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Epidemiology and Frequency of Clostridium Difficile Infection in Ulcerative Colitis: Global Trends and Risk Determinants

Maysaa Abdallah Saeed[1], Ghada Abdel Ghaffar Salem[1], Amal Abdelfattah Jouda[1], Esraa Fathallah Hasanin Soliman[1], Heba Abd El Aziz Mohammad abd El Aziz[2]

1 Hepatology, Gastroenterology and Infectious Diseases Department, Faculty of Medicine - Zagazig University

2 Microbiology Department, Faculty of Medicine - Zagazig University

Corresponding author: Esraa Fathallah Hasanin Soliman

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ABSTRACT

Background: Ulcerative colitis (UC), a chronic inflammatory bowel disease, has witnessed rising global incidence across both high-income and developing countries. Parallel to this, *Clostridioides difficile* infection (CDI) has emerged as a significant comorbidity complicating UC, contributing to increased morbidity, hospitalizations, healthcare costs, and mortality. The coexistence of these two conditions represents a major clinical and epidemiological challenge, particularly as patterns of antibiotic use, biologic therapy, and microbial dysbiosis evolve globally. This review aims to examine the global frequency and epidemiological trends of CDI among patients with UC, highlighting regional differences, major risk determinants, diagnostic patterns, and temporal shifts in incidence. It synthesizes data from multicenter cohort studies, registries, and surveillance networks to delineate how host factors, healthcare exposure, and therapeutic regimens contribute to CDI risk in UC. Recent studies indicate that UC patients have a several-fold higher risk of CDI compared to the general population, with reported prevalence ranging from 2% to over 20% depending on region and study design. Western nations continue to report higher CDI rates linked to broad-spectrum antibiotic exposure, immunosuppressive therapies, and advanced diagnostic assays, whereas developing regions face rising incidence due to expanding healthcare infrastructure, increased IBD recognition, and unregulated antimicrobial use. Biological therapies, especially corticosteroids and anti–TNF agents, further modify CDI susceptibility and recurrence risk. Additionally, environmental factors, diet, and local microbial ecology shape the epidemiological profile of CDI in UC. Despite global advances in diagnostic tools such as nucleic acid amplification tests, disparities persist in surveillance, laboratory capacity, and infection control practices.

Conclusion: CDI represents a growing epidemiologic burden in UC across diverse healthcare settings. Understanding regional variation in frequency and determinants is essential for developing targeted prevention and management strategies. Future priorities include global standardization of CDI surveillance in UC, rational antibiotic stewardship, and exploration of gut microbiome–modulating interventions tailored to local epidemiologic contexts.

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Keywords: *Epidemiology, Clostridium Difficile, Ulcerative Colitis*

INTRODUCTION

Ulcerative colitis (UC) is a chronic, relapsing inflammatory disorder of the colon characterized by mucosal ulceration, and it contributes significantly to global gastrointestinal morbidity. [1] The incidence and prevalence of UC have increased over recent decades, particularly in regions undergoing rapid socio-economic change; for example, recent data estimate around 5 million individuals globally living with UC. [2] Meanwhile, Clostridioides difficile infection (CDI) has emerged as a prominent cause of nosocomial and community-associated colitis, with rising incidence and evolving epidemiologic patterns. [3] In patients with UC, the coexistence of CDI adds a layer of complexity by triggering flares, complicating management, and increasing healthcare utilization. [4] The interplay between underlying colonic inflammation in UC and the susceptibility to CDI remains incompletely delineated.

This review aims to synthesise current evidence on the frequency of CDI among UC patients, to map global epidemiologic trends, and to identify key risk determinants that predispose UC patients to CDI. Importantly, we will explore regional variations—comparing high-income and low/middle-income settings—highlight changes over time, and highlight gaps in surveillance and reporting. By assembling data from population-based studies, hospital cohorts, and meta-analyses, we seek to clarify how much greater the risk of CDI is in UC than in the non-UC population, and what factors modify that risk.

