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Review Article

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Efficacy of Bezlotoxumab in Preventing Recurrent Clostridioides Difficile Infection: A Narrative Review

Simardeep Singh [1], Palak Gupta [2], Gaurab Shrestha [3], Biswajyoti Das [4], Mayank Dhalani *[5], Akhil Pawa [6], Rohit Jain [7]

[1]MedStar Health Georgetown University (Baltimore) Program, United States.
[2]Maharishi Markandeshwar Institute of Medical Sciences and Research, Ambala, Haryana, India.
[3]KIST Medical College & Teaching Hospital, Imadol, Lalitpur, Nepal.
[4]Maulana Azad Medical College, New Delhi, India.
[5]GMERS Medical College & Hospital, Gotri, Vadodara, Gujarat, India.
[6]St. George's University School of Medicine, Grenada, West Indies.
[7]Department of Medicine, Penn State Milton S. Hershey Medical Center, PA, United States.

*Corresponding authors: Mayank Dhalani; *mayankdhalani1999@gmail.com*

Abstract

Clostridioides difficile infection remains a leading cause of healthcare-associated diarrhea, linked primarily to broad-spectrum antibiotic use and gut microbiome disruption. Clostridioides difficile infection causes significant morbidity, mortality, and financial burden, with a high recurrence rate. Recurrence is driven by persistent spores, dysbiosis, and inadequate host immune responses to toxins A and B, particularly toxin B, the principal virulence factor. Standard treatments with vancomycin or fidaxomicin achieve initial cure but fail to prevent relapse. Alternative strategies such as fecal microbiota transplantation show promise but face challenges regarding accessibility, safety, and regulatory approval. Bezlotoxumab, a fully human monoclonal antibody targeting C. difficile toxin B, represents a novel adjunctive therapy to reduce recurrence risk. Trials have significantly reduced recurrent Clostridioides difficile infection, with the greatest benefit observed in elderly, immunocompromised, and high-risk patients. This review highlights the clinical role of bezlotoxumab in preventing recurrent Clostridioides difficile infection, emphasizing its therapeutic and economic potential while underscoring the need for further research to expand its application in primary Clostridioides difficile infection management.

Keywords: ***Recurrent Clostridioides difficile; Antibiotic therapy; Bezlotoxumab; Fecal microbiota transplantation; Gut microbiota***

Introduction

Clostridioides difficile (C. difficile) is a Gram-positive, spore-forming, toxin-producing anaerobic bacillus identified as a leading cause of healthcare-associated infections [1]. In the U.S., CDI accounts for 15-20% of all antibiotic-associated diarrhea, impacting around 500,000 individuals and causing approximately 30,000 deaths annually [2]. The incidence rate in 2022 was 116.1 cases per 100,000 persons, with a higher prevalence in women (134.2 cases) than men (97.5 cases) [3]. The resilience of C. difficile spores in adverse environments significantly contributes to their transmission and recurrence [4]. CDI presents a broad clinical spectrum, ranging from asymptomatic colonization to severe complications such as pseudomembranous colitis and toxic megacolon [5]. The infection imposes a significant healthcare burden due to its high recurrence rate, defined as a new episode occurring within eight weeks following the resolution of a previous CDI. Recurrent CDI (rCDI) accounts for 75,000 to 175,000 additional cases annually in the U.S., prolonging hospital stays by 2.8 to 10.4 days and increasing treatment costs, often exceeding $42,000 per case [6]. Current treatments for CDI include vancomycin or fidaxomicin, which achieve initial clinical cure rates of over 80 % [7,8]. However, recurrence occurs in approximately 25% of cases following the first episode, and risk increases with each subsequent episode [9]. This recurrence is primarily due to microbiome dysbiosis caused by antibiotic treatments and the resilience of C. difficile spores, which are not eradicated by antibacterial therapies [10]. Significant risk factors for CDI include advanced age (≥65 years), antibiotic usage (the most critical modifiable factor), gastric acid suppression, and a history of severe CDI, defined by a Zar score ≥ 2 (scores range from 1 to 8, with higher scores indicating increased severity). Infection with hypervirulent strains, such as NAP1/BI/027, further elevates risk [11]. Additional risk factors encompass severe comorbidities, renal insufficiency, extended hospitalization durations, and inadequate adaptive immune responses to C. difficile toxins A and B [12]. CDI commonly arises during or within one month of antibiotic treatment, with the risk persisting for up to 90 days. Exposure to proton pump inhibitors (PPIs) has been identified in approximately 31% of community-acquired CDI cases without prior antibiotic use [13]. Older people are particularly susceptible, exhibiting a 5.7-fold increased incidence and accounting for over 80% of CDI-related fatalities [14]. Recurrence of CDI is notably high among

