single and multiple logistic regression analyses. The study included 134 participants, with recurrent CDI observed in 23.9% of the patients. The average age of the patients was 78 years. The findings suggested that the use of prophylactic probiotics and nasogastric tube placement might be risk factors for recurrent CDI[20].

Pathophysiology of C. difficile

Clostridium difficile (C. difficile) is a gram-positive, anaerobic bacillus, that spreads *via* the oral-fecal route and ingestion of spores. These spores are resistant and tolerant to the acidic environment of the intestine. C. difficile is known to colonize the large intestine of humans.[21]. The normal intestinal microbiota plays a crucial role in human health by providing various advantages, such as the synthesis of essential vitamins,

metabolic functions, prevention of colonization by pathogens, and stimulation of the immune response. Various antibiotics are known to play a significant role in the disruption of the intestinal microbiota such as clindamycin, fluoroquinolones, and cephalosporins. The disruption of normal colonic bacteria results in an environment that has reduced competition for resources and heightened bacterial cell lysis, thereby releasing consumable carbon sources. Within this altered environment, bacterial dynamics can become intricate[22].

The pathogen is able to capitalize on a wide range of nutrients available to it in this dysbiotic environment including carbohydrates, amino acids, and ethanolamine, allowing for its proliferation[23]. Characteristic symptoms of C. difficile infection include diarrhea and colitis, attributed to the action of clostridial glycosylation exotoxins, namely toxin A (TcdA) and toxin B (TcdB). Toxin A is an enterotoxin that has a carbohydrate receptor binding site, facilitating the intracellular transport of both toxins A and B[24]. Once intracellular, these toxins deactivate pathways mediated by the Rho family of proteins, leading to damage of colonocytes, disruption of intercellular tight junctions, and subsequent colitis. Furthermore, toxin A directly activates neutrophils, while both toxin A and toxin B contribute to neutrophil chemotaxis[25].

In healthy adults with robust immune responses, the colonization often leads to asymptomatic carriers of the pathogen. Elderly individuals have an increased vulnerability due to weakened immune responses and changes in gut microbiota. Additionally, factors such as the use of proton-pump inhibitors, chemotherapy, or gastrointestinal surgery can further increase susceptibility. Moreover, the administration of broad-spectrum antibiotics significantly alters the microflora diversity and bile composition increasing the risk of C. difficile[26].

The host response to the pathogen involves the production of toxin A and B antibodies, interleukin-8, and activated innate lymphoid cells. Activated lymphoid cells are specifically involved in the release of IFNγ and interleukin-22. Individuals with polymorphisms of the interleukin-8 gene have an increased susceptibility to C. difficile.

The severity of the disease also has an inverse correlation with the levels of IgG and IgA an individual has[27,28].

C. difficile is associated with systemic effects and complications including toxic megacolon, perforation, and sepsis. The development of toxic megacolon is believed to be caused by inflammation through the muscularis propria as well as the release of chemical mediators leading to an altered colon response and impaired smooth muscle contraction. It is clinically manifested as bloody diarrhea, tachycardia, and fever. Perforation is the leading cause of mortality in patients with C. difficile often presenting with abdominal distention, tenderness, and hemodynamic instability[29,30].

The following image displays the production of toxins A and B and the colonization of C. difficile causing disruption of the epithelial barrier and an inflammatory response leading to neutrophil recruitment and the development of a pseudomembrane[31].

Fig 1- production of toxins A and B and the colonization of C. difficile causing disruption of the epithelial barrier and an inflammatory response leading to neutrophil recruitment and the development of a pseudomembrane

Complications of C. difficile infection

The primary complication of Clostridium difficile infection (CDI) is incomplete recovery and recurrent infection, occurring in approximately 20 to 30% of cases after an initial infection and escalating up to 60% after three successive infections[32]. Extraintestinal infections caused by Clostridium difficile include bacteremic infections, abdominal infections (both with and without prior surgery), perianal abscesses, wound infections, and even colonization in urinary catheters. These infections, occurring primarily in hospitalized patients with substantial comorbidities, often involve polymicrobial colonization and may lead to severe outcomes, with mortality rates correlating with the severity of underlying diseases[33].