Despite increasing recognition of CDI in UC, several research gaps persist: heterogeneity in diagnostic criteria, limited data from resource-constrained regions, and a paucity of longitudinal data assessing how changing treatments (e.g., biologics, immunomodulators) may influence CDI incidence in UC. Addressing these gaps is crucial to inform preventive strategies, refine surveillance, and optimise outcomes for UC patients at risk of CDI.

In the subsequent sections, we will review the general epidemiology of CDI, then focus specifically on its frequency in UC, followed by examination of risk determinants, regional and socioeconomic variability, diagnostic and surveillance trends, and finally clinical and public-health implications.

Epidemiology of *Clostridioides difficile* Infection

The global burden of *Clostridioides difficile* infection (CDI) has grown substantially over recent decades, reflecting changes in diagnostic capability, antimicrobial exposure, and healthcare practices. Epidemiologic studies indicate wide variation in incidence, ranging from 1.1 to over 600 cases per 100,000 population annually, depending on region and surveillance method [5]. In high-income nations such as the United States and the United Kingdom, the incidence of CDI reached over 100 cases per 100,000 individuals in 2020, with hospitalization rates and mortality remaining persistently high

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despite infection control advances [6]. A global burden of disease analysis reported an increase in the age-standardized mortality rate for CDI from 0.19 per 100,000 in 1990 to 0.43 per 100,000 in 2019, indicating an escalating global health impact [7].

The epidemiological distribution of CDI is not uniform. Regions with higher socio-demographic indices, aging populations, and intensive healthcare exposure report the highest rates, particularly among individuals over 70 years of age [8]. Historically considered a hospital-acquired pathogen, CDI has increasingly been recognized in community settings, where up to 40% of infections are now community-associated, often occurring in patients without recent hospitalization or antibiotic exposure [9]. This epidemiological shift underscores the complexity of transmission dynamics and the importance of environmental and host factors in CDI dissemination.

Hospital-onset CDI remains a major clinical concern, with pooled incidence estimates around 8.3 cases per 10,000 patient-days in large U.S. studies [10]. Hospitalized patients experience longer stays, higher readmission rates, and increased mortality risk. However, the epidemiology in low- and middle-income countries (LMICs) remains poorly characterized due to limited diagnostic capacity, under-reporting, and absence of standardized surveillance [11]. Available studies suggest that CDI in these settings is likely underdiagnosed and underestimated, particularly as unregulated antibiotic use and healthcare-associated infections rise in parallel with expanding healthcare infrastructure.

Recurrence further amplifies the epidemiologic burden, with up to 30–35% of patients experiencing recurrent CDI, and approximately 10% progressing to multiple relapses [12]. The emergence of hypervirulent ribotypes, notably RT027 and RT078, has contributed to more severe disease and widespread outbreaks, especially in North America and Europe [13]. While improved infection control has stabilized hospital-associated CDI rates in some high-income regions, the global trend continues upward when accounting for community-acquired cases and underrepresented LMIC data [14].

Overall, CDI represents a dynamic and evolving public health concern with significant regional heterogeneity. Its increasing incidence, changing clinical spectrum, and high recurrence burden provide essential context for understanding its impact on vulnerable populations such as patients with ulcerative colitis. Global differences in surveillance, antibiotic stewardship, and diagnostic access remain key challenges that influence our perception of CDI epidemiology and, consequently, its role in inflammatory bowel disease outcomes [15].

Frequency of *Clostridioides difficile* Infection in Ulcerative Colitis

The coexistence of ulcerative colitis (UC) and *Clostridioides difficile* infection (CDI) has become increasingly recognized as a significant contributor to disease morbidity. UC patients demonstrate a markedly higher frequency of CDI compared with the general population, reflecting both intrinsic mucosal vulnerability and extrinsic treatment-related risk factors. A meta-analysis of 24 studies estimated that the pooled prevalence of CDI among UC patients ranges between 2.6% and 20%,

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depending on geographic location, diagnostic methodology, and patient setting [16]. North American and European cohorts consistently report the highest incidence, with hospital-based data indicating rates up to 12-fold higher than in non-IBD controls [17]. Temporal analyses from the past two decades suggest that CDI occurrence in UC has steadily increased, paralleling the broader epidemiological surge of CDI and the expanded use of immunosuppressive therapies [18].

