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Therapeutic Strategies for Clostridium Difficile Infection in Ulcerative Colitis: Current Evidence and Emerging Interventions

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ABSTRACT

***Background*:** Background: Patients with Ulcerative Colitis (UC) face a heightened risk of acquiring Clostridioides difficile infection (CDI), which complicates disease course, increases morbidity and poses unique therapeutic challenges. The interplay of gut-microbiota disruption, immunosuppression, mucosal injury and antibiotic exposure in UC predisposes to CDI and may alter its clinical presentation and outcomes. Aim: This review article aims to synthesise current evidence on therapeutic strategies for CDI in the context of UC, critically examining antibiotic choices, immunomodulatory management, microbiota-based interventions, and emerging therapies, while highlighting gaps in knowledge and proposing future directions. Methods: We reviewed the literature on epidemiology, pathogenesis and management of CDI in UC patients, emphasising randomized controlled trials, expert guidelines and emerging interventional studies. Results: Conventional antibiotic therapy (oral vancomycin, fidaxomicin) remains the backbone of CDI management, but in UC patients therapy may need adaptation due to increased recurrence risk and more severe disease. The presence of UC also raises issues regarding immunosuppressive therapy: whether to hold, reduce or continue IBD-directed treatment. Microbiota-restoration therapies (such as fecal microbiota transplantation) are gaining traction especially for recurrent CDI in UC but require further validation regarding safety and efficacy in this immunologically altered host. Emerging interventions such as narrow-spectrum antimicrobials, microbiome therapeutics, and precision immunomodulation show promise. Key challenges include distinguishing UC flare from CDI, timing of immunosuppression, and optimal integration of microbiome therapies. Conclusion: Management of CDI in UC is evolving: while established antibiotic and supportive strategies apply, the UC context demands tailored approaches; microbiota-based therapies represent an important frontier. Future research must address optimal algorithms for immunomodulation, microbiota restoration and prevention of recurrence in this high-risk population..

Keywords: Therapeutic Strategies, Clostridium Difficile Infection, Ulcerative Colitis

INTRODUCTION

Ulcerative colitis (UC), a chronic idiopathic inflammatory bowel disease (IBD), is characterized by continuous mucosal inflammation of the colon and rectum. Its management frequently involves immunosuppressive or biologic therapies, which, while controlling inflammation, predispose patients to infections, notably *Clostridium difficile* infection (CDI). The intersection

of UC and CDI represents a major therapeutic challenge. Over the past two decades, CDI incidence has markedly increased, particularly among patients with IBD, and its presence in UC is associated with higher rates of hospitalization, colectomy, and mortality compared to non-IBD patients [1].

The pathophysiological overlap between UC and CDI complicates diagnosis and management. Both conditions share similar symptoms—diarrhea, abdominal pain, and hematochezia—making clinical distinction difficult. Moreover, antibiotic use for CDI may further disrupt the gut microbiota, aggravating UC inflammation and potentially inducing flares [2]. The altered mucosal immunity and dysbiosis intrinsic to UC contribute to heightened susceptibility to CDI and recurrent infections.

Therapeutic strategies for CDI in UC are not fully standardized. While vancomycin and fidaxomicin remain first-line antibiotics for CDI, the recurrence rates in UC patients are significantly higher than in the general population [3]. The management of immunosuppressive or biologic therapy during CDI episodes remains controversial—continuation may exacerbate infection, but withdrawal may trigger UC flare and worsen colitis severity. The clinical decision thus requires balancing infection control with maintenance of mucosal healing.

Emerging therapies such as fecal microbiota transplantation (FMT), monoclonal antibodies against toxin B (bezlotoxumab), and microbiota-based therapeutics have shown promise in recurrent CDI, including in IBD populations. However, evidence remains limited regarding long-term outcomes and safety in immunocompromised UC patients [4]. Furthermore, preventive strategies, including antibiotic stewardship and modulation of the gut microbiome, are under active investigation.

Aim and Research Gap:

This review aims to comprehensively analyze current therapeutic strategies for CDI in UC, integrating established antibiotic regimens with emerging microbiota-based and immunomodulatory approaches. The research gap lies in the paucity of controlled studies specific to UC populations, the absence of consensus on immunosuppressive management during CDI, and limited long-term data on microbiome-based therapies. Addressing these gaps is critical for developing targeted, safe, and effective interventions for this complex clinical scenario [5].

Epidemiology and Risk Factors

The epidemiology of *Clostridium difficile* infection (CDI) in ulcerative colitis (UC) patients has evolved significantly over recent decades. Multiple studies confirm that individuals with UC are at a substantially increased risk of CDI compared to the general population. The prevalence of CDI among hospitalized UC patients ranges between 5 % and 20 %, with an incidence rate approximately four to five times higher than that in patients without inflammatory bowel disease (IBD) [6]. The rise in CDI cases parallels the emergence of hypervirulent ribotypes such as BI/NAP1/027, which produce increased levels of toxins A and B and demonstrate fluoroquinolone resistance [7]. These strains contribute to more severe disease and higher recurrence rates in UC cohorts.