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immunocompromised individuals, with rates up to 40%, likely due to frequent antimicrobial use, compromised immune function, increased healthcare exposure, and elevated C. difficile colonization rates [15]. Standard CDI treatment typically involves metronidazole, vancomycin, or fidaxomicin, although these agents are less effective in preventing recurrence. While fidaxomicin may reduce recurrence rates in patients with non-NAP1/BI/027 strains, it has not demonstrated superiority over oral vancomycin for mild to moderate CDI [16]. Fecal microbiota transplantation (FMT) has shown efficacy in recurrent CDI (rCDI) management; however, issues with regulatory approval, standardization, and safety concerns limit its broader application. Recent studies have explored the potential of bezlotoxumab, a monoclonal antibody targeting C. difficile toxin B, for its preventative capabilities against rCDI recurrence [9]. This review focuses on the pathophysiology of rCDI and the effectiveness of bezlotoxumab in recurrence prevention.

Pathophysiology

Clostridioides difficile infection is primarily driven by toxins A and B, encoded by the tcdA and tcdB genes, respectively, which significantly contribute to the pathogen's virulence [17]. While initially regarded as the principal virulence factor, toxin A's role was reevaluated after toxin B was found to be a more potent cytotoxin [18]. Additionally, some C. difficile strains produce a third toxin, the binary toxin C. difficile transferase (CDT), which disrupts the actin cytoskeleton, enhancing bacterial adhesion and tissue invasion [19,20]. Upon ingestion, C. difficile spores survive the gastric environment and reach the colon. Here, spores can remain dormant or transform into vegetative cells. Primary bile acids facilitate germination via the C. difficile germinant receptor CspC, whereas secondary bile acids produced by a healthy gut microbiota inhibit this process [21]. The pathogenesis of CDI is influenced by colonization resistance of the gut microbiota and the host immune response, both of which are compromised by broad-spectrum antibiotics, leading to overgrowth and toxin production [22].

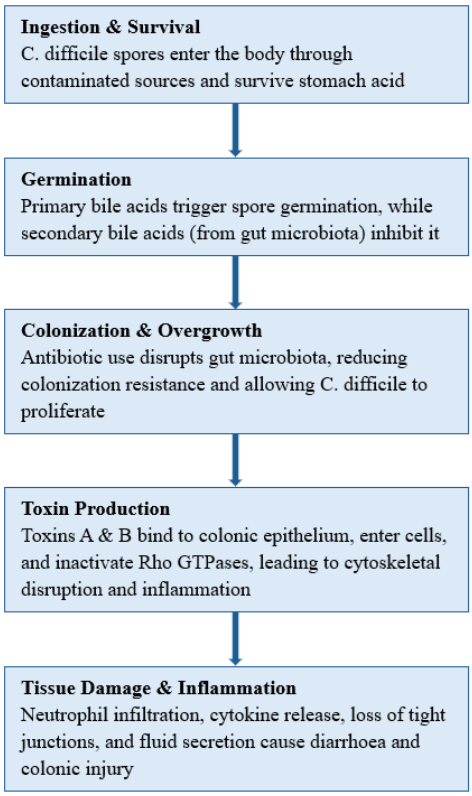

Figure 1: Pathogenesis of C. difficile Infection

This figure illustrates the pathogenesis of C. difficile infection, highlighting antibiotic-induced dysbiosis, bacterial overgrowth, and toxin-mediated epithelial injury.

Toxins A and B exert their effects by binding to colonic epithelial receptors, entering cells through receptor-mediated endocytosis, and inactivating Rho family GTPases. This results in cell damage, inflammatory responses, and characteristic CDI symptoms [17,23,24].

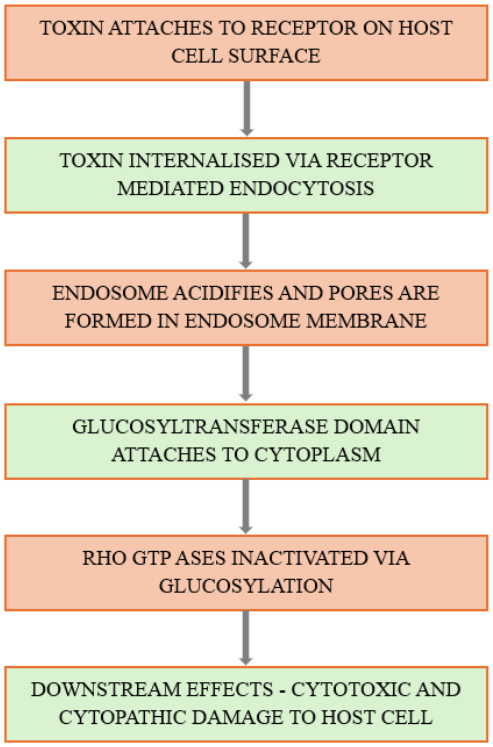

Figure 2: Biochemical mechanism of action of the toxins

This figure illustrates how toxins A and B disrupt cytoskeletal integrity and epithelial tight junctions, leading to inflammation and mucosal damage.