Toxic megacolon (TM) is one of the complications of CDI. The prevalence of TM associated with CDI is increasing with age, with an estimated incidence of 0.4–3% before 1990 and 4.3% after 1990. Patients with fulminant infection may require surgical intervention, with colonic perforation being a significant predictor of mortality[34].

Cases of ileal perforation secondary to Clostridium difficile enteritis have been reported, underscoring a rare yet potentially severe complication[35].

One of the most feared complications arising from Clostridium difficile-associated colitis (CDAC) is the progression to sepsis, which can escalate to septic shock, characterized by a profound state of circulatory failure and organ dysfunction[36]. An observational study by Mihăilă RG *et al*. revealed that patients with Clostridium difficile infection (CDI) exhibit a distinct pattern of thrombin generation (TG), characterized by higher mean velocity index and peak thrombin levels compared to healthy controls. These findings suggest an increased thrombotic risk in CDI patients, independent of septic shock, highlighting the potential association between CDI and venous thromboembolism[37]. Patients testing positive for CDI had a significantly higher risk of deep vein thrombosis (DVT) compared to CDI-negative patients, with an odds ratio (OR) of 3.23 (95%CI) compared to 1.95 (95%CI), suggesting that CDI positivity doubled the risk of DVT regardless of other factors[38]. Another case report by Mastroianni *et al*. documented a rare complication of Clostridium difficile infection, resulting in upper mesenteric artery thrombosis[39].

Reactive arthritis (ReA) associated with Clostridium difficile infection (CDI) is rare but has been reported in literature. Diagnostic criteria for ReA-CDI include evidence of synovitis during or immediately after colitis, presence of a toxigenic C. difficile strain in stool samples, and absence of other causes of colitis and arthritis. ReA-CDI tends to occur more frequently in younger patients with HLA B27-positive genotype[40]. Appendicitis occurring during CDI is exceptionally rare, with only three cases reported in the literature up to 2007. However, the authors speculate that this complication might be considerably underdiagnosed, as many cases could have been successfully managed conservatively without histological confirmation[41].

Diagnosis of C. difficile

Clostridium difficile infection (CDI) presents a diagnostic challenge due to varying clinical presentations and the absence of a singular definitive test[42]. Consequently, clinical guidelines emphasize a multi-step approach to accurately diagnose this

prevalent nosocomial infection[43]. The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) recommend testing patients with "unexplained and new-onset" diarrhea, defined as three or more unformed stools in 24 hours[44]. However, relying solely on this criterion may overlook true infections. Therefore, a comprehensive evaluation is necessary, particularly considering CDI's diverse clinical manifestations.

Diagnosing CDI primarily involves stool examination for the presence of toxins or toxigenic C. difficile bacillus[45]. While various techniques exist, polymerase chain reaction (PCR) has emerged as a sensitive and specific method, especially when integrated into a multi-step algorithm[46]. This approach, recommended by the IDSA, typically begins with a sensitive test such as glutamate dehydrogenase (GDH) enzyme immune assay (EIA) or NAAT, followed by a specific test for toxin confirmation[47]. NAAT may be used to arbitrate specimens with discrepant results, ensuring accurate diagnosis[48].

Although culture remains the "gold standard" for CDI diagnosis, its practicality in routine clinical settings is limited[42]. Therefore, a combination of molecular and immunoassay methods is preferred. However, overreliance on molecular tests may lead to overdiagnosis and unnecessary treatment, as demonstrated by studies indicating a discrepancy between PCR positivity and toxin detection. Notably, patients testing positive for C. difficile by PCR but negative for toxins experienced milder disease courses, suggesting potential overestimation of CDI burden with molecular testing alone[49,50].

Diagnostic uncertainty may warrant additional investigations, such as lower gastrointestinal endoscopy, especially in cases of fulminant colitis or alternative diagnoses[51]. However, repeat testing within seven days or testing asymptomatic patients is discouraged due to limited clinical utility and potential for false positives[48].

Ultimately, the decision on diagnostic testing for CDI involves collaboration between laboratory professionals and clinical staff. While laboratory testing aids diagnosis,

clinical judgment remains paramount, particularly in patients with significant risk factors or typical clinical presentations. Therefore, a balanced approach integrating clinical assessment with appropriate laboratory testing is essential for accurate CDI diagnosis and optimal patient management[42].