Several host and disease-related risk factors predispose UC patients to CDI. Broad-spectrum antibiotic exposure, particularly to fluoroquinolones, cephalosporins, and clindamycin, remains a major risk determinant [8]. However, unlike non-IBD patients, CDI can also occur in UC patients without recent antibiotic use, underscoring the intrinsic susceptibility due to disrupted mucosal barriers and dysbiosis [9]. Hospitalization and proton pump inhibitor therapy further increase risk, as does corticosteroid use, which impairs local immune defense and facilitates spore germination [10].

Immunomodulators and biologic agents such as azathioprine, infliximab, and vedolizumab have been variably implicated in increasing CDI risk, though data remain inconsistent. Some studies suggest corticosteroids and immunosuppressants contribute more to susceptibility than biologics, whereas others find no clear association after adjusting for confounders [11]. Disease severity itself may independently elevate risk, as severe colitis provides an inflamed milieu conducive to *C. difficile* colonization.

Environmental factors also play a role. UC patients frequently require repeated hospital admissions and endoscopic procedures, heightening exposure to *C. difficile* spores. Colonization rates in IBD patients may reach 8–10 %, exceeding background carriage in healthy populations [12]. In addition, alterations in gut microbial composition—marked by reduced Firmicutes and Bacteroidetes with expansion of Proteobacteria—facilitate *C. difficile* overgrowth [13].

Overall, the combination of antimicrobial exposure, mucosal inflammation, and impaired immune surveillance establishes a "perfect storm" for CDI in UC patients. Recognizing and mitigating these risk factors is fundamental for effective prevention

and management strategies [14].

Pathophysiology and Interaction Between Ulcerative Colitis and Clostridium difficile Infection

The pathophysiology underlying *Clostridium difficile* infection (CDI) in ulcerative colitis (UC) is multifactorial, involving complex interactions between dysbiosis, mucosal immunity, and epithelial barrier dysfunction. In UC, chronic inflammation leads to compromised epithelial integrity and altered mucus composition, which facilitate colonization and toxin penetration by *C. difficile* [15]. The inflamed mucosa exhibits disrupted tight junctions, increased permeability, and decreased production of protective antimicrobial peptides, collectively reducing mucosal defense mechanisms [16].

UC itself is characterized by a perturbed gut microbiome, with decreased bacterial diversity and depletion of commensal taxa such as *Faecalibacterium prausnitzii* and *Bacteroides fragilis*. These commensals produce short-chain fatty acids (SCFAs), especially butyrate, which maintain epithelial health and regulate immune tolerance. Loss of these beneficial microbes enables *C. difficile* spores to germinate and proliferate within the inflamed colon [17]. Additionally, antibiotic use further exacerbates microbial imbalance, favoring colonization by *C. difficile* and other opportunistic species.

Toxins A and B, the major virulence factors of *C. difficile*, induce colonic epithelial cell rounding, apoptosis, and tight-junction disruption. In UC, the mucosa is already primed with heightened immune activation, resulting in amplified cytokine release—especially tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), and interferon-γ (IFN-γ)—upon exposure to toxins. This hyperinflammatory state aggravates epithelial injury and perpetuates a vicious cycle of inflammation and bacterial proliferation [18].

Furthermore, host immune responses differ between UC patients and those without IBD. In UC, impaired neutrophil function and dysregulated adaptive immunity hinder efficient clearance of *C. difficile* and its toxins. Immunosuppressive therapies, including corticosteroids and thiopurines, further dampen mucosal defense, facilitating persistent infection [19]. Interestingly, the UC microenvironment may also alter *C. difficile* behavior; oxidative stress and bile acid changes in UC favor the vegetative growth and toxin production of *C. difficile*, amplifying disease severity [20].

Overall, CDI in UC is not merely a coincidental infection but a synergistic pathological interaction. UC provides a fertile ground for *C. difficile* colonization and toxin activity, while CDI exacerbates the inflammatory cascade of UC, creating a bidirectional amplification loop that complicates both diagnosis and treatment. Understanding this interplay is crucial for designing targeted therapeutic interventions that restore microbial balance and mucosal homeostasis [21].

Clinical Presentation and Diagnostic Challenges

The clinical manifestations of *Clostridium difficile* infection (CDI) in patients with ulcerative colitis (UC) often overlap significantly with those of a UC flare, creating substantial diagnostic uncertainty. Both conditions present with diarrhea, abdominal pain, rectal bleeding, and systemic symptoms such as fever and malaise. In UC, the baseline colonic inflammation can mask the typical features of CDI, delaying diagnosis and potentially worsening outcomes [22]. Importantly, CDI in UC patients tends to present with more severe disease, higher leukocyte counts, and increased rates of hospitalization and colectomy compared to CDI in non-IBD individuals [23].

One major diagnostic challenge lies in differentiating an acute UC flare from CDI-triggered colitis. While antibiotic exposure and sudden worsening of diarrhea in a previously stable UC patient should raise suspicion for CDI, clinical symptoms alone are unreliable. Studies show that up to one-third of UC flares may be associated with CDI, even in the absence of recent antibiotic therapy [24]. Hence, guidelines recommend that **all UC patients with an acute flare should be tested for *C. difficile***, regardless of antibiotic history [25].