Additionally, factors such as flagellar expression, type IV pili, and adhesion proteins like fibronectin-binding protein A and Cwp84 are crucial for colonization, biofilm formation, and further pathogenesis [25]. Recurrent Clostridioides difficile infection (rCDI) occurs due to either a relapse with the same strain or reinfection with a different strain [26].

Prevention of rCDI involves reducing patient susceptibility by managing modifiable risk factors, such as minimizing antibiotic use, avoiding gastric acid suppressants, and reducing hospital stays, as well as preventing transmission of the organism through the implementation of contact precautions, promotion of hand hygiene, and ensuring thorough environmental cleaning and disinfection [27]. A new approach to preventing recurrent C. difficile infection involves monoclonal antibodies targeting C. difficile toxins to provide passive immunity alongside antibiotics [28]. Higher levels of circulating antibodies against toxins A and B have correlated with protection against recurrent CDI [29]. Bezlotoxumab is a fully humanised IgG1/ kappa monoclonal antibody that binds to toxin B produced by C. difficile, neutralizing its pro-inflammatory effects [30]. The Fab segment of bezlotoxumab binds to two distinct sites within the N-terminal half of the combined repetitive oligopeptide (CROP) domain of toxin B, partially blocking two of the four carbohydrate-binding pockets of the toxin. This binding prevents toxin B from interacting with the host receptor CSPG4 (chondroitin sulfate proteoglycan 4), inhibiting the toxin's ability to intoxicate

mammalian host cells [31]. In healthy individuals, bezlotoxumab is concentrated on the basolateral side of the intestinal epithelium, with limited leakage into the gut lumen. However, in CDI-infected individuals, toxins alter epithelial cells and disrupt the gut wall barrier function, allowing paracellular translocation of the antibody into the gut lumen. This results in the neutralization of toxins, recovery of the epithelium, and reestablishment of the gut barrier [9]. This mechanism suggests that bezlotoxumab may be particularly effective in patients with severe CDI, as increased epithelial disruption facilitates greater antibody penetration into the gut lumen, enhancing its therapeutic impact [32].

Discussion

Bezlotoxumab has emerged as an effective therapeutic agent in mitigating Clostridioides difficile infection recurrence and substantially improving clinical outcomes. Evaluating its efficacy across multiple studies establishes its preventive capabilities against rCDI.

The MODIFY I and II trials, documented by Wilcox *et al*.[18], reveal a substantial reduction in recurrence rates, particularly among older adults and those with prior CDI episodes [33]. An observational study by Escudero Sanchez *et al*.[34] supports its effectiveness, reporting a recurrence rate of 14.3%, consistent with MODIFY trials. This study identified the 027 ribotype as a significant risk factor for recurrence but found no substantial impact from other variables like renal impairment or fidaxomicin treatment. Despite some limitations due to its retrospective nature, the study confirms the general applicability of the MODIFY trial findings in a clinical setting.

A systematic review by Thandavaram *et al*.[17] highlights the role of bezlotoxumab in significantly diminishing recurrence rates among high-risk populations, such as older people, immunocompromised patients, and transplant patients. The MODIFY trials confirmed that bezlotoxumab reduced the rCDI rate significantly in high-risk adults compared to placebo (16.5 % vs 26.6 %, 95% CI -14.0 to -6.0, p <0.0001), with a number needed to treat (NNT) to prevent a single episode of recurrent Clostridioides difficile infection was 10. In patients aged 65 or older and those with prior C. difficile infection, the NNT decreased to 6.[17]. The MODIFY III trial, a multicenter, double-blind, placebo-controlled study involving 143 pediatric participants, demonstrated a reduced rCDI rate from 14.7% in the placebo group to 11.2% in those treated with bezlotoxumab [35].

Bezlotoxumab is not only recommended for rCDI but is also being considered for use in special conditions, as evidenced by various studies discussed further. Bezlotoxumab has demonstrated substantial benefits in reducing the need for fecal microbiota transplantation (FMT). Some patients awaiting FMT no longer require it due to the prevention of further recurrences. The cure rates post-standard antibiotic therapy with bezlotoxumab addition were higher in patients experiencing their first recurrence than those with multiple recurrences, highlighting its effectiveness [36].