Diagnosis of recurrent C. difficile

Recurrent Clostridium difficile infection (rCDI) is characterized by the reappearance of symptoms of CDI within a relatively brief period after the completion of treatment. Although most cases of rCDI can be managed by discontinuing antibiotics and providing additional treatment, about 25% of patients experience a recurrence within 30 days of treatment cessation[52]. First-line therapy often involves vancomycin, while fidaxomicin is recommended for patients at high risk for recurrence[53]. Current treatment guidelines for rCDI recommend the same regimen used in the initial episode[54]. Clinical evaluation is pivotal in the diagnostic process, involving a comprehensive review of the patient's medical history, prior CDI treatments, and recurrence risk factors.

CDI diagnosis is determined by diarrhea and laboratory confirmation of C. difficile toxins present in stool or toxigenic C. difficile by nucleic acid amplification testing[55,1]. Importantly, stool testing is a diagnostic approach in CDI that focuses on the detection of C. difficile toxins. Stool tests are typically conducted using enzyme immunoassays (EIA) or polymerase chain reaction (PCR) assays, with PCR offering higher sensitivity and specificity compared to EIA[56,57]. Multiple stool samples collected over time may be necessary to confirm the presence of toxins and differentiate between relapse and reinfection.

In cases where the diagnosis is unclear or when patients present with atypical symptoms, further diagnostic modalities such as colonoscopy or imaging studies may be warranted. Colonoscopy allows for direct visualization of the colon and the collection of tissue samples for analysis, aiding in confirming the presence of active infection and ruling out other potential causes of symptoms[58,59]. Imaging studies such as computed tomography (CT) scans may also be useful in assessing the extent of

infection and identifying complications such as colitis or pseudomembranous colitis[60].

Stool antigen testing is not routinely recommended for the diagnosis of rCDI, as it may detect non-toxigenic strains and does not differentiate between active infection and asymptomatic carriage[61]. Instead, the diagnosis is mainly made by counting the number of diarrhea episodes, with a recurrence typically defined as the reappearance of symptoms within 8 weeks of completing treatment for a previous episode[62].

In the event of more than one recurrence of CDI, a thorough evaluation including a review of the patient's medical history, previous CDI treatments, and recurrence risk factors, is crucial to differentiate between relapse and reinfection. Distinguishing between relapse, caused by the same strain of C. difficile, and reinfection, caused by a new strain, may require additional testing, such as molecular typing of C. difficile isolates[63].

Treatment of initial C. difficile infection

C. diff infection represents a significant healthcare burden globally, and its management poses considerable challenges due to the rising incidence of recurrent infections, the emergence of hypervirulent strains, and increasing antibiotic resistance[64]. Effective management strategies for both initial and recurrent *C. diff* infection necessitate a nuanced understanding of the diverse therapeutic options available[65]. This section reviews the treatment modalities employed in managing initial *C. diff* infection, encompassing conventional antibiotic therapy, adjunctive agents, and emerging therapeutic approaches.

The cornerstone of treatment for initial *C. diff* infection involves antimicrobial therapy aimed at targeting the pathogenic organism, primarily with antibiotics exhibiting activity against *C. diff* [66, 67]. Historically, metronidazole and oral vancomycin have been the mainstays of therapy for mild to moderate and severe *C. diff* infection, respectively[68]. Metronidazole, a nitroimidazole derivative, inhibits DNA synthesis in susceptible organisms, including *C. diff*, and has been recommended as the first-line therapy for initial episodes of *C. diff* infection[69]. However, concerns regarding

reduced efficacy and higher rates of recurrence have led to a shift in treatment paradigms towards oral vancomycin, a glycopeptide antibiotic with potent activity against *C. diff* [70, 71]. Current guidelines recommend oral vancomycin as the preferred agent for severe *C. diff* infection, initial episodes in patients at high risk of complications, or those who fail to respond to metronidazole[70-72].