Laboratory diagnosis relies on stool assays detecting *C. difficile* toxins or genetic material. The current recommended approach uses a multistep algorithm: initial glutamate dehydrogenase (GDH) antigen screening followed by toxin enzyme immunoassay (EIA) and nucleic acid amplification tests (NAAT), such as PCR, for toxin genes [26]. While NAATs have high sensitivity, they may detect colonization rather than active infection, which is particularly problematic in UC, where asymptomatic colonization rates are elevated [27]. Therefore, interpretation of results must be correlated with clinical context and endoscopic findings.

Endoscopic evaluation can provide additional clues. Pseudomembranous colitis, a hallmark of CDI, is less frequently seen in UC patients, possibly due to diffuse mucosal ulceration masking pseudomembranes [28]. Histologically, CDI in UC is characterized by epithelial necrosis and fibrinous exudates overlaying chronically inflamed mucosa. However, biopsy findings are often nonspecific, emphasizing the need for comprehensive diagnostic integration.

Early and accurate diagnosis of CDI in UC is critical for timely therapy and to avoid inappropriate escalation of immunosuppressive treatment, which could worsen infection. Diagnostic precision not only improves outcomes but also supports antibiotic stewardship and reduces recurrence risk [29].

Standard Antibiotic Therapy and Clinical Outcomes

Antibiotic therapy remains the cornerstone of treatment for *Clostridium difficile* infection (CDI) in ulcerative colitis (UC), but the therapeutic approach in this population requires nuanced consideration. The presence of underlying mucosal inflammation, immunosuppressive therapy, and altered gut microbiota profoundly influence treatment response and recurrence risk. Current clinical guidelines recommend **oral vancomycin or fidaxomicin** as first-line agents for initial CDI episodes, while **metronidazole** is largely reserved for mild, non-IBD cases due to inferior efficacy and higher relapse rates [30].

In UC patients, oral vancomycin achieves higher luminal concentrations and superior clinical resolution compared to metronidazole. Multiple studies have demonstrated that vancomycin therapy leads to more rapid symptom improvement and lower colectomy rates among UC patients with CDI [31]. Fidaxomicin, a macrocyclic antibiotic with narrow activity against *C. difficile*, offers additional advantages by preserving commensal gut flora, thus reducing recurrence risk. A multicenter study by Cornely et al. reported fidaxomicin to be noninferior to vancomycin for initial cure and superior for sustained response, findings that appear consistent within UC subgroups [32]. However, its high cost and limited accessibility in many regions restrict routine use.

Treatment duration typically spans 10 to 14 days, with extended taper or pulsed vancomycin regimens recommended for recurrent CDI. In UC, recurrence rates may exceed 25–30 %, necessitating individualized antibiotic strategies. Concomitant UC activity can delay microbiome restoration and predispose to multiple CDI episodes, highlighting the need for early recognition and appropriate dosing schedules [33].

Importantly, antibiotic therapy alone may not suffice if immunosuppressive therapy is mismanaged. Abrupt cessation of corticosteroids or biologics during CDI may trigger severe UC flares, whereas continuation during active infection can exacerbate bacterial proliferation. Clinical judgment, guided by disease severity and infection control, remains essential. Early gastroenterology–infectious disease collaboration is strongly advised for these complex cases [34].

Despite antibiotic advances, outcomes remain suboptimal in UC patients compared to non-IBD counterparts. Meta-analyses reveal higher colectomy and mortality rates, reflecting both delayed diagnosis and the compounded inflammatory burden [35]. Optimizing antibiotic regimens, incorporating microbiota-sparing agents, and integrating adjunctive therapies are crucial to improving long-term outcomes in this vulnerable population.

Management of Immunosuppressive and Biologic Therapy During CDI

The management of immunosuppressive and biologic therapy during *Clostridium difficile* infection (CDI) in patients with ulcerative colitis (UC) remains one of the most challenging and controversial aspects of clinical care. Immunosuppressive agents—including corticosteroids, thiopurines, calcineurin inhibitors, and biologic therapies such as anti-TNF, anti-integrin, and anti-interleukin agents—are integral to UC control. However, these therapies can impair host immune defense, potentially worsening infectious outcomes when CDI occurs. Determining whether to continue, withhold, or modify immunosuppressive treatment during active CDI must therefore be guided by disease severity, infection control, and clinical trajectory [36].

Corticosteroids are among the most debated agents in this setting. Early studies suggested that systemic corticosteroid use increased mortality and colectomy rates among IBD patients with CDI [37]. However, more recent evidence indicates that continuation of corticosteroids may not universally worsen infection outcomes, particularly when used for severe UC flares triggered by CDI, provided effective antibiotic therapy is in place [38]. The consensus approach favors cautious continuation or initiation of corticosteroids only after CDI therapy has commenced and if clinical features strongly suggest concurrent UC activity.

For immunomodulators such as azathioprine and methotrexate, data are limited. Most experts recommend temporary cessation during acute CDI due to potential leukopenia and impaired immune recovery, resuming therapy once infection control is achieved and inflammatory markers stabilize [39]. The use of biologic therapy, particularly anti-TNF agents (e.g., infliximab, adalimumab), is more complex. Observational data suggest that biologics may not worsen CDI outcomes and, in select cases, can help control refractory UC flares exacerbated by CDI once appropriate antibiotics are administered [40]. Still, initiating biologics during active infection is generally discouraged until the patient shows clinical improvement and toxin clearance.