A multicenter RCT by Allegretti *et al*.[37] evaluated the efficacy of bezlotoxumab plus FMT in IBD patients with rCDI. Sixty-one patients were randomized to receive colonoscopic FMT with either bezlotoxumab or placebo. The primary endpoint, defined as the recurrence of C. difficile by week 8, showed no significant advantage of the combination therapy over FMT alone. Decolonization rates were not statistically significant between groups at weeks 1 and 12, though a trend favored the treatment arm. However, steroid use at the time of FMT was significantly associated with ongoing C. difficile colonization at week 12 (OR: 4.90, 95% CI: 1.18-20.37, P=0.03), highlighting a key risk factor for future studies.

Johnson *et al*.[38] from the University of Colorado Hospital observed a 72% reduction [95% CI, .08-.91; p =.03) in recurrence risk among transplant recipients, highlighting bezlotoxumab's role in these specialized settings. Internationally, Oksi *et al*.[39] corroborated its efficacy in a Finnish university hospital network, particularly among immunocompromised patients, with a significant majority avoiding recurrence. A similar study by Askar *et al*.[40] presented promising early results in an immunocompromised group, significantly extending the time to recurrent infection.

In the United States, a multicenter cohort study by Hengel *et al*.[41] reported an 84.1% success rate in preventing recurrent infections when bezlotoxumab was combined with standard-care antibiotics. Similarly, a retrospective analytical study by Medaglia *et al*.[42] at an Italian tertiary care hospital reported that bezlotoxumab was administered in 64% of rCDI cases, reflecting its established role in clinical practice for managing rCDI. The frequent use of bezlotoxumab, particularly in conjunction with standard CDI therapies, underscores its perceived utility in preventing recurrence among high-risk patients.

Herrero *et al*.[43] noted that even in severe CDI cases, bezlotoxumab maintained a recurrence rate consistent with pivotal clinical studies. A comparative analysis by Alhifany *et al*.[44] evaluated bezlotoxumab against FMT, finding both treatments effective, though FMT exhibited a slightly higher success rate under certain conditions. Valerio *et al*.[45] reported that bezlotoxumab may serve as a viable alternative to FMT in cases where FMT is contraindicated, unavailable, or declined by the patient. In a Spanish cohort of patients with rCDI and multiple risk factors, bezlotoxumab achieved a recurrence prevention rate of 78.57% (11 out of 14 cases), with no reported adverse events. Contraindications to FMT may include severe immunocompromise, toxic megacolon, or gastrointestinal perforation.

Reviews by Giacobbe *et al*.[46], Alonso and Mahoney [47], and Kufel *et al*.[48] further explore the clinical and pharmacological profile of bezlotoxumab, advocating for its role in alleviating healthcare burdens associated with recurrent CDI. Kelly and Sangha [49] conclude by envisioning a promising future for treating recurrent CDI with bezlotoxumab, particularly recommending its use in older patients with multiple risk factors, which include age > 65, immunocompromised state, and prior IV antibiotic use.

Bezlotoxumab demonstrates a generally acceptable tolerability profile, although infusion-related reactions constitute the most frequently observed adverse drug reaction (ADR), occurring in approximately 10% of treated patients. Within the initial four weeks post-infusion, commonly reported ADRs, including nausea (7%), pyrexia (5%), and headache (4%), exhibited no statistically significant difference in incidence when compared to placebo [9]. Analysis of severe ADRs within a 12-week timeframe revealed rates of 29% and 33% for the bezlotoxumab and placebo groups, respectively. Prominent severe ADRs encompassed sepsis, pneumonia, acute kidney injury, urinary tract infections, and heart failure. Notably, 12-week mortality rates were comparable between the bezlotoxumab and placebo groups, registering at 7.1% and 7.6%, respectively, indicating no significant increase in mortality associated with bezlotoxumab administration [9]. However, caution is advised when prescribing bezlotoxumab, especially to patients with a history of congestive heart failure (CHF). Clinical trials reported a higher incidence of heart failure (2% vs. 1%) in those treated with bezlotoxumab compared to placebo. Furthermore, patients treated with bezlotoxumab with pre-existing CHF showed increased rates of treatment-emergent adverse events (83.9% vs.

70.2%), serious adverse events (53.4% vs. 48%), and mortality (19.5% vs. 12.5%). Cardiovascular-related deaths were also more common in this group (14.3% vs. 6.8%) [18,34,50-52].