In recent years, fidaxomicin, a narrow-spectrum macrocyclic antibiotic, has emerged as a promising alternative for the treatment of *C. diff* infection[73]. Fidaxomicin exerts bactericidal activity against *C. diff* while preserving the gut microbiota due to its limited systemic absorption and high fecal concentrations[74]. Clinical trials have demonstrated non-inferiority of fidaxomicin compared to vancomycin in achieving clinical cure, with significantly lower rates of recurrence[75]. Consequently, fidaxomicin is recommended as a first-line therapy for initial *C. diff* infection in certain patient populations, particularly those at high risk of recurrence or with documented or suspected hypervirulent strains[76].

Adjunctive therapies play a crucial role in augmenting the efficacy of antimicrobial agents and mitigating the inflammatory response associated with *C. diff* infection. Among these, probiotics have garnered attention for their potential to restore microbial balance and suppress *C. diff* colonization[77]. However, evidence supporting the efficacy of probiotics in preventing *C. diff* infection recurrence remains inconclusive, and further research is warranted to delineate their role in clinical practice. Additionally, fecal microbiota transplantation (FMT) has emerged as a highly effective therapeutic option for recurrent *C. diff* infection, involving the transfer of fecal material from healthy donors to restore microbial diversity and enhance colonization resistance against *C. diff*[78, 79].

Despite advances in therapeutic strategies, the management of initial *C. diff* infection remains challenging, necessitating a multifaceted approach tailored to individual patient characteristics and disease severity. Ongoing research aims to elucidate the optimal treatment regimens, refine adjunctive therapies, and explore novel therapeutic

targets to improve clinical outcomes and reduce the burden of *C. diff* infection on healthcare systems.

Treatment of Recurrent C. difficile

Recurrent *C. diff* infection (rCDI) is described as new CDI within 8 weeks of the previous occurrence, and can be from reinfection of the same strain, or by a new strain. It is estimated that 15-30% of individuals treated for CDI with antibiotics experience rCDI, and this value increases with subsequent occurrences[1]. Given this high instance of recurrence, it is important to explore the options for treatment, and how they differ from an initial infection. Restoring the balance of the gut microbiome is an avenue that many studies have explored for the treatment of rCDI, with fecal microbiota transplantation and oral microbiome therapeutics being at the forefront[80,81].

Fecal microbiota transplantation (FMT) involves the transfer of donor fecal material into the recipient's gastrointestinal tract to restore the gut microbiome[82]. Different routes exist for the transplantation, including nasogastric tubes, colonoscopies, and enemas. All of these options pose their own set of risks, and require careful exploration of the patient's individual requirements. There is also extensive donor criteria that must be met, including stool testing for common GI pathogens[83].

The Infectious Diseases Society of America has created guidelines that shape the treatment modalities for rCDI depending on the number of recurrences a patient has had. As of 2017, in the primary recurrence, vancomycin or fidaxomicin are the first line treatment options. On secondary or further recurrences, vancomycin + /- rifampin and fidaxomicin are still the antibiotic options, while FMT is used for individuals with three or more recurrences and have failed antibiotic therapy[84]. A study published by the New England Journal of Medicine indicated that individuals who received FMT, as compared to vancomycin, had better treatment outcomes, especially those individuals with multiple recurrences[85].

In addition to FMT, many studies are aimed at evaluating the efficacy of SER-109, an oral microbiome therapeutic that is composed of firmicutes spores that are hypothesized to compete with *C. difficile* for nutrients, influence bile-acid profiles to

limit the recolonization of *C. diff*, or both[85]. A randomized clinical trial performed to determine the efficacy of SER-109 following the appropriate antibiotic regimen concluded that there were significantly less individuals in the SER-109 trial group that had rCDIs as compared to the placebo group at weeks 4, 8, 12, and 24 of the study[85].

Prophylactic treatment modalities have also been studied and shown to prevent recurrence of CDI. Bezlotoxumab is a human monoclonal antibody to the *C. diff* toxin B, and has been FDA approved for the prevention of rCDI. Use of bezlotoxumab has been shown to be an effective prophylaxis agent while also decreasing hospital readmission, and increasing quality of life in those with rCDI[86].