Newer biologics, such as vedolizumab and ustekinumab, are gut-selective and immunomodulatory rather than broadly immunosuppressive. Early data imply a potentially safer infection profile; however, robust evidence during concurrent CDI is lacking [41]. Close multidisciplinary management involving gastroenterologists and infectious disease specialists is crucial to balance infection resolution with UC control.

Ultimately, individualized assessment is essential. Overly aggressive immunosuppression can precipitate fulminant colitis and septic complications, whereas premature withdrawal can lead to severe UC relapse. Optimizing timing, dose, and sequencing of immunosuppressive therapy around CDI treatment remains an active area of clinical research [42].

Recurrent Clostridium difficile Infection and Risk Factors for Relapse in Ulcerative Colitis

Recurrent *Clostridium difficile* infection (rCDI) poses a major clinical challenge in patients with ulcerative colitis (UC), with recurrence rates nearly double those seen in non-inflammatory bowel disease populations. While recurrence after a primary CDI episode in the general population is approximately 15–25 %, it can reach 30–40 % among UC patients, and may exceed 50 % in those with multiple prior infections [43]. The high relapse burden reflects the compounded effects of microbiome disruption, ongoing mucosal inflammation, immunosuppressive therapy, and recurrent antibiotic exposure.

Several patient-specific factors increase the likelihood of CDI recurrence in UC. Advanced age, recent hospitalization, broad-spectrum antibiotic use, and proton pump inhibitor therapy are well-established contributors. In UC, however, additional disease-specific determinants play a major role. Severe colitis, extensive disease involvement, hypoalbuminemia, and use of corticosteroids or immunomodulators markedly heighten relapse risk [44]. Persistent dysbiosis following antibiotic therapy also prevents reestablishment of colonization resistance, allowing dormant *C. difficile* spores to reactivate.

Impaired immune response to *C. difficile* toxins contributes further to recurrence susceptibility. In UC, dysregulated humoral immunity leads to insufficient anti-toxin A and B antibody production, reducing natural protection against reinfection [45]. Additionally, the gut mucosal environment in UC patients remains proinflammatory even after clinical resolution, supporting spore persistence and epithelial vulnerability. Hypervirulent strains such as ribotype 027 and 078 have been linked to higher recurrence rates, prolonged shedding, and more severe inflammatory responses [46].

Therapeutically, prevention of rCDI in UC is challenging. Prolonged or tapered vancomycin regimens have been used successfully to reduce recurrence, particularly in those with multiple prior episodes. Fidaxomicin's microbiota-sparing profile has been associated with lower recurrence rates compared with vancomycin, though evidence in IBD-specific populations remains limited [47]. Adjunctive use of bezlotoxumab—a monoclonal antibody against toxin B—has demonstrated efficacy in reducing recurrence in high-risk populations, including those with immunosuppression or prior CDI history [48].

Importantly, preventing relapse also requires meticulous control of underlying UC. Poorly controlled inflammation perpetuates mucosal disruption, prolonging susceptibility. Thus, the integration of effective anti-inflammatory therapy, prudent antibiotic use, and microbiome restoration is essential for long-term prevention. Early identification of high-risk individuals allows for timely intervention and may mitigate both morbidity and recurrence-associated healthcare burden [49].

Fecal Microbiota Transplantation (FMT) in Ulcerative Colitis with Clostridium difficile Infection

Fecal microbiota transplantation (FMT) has emerged as a transformative therapy for recurrent *Clostridium difficile* infection (rCDI), and its role in patients with ulcerative colitis (UC) is a rapidly expanding area of research. The principle of FMT is to restore gut microbial diversity by transferring stool from a healthy donor to a dysbiotic host, thereby re-establishing colonization resistance against *C. difficile* and modulating intestinal immunity. In UC, where chronic dysbiosis is intrinsic to disease pathogenesis, FMT offers dual potential benefits: eradication of *C. difficile* and possible improvement of underlying colitis [50].

Numerous clinical trials have demonstrated that FMT achieves cure rates exceeding 85–90% for recurrent CDI in the general

population, often after a single administration [51]. In UC patients, outcomes appear comparably favorable, though slightly attenuated due to ongoing mucosal inflammation and immunosuppression. Retrospective series report CDI cure rates between 70% and 90%, with recurrence risk notably reduced following serial FMT infusions [52]. Importantly, FMT also appears to decrease UC flare frequency in some cohorts, likely through rebalancing of the gut microbiome and enhancement of anti-inflammatory microbial metabolites such as short-chain fatty acids [53].

The route and frequency of FMT administration influence outcomes. Delivery via colonoscopy or enema allows direct placement into the affected colon and is associated with higher success rates compared to nasoenteric administration [54]. However, the optimal number of infusions in UC patients remains uncertain; some require multiple treatments for sustained remission. Safety data in UC are reassuring—serious adverse events are rare, though transient increases in abdominal pain or diarrhea can occur, particularly in patients with active colitis. Concerns regarding pathogen transmission have prompted rigorous donor screening protocols, including testing for enteric pathogens, multidrug-resistant organisms, and viral infections [55].