Existing literature substantiates the application of bezlotoxumab not only in rCDI but also in primary CDI cases among high-risk populations. The guidelines from the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) recommend considering bezlotoxumab for patients with primary CDI, for patients over 65 or with compromised immune systems, due to their higher risks of severe or recurrent infections [38,53]. In contrast, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) advises reserving bezlotoxumab for the treatment of a second or subsequent episode of rCDI in combination with standard-of-care antibiotics [38,53].

Despite strong evidence supporting its efficacy in preventing rCDI, the adoption of bezlotoxumab across Europe remains constrained, primarily due to its high cost. However, cost-effectiveness models suggest that bezlotoxumab could be economically favorable for preventing rCDI recurrences. Initial economic assessments indicated that bezlotoxumab was cost-effective compared to placebo for specific patient subgroups, including those aged ≥65 years (Incremental Cost-Effectiveness Ratios [ICER] of USD 15,298/QALY), immunocompromised patients (ICER of USD 12,597/QALY), and patients with severe CDI (ICER of USD 21,430/QALY) [54]. A more recent study comparing bezlotoxumab with other CDI therapies revealed that the combination of bezlotoxumab and vancomycin offered more cost-effective outcomes than vancomycin alone, with a notable incremental net monetary benefit of USD 17,011 [55]. However, this combination was less advantageous than standard fidaxomicin due to the higher cost of bezlotoxumab and lower QALY gains [56].

Moving forward, the strategic focus on bezlotoxumab may expand beyond exclusive use in high-risk patients to broader applications in primary CDI management, contingent on its overall patient benefits and cost-effectiveness.

Conclusion

Bezlotoxumab, a monoclonal antibody targeting the toxin B of Clostridioides difficile, represents a significant advancement in treating recurrent C. difficile infections. Endorsed by current clinical guidelines, bezlotoxumab effectively reduces recurrence rates, offering a valuable alternative to traditional therapies like oral vancomycin, fidaxomicin, and fecal microbiota transplantation (FMT). While its upfront costs are notable, the long-term economic perspective is promising due to decreased recurrence rates and shortened treatment durations. Bezlotoxumab is particularly beneficial for high-risk populations such as older people, immunocompromised patients, transplant patients, and long-term antibiotic users. However, it is contraindicated for patients with congestive heart failure (CHF) due to an increased risk of adverse cardiovascular events. The exact reason is still unclear, but a possible explanation is that monoclonal antibodies may trigger cytokine release and inflammation, which can worsen existing cardiovascular conditions. Additionally, they can promote fluid retention, further exacerbating heart failure symptoms [29]. Further research is warranted to establish its role in the primary prevention of CDI, potentially expanding its clinical application and enhancing patient outcomes in broader patient groups.

List of abbreviations

ADR: Adverse Drug Reaction
BI/NAP1/027: North American Pulsed-field type 1 / Ribotype 027 (hypervirulent strain)
CDI: Clostridioides difficile Infection
CHF: Congestive Heart Failure
CROP: Combined Repetitive Oligopeptide (domain of toxin B)
CspC: Clostridioides difficile germinant receptor CspC
CDT: Clostridioides difficile Transferase (binary toxin)
FMT: Fecal Microbiota Transplantation
GTPases: Guanosine Triphosphatases (Rho family)
IBD: Inflammatory Bowel Disease
ICER: Incremental Cost-Effectiveness Ratio
IDSA: Infectious Diseases Society of America
IgG1: Immunoglobulin G1
IV: Intravenous
NAP1: North American Pulsed-field type 1 strain
NNT: Number Needed to Treat
OR: Odds Ratio
PPIs: Proton Pump Inhibitors
QALY: Quality-Adjusted Life Year
RCT: Randomized Controlled Trial
rCDI: Recurrent Clostridioides difficile Infection
SHEA: Society for Healthcare Epidemiology of America
tcdA / tcdB: Genes encoding toxins A and B
US / U.S.: United States
USD: United States Dollar

Declarations

Ethical Considerations

As this is a review article, no ethical approval was needed.

Conflicts of Interest

The authors declared no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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Consent for publication

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Data Availability

As this is a review article, no new data were generated and are therefore not available.

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Author Contributions

SS: Conceptualization, Methodology, Software, Original Draft Preparation
PG: Data Curation, Formal Analysis, Visualization, Review, and Editing

GS: Data Curation, Formal Analysis, Visualization, Review, and Editing
BD: Data Curation, Formal Analysis, Visualization, Review and Editing
MD: Conceptualization, Formal Analysis, Visualization, Review, and Editing
AP: Data Curation, Formal Analysis, Visualization, Review, and Editing
RJ: Formal Analysis, Visualization, Review, and Editing

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