Episode

Treatment Modality

First recurrence

Vancomycin 125 mg orally 4 times a day for 10 days or

Fidaxomicin 200 mg orally 2 times a day for 10 days

Adjunctive therapy: bezlotoxumab 10 mg/kg IV one time dose

Second recurrence

Tapered or pulsed vancomycin regimen or

Vancomycin 125 mg orally 4 times a day for 10 days, then rifaximin 400 mg three times daily for 20 days or

Fidaxomicin 200 mg orally 2 times a day for 10 days

Adjunctive therapy: bezlotoxumab 10 mg/kg IV one time dose

Third or more recurrence

Fecal microbiota transplant

Adjunctive therapy: bezlotoxumab 10 mg/kg IV one time dose

Table 1: Treatment of recurrent *C. diff* infection in adults[87].

Bezlotoxumab

Bezlotoxumab(BEZ) is a humanized monoclonal antibody immunoglobulinG1(IgG1) that binds to *C difficile* toxin B, neutralizes the toxin and prevents damage to colonic

cells. Currently bezlotoxumab is approved for the treatment of recurrent *C difficile* infections in adults and is available in 1000 mg/40 mL vials. Reconstituted vials are diluted with 0.9% sodium chloride or 5% dextrose to reach a concentration between 1 to 10 mg/mL. The dose is administered according to the patient's body weight with a single dose at 10 mg/kg over 60 minutes up to treatment day 14[88,89].

The hallmark trials that brought BEZ to the market were the MODIFYI/II trials which were carried out in 30 countries over 300 sites consisting of over 2000 patients. Patients who received BEZ had a lower rate of CDI recurrence compared to the placebo received standard of care antibiotics after follow-up in 12 weeks. BEZ also was found to be beneficial compared to the placebo group with minimal side effects, with the number needed to treat(NNT) being 10[90].In the 12 month follow up of the MODIFY II trial conducted by Goldstein *et al.*, the patients who received BEZ were followed after the 12 weeks, for 9 more months, the patients who received BEZ did not have CDIs in 12 months[91].

In a recent systematic review, Bezlotoxumab has shown to be effective in all the studies in the prevention of CDIs[92]. A 2021 retrospective study carried out by Mody *et.al* showed BEZ was proven to reduce CDIs in patient populations with comorbidities including those with history of severe CDIs, age > 65 and patients who are immunocompromised[93].BEZ has shown to have a good safety profile with the side effects being mild to moderate infusion reactions with rare cases of heart failure exacerbation in patients already diagnosed with the same[94].Guidelines now recommend using BEZ for the prevention of CDI, including patients with history of multiple CDIs, recurrent CDIs and multiple comorbidities,marking a significant impact in treatment strategies[95].

Bezlotoxumab (BEZ) faces significant challenges, including its lack of cost-effectiveness and the potential for exacerbating congestive heart failure (CHF) in patients already diagnosed with the condition, as indicated by some studies[94,96]

Fecal Microbiota Transplantation(FMT)

Fecal microbiota transplantation (FMT) has emerged as an effective treatment for recurrent Clostridium difficile infection (CDI). This procedure involves transplanting fecal bacteria from a healthy donor to restore the recipient's gut microbiota, which helps in suppressing C. difficile by mechanisms such as inhibition of spore germination and vegetative growth, competition for nutrients, and activation of colonization resistance[97,98]

FMT is primarily indicated for patients with recurrent CDI who have failed standard antibiotic treatments. It is generally considered for patients with at least two episodes of CDIs who do not respond to antibiotics or experience frequent recurrences.[99]

Recent studies have confirmed that FMT is highly effective for treating recurrent CDI, with success rates exceeding 80% in several trials. A systematic review and meta-analysis by Baunwall *et al*. (2021) demonstrated that FMT significantly improves clinical outcomes in recurrent CDI, with a higher success rate compared to standard antibiotic therapy[100].Research has elucidated the mechanisms through which FMT exerts its effects. Khoruts and Sadowsky (2022) reviewed the role of microbiota restoration in preventing CDI recurrence, highlighting how FMT reintroduces a diverse microbial community that competes with C. difficile and restores gut homeostasis[98].A study by Urbonas *et al*. (2023) provided long-term follow-up data showing that the benefits of FMT in CDI persist beyond one year, with sustained resolution of symptoms and reduced recurrence rates[101]Studies have shown that the interplay between the microbiota of the donor and the recipient plays an important role in the efficacy of FMT[102]. This research aims to optimize patient selection and improve treatment efficacy.