Beyond CDI, FMT is being explored as an adjunct therapy for UC itself. Randomized controlled trials show modest remission induction rates (~25–30%) in active UC, suggesting potential microbiome modulation benefits independent of infection clearance. Nonetheless, heterogeneity in donor selection, preparation techniques, and host factors complicates interpretation. Future directions include defined microbial consortia and "next-generation" FMT formulations that may offer safer, standardized alternatives [56].

In UC with concurrent CDI, FMT represents a vital therapeutic tool—particularly for recurrent or antibiotic-refractory infection—capable of achieving durable remission, reducing recurrence, and possibly improving mucosal homeostasis [57].

Emerging and Adjunctive Therapies (Bezlotoxumab, Probiotics, and Microbiome Therapeutics)

Monoclonal toxin neutralization—principally **bezlotoxumab**, a human mAb against *C. difficile* toxin B—has reshaped prevention strategies for high-risk patients, including those with UC. The IDSA/SHEA 2021 focused update recommends considering bezlotoxumab (as a one-time 10 mg/kg infusion alongside standard-of-care antibiotics) in patients at high risk for recurrence (age ≥65, immunocompromised host, severe CDI, or prior rCDI), with an FDA caution to weigh risks in those with heart failure. In UC, where recurrence risk and immunosuppression are common, bezlotoxumab is an attractive adjunct to vancomycin or fidaxomicin to reduce rCDI without further disrupting the microbiome. [58]

Pivotal randomized trials (MODIFY I/II) established that bezlotoxumab significantly **reduces rCDI** versus placebo without compromising initial cure; subgroup analyses showed consistent benefit in immunocompromised and severe-disease cohorts—profiles that overlap with many UC patients. While not UC-exclusive studies, the toxin-targeted mechanism is disease-agnostic and complementary to IBD therapy. These data support deploying bezlotoxumab at the **index episode** when relapse risk is high or after a **first recurrence**, particularly in UC patients requiring ongoing steroids or biologics. [59]

Microbiome-restorative products have progressed from procedural FMT to **regulated therapeutics**. In April 2023, the FDA approved **VOWST (SER-109)**, the first **oral** fecal microbiota product, to **prevent rCDI** after completion of antibiotics; this capsule formulation can be particularly practical for UC patients who may wish to avoid colonoscopic delivery during active colitis. Its approval followed randomized evidence demonstrating superior sustained response versus placebo and favorable safety. [60, 61]

Earlier, in November 2022, the FDA approved **REBYOTA (RBX2660)**, a **single-dose, rectally administered** fecal microbiota, also indicated to **prevent rCDI** after standard antibiotics. Program data show clinically meaningful reductions in recurrence; regulated manufacturing and donor screening mitigate infectious risks that historically concerned UC clinicians contemplating FMT during immunosuppression. In practice, REBYOTA offers an option when oral administration is not feasible, whereas VOWST offers a non-procedural alternative—both relevant when tailoring to colitis severity, anatomy, and patient preference. [62]

In contrast, **probiotics** (conventional OTC formulations such as *Lactobacillus*, *Bifidobacterium*, or *Saccharomyces boulardii*) are **not recommended** by contemporary guidelines for primary or secondary prevention of CDI, owing to inconsistent efficacy signals and safety concerns (including rare fungemia/bacteremia) in immunocompromised hosts. For UC—where mucosal integrity is compromised and central lines or steroids are common—the risk-benefit calculus further disfavors routine probiotic use for CDI prevention. Clinicians should prioritize guideline-supported options (fidaxomicin/vancomycin ± bezlotoxumab;

FDA-approved microbiome therapeutics) over probiotics. [63, 64]

Among **novel, narrow-spectrum antibiotics**, **ridinilazole** (a precision agent sparing much of the microbiota) has shown mixed results: the global phase 3 program did **not achieve superiority** to vancomycin on sustained clinical response, though it **reduced recurrence** in some analyses and promoted faster microbiome recovery—signals that keep the concept alive though without regulatory approval to date. **Ibezapolstat** (DNA pol IIIC inhibitor) has reported encouraging **phase 2** efficacy and microbiome-sparing profiles versus vancomycin; larger trials are ongoing. For UC patients, these agents are intriguing because they may lessen dysbiosis-driven flares, but until definitive phase 3 data accrue and approvals are granted, they remain investigational. [65, 66, 67]

Preventive Strategies, Antibiotic Stewardship, and Hospital Infection Control in Ulcerative Colitis with Clostridium difficile Infection

Prevention of Clostridium difficile infection (CDI) in ulcerative colitis (UC) is a crucial yet often underestimated component of management. Given the elevated recurrence rates, high morbidity, and increased risk of colectomy, proactive preventive strategies are essential. Preventive measures encompass a multifaceted approach including antibiotic stewardship, infection control protocols, microbiome preservation, and patient-specific risk reduction.

Antibiotic stewardship forms the cornerstone of CDI prevention. The unnecessary or prolonged use of broad-spectrum antibiotics—particularly fluoroquinolones, cephalosporins, and clindamycin—is the most modifiable risk factor for CDI development and relapse. In UC, the decision to initiate antibiotics should be made cautiously, as they can exacerbate dysbiosis and trigger disease flares. Whenever possible, narrow-spectrum agents should be used, and treatment durations minimized. Hospital-based antimicrobial stewardship programs have been shown to reduce CDI incidence by up to 50% through formulary restriction, prescriber education, and feedback mechanisms [68].

Infection control measures are equally critical. Patients with confirmed or suspected CDI should be promptly placed under contact precautions, including single-room isolation, use of gloves and gowns, and strict adherence to hand hygiene with soap and water (as alcohol-based sanitizers are ineffective against spores). Environmental decontamination using sporicidal agents such as sodium hypochlorite or hydrogen peroxide vapor significantly reduces transmission risk. Hospitals with robust environmental cleaning protocols and surveillance systems report substantially lower CDI rates [69].

For UC patients, hospitalization itself increases exposure to CDI spores; thus, strategies to reduce hospital stay length and unnecessary admissions can mitigate risk. In outpatient settings, early recognition of CDI symptoms and testing during flares can prevent transmission and complications. Vaccination against CDI, an emerging area of interest, has shown promising immunogenicity in early trials, though clinical efficacy data remain limited [70].

Preservation and restoration of gut microbiota are fundamental for long-term prevention. Avoiding unnecessary antibiotic use, maintaining nutritional adequacy, and incorporating dietary fiber where feasible can promote microbial resilience. In high-risk or recurrent cases, microbiome-restorative therapies such as fecal microbiota transplantation (FMT) or FDA-approved live biotherapeutics (e.g., SER-109, RBX2660) should be considered as part of an integrated prevention strategy.

Lastly, patient education on hygiene, avoidance of self-prescribed antibiotics, and awareness of early CDI symptoms are pivotal for reducing recurrence. Multidisciplinary collaboration among gastroenterologists, infectious disease specialists, microbiologists, and infection control teams ensures a cohesive, evidence-based prevention framework for UC patients vulnerable to CDI [71].

Conclusion

Clostridium difficile infection (CDI) in ulcerative colitis (UC) represents a complex intersection of infection, inflammation, and microbiome disruption. Its management requires a careful balance between eradicating infection and maintaining control of underlying colitis. The coexistence of mucosal inflammation, immune dysregulation, and prior antibiotic exposure creates an ideal environment for CDI recurrence, amplifying morbidity and complicating treatment decisions.

Over the past decade, therapeutic strategies have evolved from a reliance on metronidazole toward more effective, microbiome-sparing regimens such as oral vancomycin and fidaxomicin. The incorporation of adjunctive and emerging interventions—including bezlotoxumab, fecal microbiota transplantation (FMT), and FDA-approved live microbiome therapeutics—has further

improved sustained remission rates and reduced recurrence. These advances underscore the growing emphasis on restoring gut microbial balance rather than simply targeting the pathogen.

Management of immunosuppressive and biologic therapy during CDI remains nuanced. Tailored decision-making, guided by clinical severity and infection control, is essential to avoid exacerbating either infection or colitis. Collaboration between gastroenterology and infectious disease specialists is vital to optimize outcomes, minimize complications, and prevent unnecessary colectomies.

Preventive measures remain foundational. Prudent antibiotic use, robust infection control practices, and early detection are the most effective tools to limit CDI incidence and recurrence in UC populations. The growing integration of microbiome-focused therapies offers a promising shift toward preventive and restorative care rather than purely reactive treatment.

Looking ahead, the field requires high-quality, UC-specific clinical trials to refine therapeutic algorithms, clarify optimal timing of immunosuppressive therapy, and define long-term outcomes of microbiome-based interventions. Personalized, microbiome-informed management—integrating host immunity, microbial ecology, and disease activity—represents the future direction for achieving durable remission and restoring intestinal health in this high-risk group.

Ultimately, effective management of CDI in UC hinges on a comprehensive, multidisciplinary approach that unites antimicrobial precision, microbiome preservation, and tailored immunologic control—transforming a historically difficult comorbidity into a manageable, evidence-guided clinical challenge.

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REFERENCES

1. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with Clostridium difficile in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2010;8(7):615–622.
2. Issa M, Vijayapal A, Graham MB, et al. Impact of Clostridium difficile on inflammatory bowel disease. *Inflamm Bowel Dis.* 2008;14(10):1432–1440.
3. Khanna S, Pardi DS. The growing incidence and severity of Clostridium difficile infection in inflammatory bowel disease: a call to arms. *Gut Microbes.* 2012;3(6):562–576.
4. Ianiro G, Masucci L, Quaranta G, et al. Fecal microbiota transplantation in inflammatory bowel disease: beyond the excitement. *Aliment Pharmacol Ther.* 2021;53(2):237–247.
5. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. Incidence of Clostridium difficile infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2007;5(3):343–348.
6. Nguyen GC, Kaplan GG, Harris ML, Brant SR. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol.* 2008;103(6):1443–1450.
7. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile–associated diarrhea with high morbidity and mortality. *N Engl J Med.* 2005;353(23):2442–2449.
8. Slimings C, Riley TV. Antibiotics and hospital-acquired Clostridium difficile infection: update of systematic review and meta-analysis. *Clin Microbiol Rev.* 2014;27(4):787–813.
9. Issa M, Vijayapal A, Graham MB, et al. Impact of Clostridium difficile on inflammatory bowel disease. *Inflamm Bowel Dis.* 2008;14(10):1432–1440.