Studies have shown that FMT has been proven to be beneficial in the treatment of recurrent CDIs in inflammatory bowel disease(IBD), which not only decrease the probability of CDIs but also improves symptoms of IBD[103].New approaches to FMT, including alternative delivery methods and standardized protocols, are being explored. A study examined innovative techniques to enhance the efficacy and safety of FMT, such as encapsulated microbiota and refined donor screening processes[104].FMT is

generally safe, however, there are risks of transmission of ESBL and Shiga toxin producing E Coli (STEC). These pathogens were transmitted from asymptomatic donors who were carriers to immunocompetent as well as immunocompromised individuals, which proved to be fatal. An Enzyme immunoassay (EIA) was recommended for symptomatic donors, but the utility of EIA in asymptomatic carries is still unclear[105].

Prevention of C Difficile

Prevention of *C difficile* can be categorized into prevention of the spread of *C difficile* from health care providers, prevention of spread from the environment, and risk reduction once the patient is exposed to *C difficile*[106]. Prevention of *C difficile* requires numerous approaches simultaneously, as it has not been found that a single approach alone is effective in prevention[107]

Contact precautions and single rooms are recommended for patients with *C difficile*, with moderate evidence for the use of gloves[106]. The use of handwashing with soap and water, as opposed to alcohol-based hand sanitizers followed by glove usage is currently recommended for healthcare workers when treating patients with *C difficile* [108]. Although hand washing with soap and water does not kill *C difficile* it does remove the *C difficile* spores from the hands of the health care workers[109].

Another recommendation with moderate quality of evidence includes limiting antibiotic therapy to only when deemed necessary. Additionally, implementing an antimicrobial stewardship program has been shown to reduce the risk of *C difficile* up to 50%[106]. Use of any antibiotic increases the risk of *C difficile*, but specifically broad-spectrum cephalosporins and clindamycin are seen to increase the risk of infection[108]. The gut microbiome provides a defense against infection with *C difficile* and the use of broad-spectrum antibiotics disrupts the gut microbiome, limiting this defense[110]. When narrow-spectrum agents are substituted appropriately the risk of acquiring *C difficile* is less. As a result, if antibiotic use is deemed necessary it is recommended that appropriate narrow-spectrum antibiotics be used[108]. Avoiding unnecessary antibiotics is the most effective prevention of *C difficile* presently[111].

In addition, because *C difficile* spores persist in the environment and are resistant to detergents use of bleach and hydrogen peroxide to clean is recommended as they are sporicidal. It is recommended that rooms of patients with *C difficile* are cleaned daily[108].

The American Journal of Gastroenterology recommends against the use of probiotics concurrent with the usage of antibiotics in the prevention of *C difficile.* There is little evidence backing the claim that probiotics improve dietary health[112].

Infection with *C difficile* can be treated with Vancomycin or Metronidazole[113]. Although oral Vancomycin is an effective treatment for *C difficile* further research must be done to assess its efficacy in prophylactic prevention of *C difficile* as well as proper dosing, but meta-analysis has shown oral Vancomycin as promising for prophylactic treatment of *C difficile*[114]. Fidoxamicin prophylaxis has also been studied and shown a decrease in *C difficile* infection in patients undergoing hematopoietic stem cell transplantation when compared to a placebo, but further research must be done[115].

Challenges and Future Direction

In the modern era, with current lifestyles posing health hazards and higher frequency of hospitalizations, there has been an increase in the incidence of *C difficile.* Gut dysbiosis has been observed in patients with prolonged hospital stay, likely due to the fact that the diagnostic assays are time consuming, and innovation of rapid diagnostic tools are necessary in diagnosis. Patients in the critical care unit are treated aggressively with antimicrobials,making them susceptible to *C difficile*[116]. A major hurdle in the treatment of *C difficile* are asymptomatic carriers. There have been cases of asymptomatic carriers of *C difficile* after a recent hospitalization. Children under the age of 2 years are also asymptomatic carrier because they lack the receptors for the toxin to bind[117,118]. In a recent study conducted by *Curry et al* in 2023, 9.9 % of patients after recent hospitalizations became carriers of asymptomatic *C difficile* and 13.4% were diagnosed with CDI[119]. Asymptomatic carriers may result in transmission of infections at a faster rate. Even though *C difficile* is susceptible to vancomycin, there

have been recent studies in Connecticut,showing emergence of strains with resistance to vancomycin[120].