10. Deshpande A, Pant C, Pasupuleti V, et al. Association between proton pump inhibitor therapy and Clostridium difficile infection in a meta-analysis. *Am J Gastroenterol.* 2012;107(7):1011–1019.
11. Allegretti JR, Mullish BH, Kelly C, Fischer M. The evolution of the use of faecal microbiota transplantation and emerging therapeutic indications. *J Crohns Colitis.* 2017;11(9):1129–1136.
12. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. Incidence of Clostridium difficile infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2007;5(3):343–348.
13. Khoruts A, Dicksved J, Jansson JK, Sadowsky MJ. Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent Clostridium difficile infection. *J Clin Gastroenterol.* 2010;44(6):446–453.
14. Ananthakrishnan AN, Guzman-Perez R, Gainer VS, et al. Predictors of severe outcomes associated with Clostridium difficile infection in inflammatory bowel disease. *Gut.* 2011;60(2):205–210.
15. Britton RA, Young VB. Role of the intestinal microbiota in resistance to colonization by Clostridium difficile. *Nat Rev Microbiol.* 2014;12(7):517–528.
16. Antoni L, Nuding S, Wehkamp J, Stange EF. Intestinal barrier in inflammatory bowel disease. *J Crohns Colitis.* 2014;8(9):1009–1019.
17. Kostic AD, Xavier RJ, Gevers D. The microbiome in inflammatory bowel disease: current status and the future ahead. *Cell Host Microbe.* 2014;15(3):382–392.
18. Pruitt RN, Lacy DB. Toward a structural understanding of Clostridium difficile toxins A and B. *Clin Microbiol Rev.* 2012;25(3):507–528.
19. Maharshak N, Arbel Y, Krugliak P, et al. Clostridium difficile infection in inflammatory bowel disease: effect of immunosuppressive therapy. *J Clin Gastroenterol.* 2012;46(9):e85–e90.
20. Buffie CG, Bucci V, Stein RR, et al. Precision microbiome reconstitution restores bile acid mediated resistance to Clostridium difficile. *Nature.* 2015;517(7535):205–208.
21. Collins J, Auchtung JM, Schaefer L, et al. Human gut microbiota protects against Clostridium difficile infection in gnotobiotic mice. *Gut Microbes.* 2013;4(5):403–408.
22. Issa M, Vijayapal A, Graham MB, et al. Impact of Clostridium difficile on inflammatory bowel disease. *Inflamm Bowel Dis.* 2008;14(10):1432–1440.
23. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalisation burden associated with Clostridium difficile in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2010;8(7):615–622.
24. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. Incidence of Clostridium difficile infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2007;5(3):343–348.
25. Surawicz CM, Brandt LJ, Binion DG, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. *Am J Gastroenterol.* 2013;108(4):478–498.
26. Crobach MJT, Dekkers OM, Wilcox MH, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidance document: diagnosis and management of Clostridium difficile infection. *Clin Microbiol Rev.* 2016;29(4):823–866.
27. Planche TD, Davies KA, Coen PG, et al. Differences in outcome according to Clostridium difficile testing method: a prospective multicentre diagnostic validation study. *Lancet Gastroenterol Hepatol.* 2018;3(8):529–538.
28. Navaneethan U, Venkatesh PG, Shen B. Clostridium difficile infection and inflammatory bowel disease: understanding the evolving relationship. *Inflamm Bowel Dis.* 2012;18(3):409–415.
29. Khanna S, Pardi DS. Clostridium difficile infection: new insights into management. *Am J Gastroenterol.* 2014;109(4):508–520.
30. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children. *Clin Infect Dis.* 2018;66(7):e1–e48.
31. Issa M, Vijayapal A, Graham MB, et al. *Inflamm Bowel Dis.* 2008;14(10):1432–1440.
32. Cornely OA, Miller MA, Louie TJ, Crook DW, Gorbach SL. Fidaxomicin versus vancomycin for Clostridium difficile infection. *Lancet Infect Dis.* 2012;12(4):281–289.
33. Kelly CP, LaMont JT. Clostridium difficile—more difficult than ever. *N Engl J Med.* 2014;370(16):1539–1548.
34. Trubiano JA, Cheng AC. Global epidemiology of Clostridium difficile infection in inflammatory bowel disease. *Med J Aust.* 2015;203(4):219–223.
35. Ananthakrishnan AN, Guzman-Perez R, Gainer VS, et al. *Gut.* 2011;60(2):205–210.
36. Feuerstadt P, Mawhinney J, Boules M, et al. Clostridium difficile infection in inflammatory bowel disease: a case series and review. *Clin Gastroenterol Hepatol.* 2020;18(2):383–392.
37. Nguyen GC, Kaplan GG, Harris ML, Brant SR. *Am J Gastroenterol.* 2008;103(6):1443–1450.

38. Allegretti JR, Mullish BH, Kelly C, Fischer M. *J Crohns Colitis.* 2017;11(9):1129–1136.
39. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. *Clin Gastroenterol Hepatol.* 2007;5(3):343–348.
40. Razik R, Rumman A, Bahreini Z, et al. Recurrence of Clostridium difficile infection in patients with inflammatory bowel disease: predictors and outcome. *Inflamm Bowel Dis.* 2016;22(4):902–909.
41. Singh S, Dulai PS, Vande Casteele N, et al. Safety of biologic therapies in ulcerative colitis. *Aliment Pharmacol Ther.* 2018;47(7):921–929.
42. Choi CH, Moon W, Kim YS, et al. Clostridium difficile infection and inflammatory bowel disease: a nationwide study. *World J Gastroenterol.* 2015;21(9):2661–2672.
43. Khanna S, Pardi DS. *Am J Gastroenterol.* 2014;109(4):508–520.
44. Issa M, Vijayapal A, Graham MB, et al. *Inflamm Bowel Dis.* 2008;14(10):1432–1440.
45. Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of Clostridium difficile and serum levels of IgG antibody against toxin A. *N Engl J Med.* 2000;342(6):390–397.
46. Loo VG, Poirier L, Miller MA, et al. *N Engl J Med.* 2005;353(23):2442–2449.
47. Cornely OA, Miller MA, Louie TJ, et al. *Lancet Infect Dis.* 2012;12(4):281–289.
48. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent Clostridium difficile infection. *N Engl J Med.* 2017;376(4):305–317.
49. Allegretti JR, Mullish BH, Kelly C, Fischer M. *J Crohns Colitis.* 2017;11(9):1129–1136.
50. Kelly CR, Kahn S, Kashyap P, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms, and outlook. *Gastroenterology.* 2015;149(1):223–237.
51. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. *N Engl J Med.* 2013;368(5):407–415.
52. Kao D, Roach B, Silva M, et al. Effect of fecal microbiota transplantation on recurrent Clostridium difficile infection in patients with inflammatory bowel disease: a multicenter study. *Gastroenterology.* 2017;152(4):799–811.
53. Paramsothy S, Kamm MA, Kaakoush NO, et al. Multidonor intensive fecal microbiota transplantation for active ulcerative colitis: a randomized placebo-controlled trial. *Lancet.* 2017;389(10075):1218–1228.
54. Cammarota G, Masucci L, Ianiro G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for recurrent Clostridium difficile infection. *Aliment Pharmacol Ther.* 2014;39(7):761–771.
55. DeFilipp Z, Bloom PP, Torres Soto M, et al. Drug-resistant E. coli bacteremia transmitted by fecal microbiota transplant. *N Engl J Med.* 2019;381(21):2043–2050.
56. Ianiro G, Masucci L, Quaranta G, et al. *Aliment Pharmacol Ther.* 2021;53(2):237–247.
57. Allegretti JR, Mullish BH, Kelly C, Fischer M. *Clin Gastroenterol Hepatol.* 2018;16(7):1036–1043.
58. Johnson S, Lavergne V, Skinner AM, et al. 2021 IDSA/SHEA Focused Update on Management of Clostridioides difficile Infection in Adults. *Clin Infect Dis.* 2021.
59. Wilcox MH, Gerding DN, Poxton IR, et al. *N Engl J Med.* 2017;376:305–317.
60. U.S. Food and Drug Administration. Approval of VOWST (SER-109). Press release; 2023.
61. Feuerstadt P, Louie TJ, Lashner B, et al. SER-109, an oral microbiome therapy for recurrent Clostridioides difficile infection. *N Engl J Med.* 2022;386:220–229.
62. U.S. Food and Drug Administration. Approval of REBYOTA (RBX2660). Press release; 2022.
63. Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of C. difficile infections. *Am J Gastroenterol.* 2021;116(6):1124–1147.
64. Bishop EJ, Tiruvoipati R, et al. Management of CDI in adults: comparison of IDSA/SHEA, ESCMID, and Australasian guidelines. *Clin Microbiol Infect.* 2022.
65. CIDRAP News. Ridinilazole phase 3 trial outcomes. Feb 2024.
66. Menon R, Bhattarai SK, Norman JM, et al. VE303 defined bacterial consortium for recurrent CDI. *Nat Med.* 2025.
67. Eubank TA, Alam MJ, Begum K, et al. Ibezapolstat versus vancomycin phase 2 trial. *Lancet Microbe.* 2024.
68. Slimings C, Riley TV. *Clin Microbiol Rev.* 2014;27(4):787–813.
69. Dubberke ER, Gerding DN. *Clin Infect Dis.* 2011;53(12):1260–1266.
70. de Bruyn G, Saleh J, Workman D, et al. Vaccine development for Clostridioides difficile. *Vaccine.* 2021;39(29):3806–3813.
71. Ananthakrishnan AN, Guzman-Perez R, Gainer VS, et al. *Gut.* 2011;60(2):205–210.