Fidaxomicin is an alternative to treat *C difficile*, has very little resistance reported compared to vancomycin, however the use is limited due to the drug's cost[121].There has been some case reports to suggest the emergence of strains of *C difficile* resistant even to fidaxomicin[122]. SARS-COV2 (COVID 19) has had a adverse impact on patients with *C difficile* infection and has shown to increase the risk of fulminant CDI in a recent study conducted by *Duhan et al*, which can be explained by the alteration of gut microbiome caused by COVID-19 at a molecular level. COVID-19 patients are treated empirically with antibiotics, which predispose these patients to *C difficile* .Providers should be mindful when treating COVID 19 patients with baricitinib as there is data predisposing them to fulminant CDI[123].

There have been recent advancements in the treatment of recurrent *C difficile,* one of which is bezlotoxumab. Recent studies have shown that when bezlotoxumab is used along with normal standard of care, it has shown to prevent recurrence of *c difficile* ,and should be considered in high risk patients irrespective of age[124].Small studies have shown that in immunocompromised patients or transplant patients who are at a higher risk of *C difficile* infections or complications have a reduced rate of recurrence of infection[125]. As mentioned before, FMT has been effective in the treatment of recurrent *C difficile,* however, a study conducted by *Porcari et al* , has shown that FMT has shown to have high efficacy in the treatment of patients with inflammatory bowel disease(IBD)[126].

Several antibiotics like cadazolid, LFF571, ramoplanin, and surotomycin have been studied initially for the treatment of *C difficile,* however have failed in the later trials[127]. Many trials are being conducted on various antibiotics including ridinilazole (ongoing Phase III), MGBBP3 (completed Phase II), CRS3123 (ongoing Phase II), DNV3837/DNV3681 (ongoing Phase II), and ibezapolstat (ongoing Phase II) for the treatment of *C difficile.* Ridinazole has shown to be superior to vancomycin in the phase

II trials with a higher sustained clinical response rate with lower recurrence in 30 days after the treatment[128].

A growing field in the treatment of *C difficile* is the application of live biotherapeutic products (LBPs) which are non vaccine live organisms used to treat and prevent *C difficile* infection. In the past 2 years, the US FDA approved 2 LBPs-al microbiota, live-jslm (Rebyota [RBL], which is a rectally administered therapeutic and live fecal microbiota spores live-brpk (Vowst[VOS] which are administered orally[129,130].The CLOVER trial to develop an mRNA vaccine to prevent *C difficile* is in the phase III stage. Another field of growing interest is Fecal virome transplantation(FVT) for achieving homeostasis of the gut microbiome and lytic phages to kill the bacteria. However, the data is very limited and more extensive studies need to be carried out[131].

CONCLUSION

Despite advancements in medical research, Clostridioides difficile infection (CDI) continues to present significant challenges in clinical management. Through this review, compelling evidence suggests that tailored therapeutic approaches, including bezlotoxumab, can substantially reduce recurrence rates by up to 40% compared to standard care alone. Additionally, fecal microbiota transplantation (FMT) demonstrates remarkable success rates exceeding 90% in refractory cases, offering a promising avenue for treatment. Complications such as toxic megacolon and sepsis, affecting 3-8% and 5-30% of CDI cases respectively, underscore the critical importance of early recognition and intervention. Diagnostic advancements, notably PCR-based methods with sensitivity and specificity exceeding 90%, enhance accuracy in identifying CDI, facilitating timely treatment initiation. By synthesizing diverse insights and empirical findings, this comprehensive review aims to empower clinicians with the knowledge necessary to mitigate CDI-associated risks and optimize patient outcomes. However, this review underscores lingering gaps in our understanding, emphasizing the imperative for further investigation into the long-term efficacy and potential adverse

effects of emerging therapies like bezlotoxumab and FMT. Additionally, the complex interplay of factors shaping CDI pathogenesis, including the gut microbiome, host immune response, and environmental influences, warrants deeper exploration. By addressing these knowledge gaps, we can refine our approach to CDI management, ultimately improving patient outcomes and reducing associated risks.

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