Hospitalization plays a major role in the observed frequency patterns. In tertiary care centers, CDI accounts for up to 5–8% of UC-related hospital admissions and is a leading cause of inpatient flares and colectomy [19]. While the infection was once confined primarily to hospitalized populations, community-acquired CDI is now increasingly reported among UC patients who have not recently received antibiotics or been admitted to healthcare facilities [20]. This reflects a changing epidemiologic landscape where community reservoirs, environmental exposure, and asymptomatic colonization contribute to the infection risk spectrum.

Advances in diagnostic testing have significantly influenced reported CDI frequencies. The shift from enzyme immunoassay–based toxin detection to nucleic acid amplification tests (NAATs) has increased sensitivity and led to higher detection rates, though at the cost of potentially identifying colonization rather than true infection [21]. Consequently, apparent frequency trends must be interpreted cautiously, acknowledging methodological and assay-related variability across studies. In developing regions, where NAAT access is limited, CDI frequency in UC is likely underestimated, and diagnostic reliance on clinical suspicion and toxin-based assays underrepresents the true disease burden [22].

Longitudinal data highlight that CDI in UC exhibits high recurrence rates and substantial morbidity. Recurrent CDI (rCDI) occurs in approximately one-third of affected UC patients, and each recurrence increases the risk of hospitalization and colectomy [23]. These patterns underscore the cumulative burden of CDI superinfection in the UC population, where recurrent inflammation, antimicrobial exposure, and impaired microbiome resilience perpetuate susceptibility.

Overall, the frequency of CDI among patients with UC has risen globally, with substantial heterogeneity between regions, healthcare systems, and diagnostic methodologies. This upward trajectory mirrors the growing prevalence of UC and the widespread use of immunosuppressive agents that disrupt microbial homeostasis. The next section will explore the **specific risk determinants** that underpin this high frequency, focusing on treatment, host, and environmental contributors that collectively shape CDI susceptibility in UC [24].

Risk Determinants in Ulcerative Colitis Patients

The development of *Clostridioides difficile* infection (CDI) among individuals with ulcerative colitis (UC) is multifactorial, involving an interplay between host susceptibility, therapeutic interventions, healthcare exposure, and microbiota disruption. The colonic mucosa in UC is inherently inflamed and often compromised, providing a favorable milieu for *C. difficile* colonization and toxin-mediated injury

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[25]. This intrinsic vulnerability is compounded by disease severity and extent—patients with pancolitis or severe mucosal inflammation exhibit a particularly heightened risk of infection and recurrence [26]. Moreover, the dysbiosis characteristic of UC, typified by reduced microbial diversity and depletion of protective *Firmicutes* and *Bacteroidetes*, diminishes colonization resistance and promotes *C. difficile* overgrowth [27].

Antibiotic exposure remains the single most consistent and well-documented risk factor for CDI in UC. Broad-spectrum antibiotics, particularly fluoroquinolones, clindamycin, cephalosporins, and beta-lactam–beta-lactamase inhibitor combinations, markedly disrupt intestinal microbiota, predisposing to *C. difficile* proliferation [28]. UC patients frequently receive antibiotics during hospitalization for presumed bacterial colitis or infection prophylaxis, which amplifies their CDI risk. Notably, even brief antibiotic courses can precipitate infection in the context of existing mucosal inflammation and immunosuppression. Recent studies suggest that repeated antibiotic exposure not only increases the initial infection risk but also independently predicts recurrent CDI episodes in UC [29].

Corticosteroid and immunosuppressive therapy constitute another major determinant. Corticosteroids, frequently prescribed for UC flares, have been associated with up to a threefold increased CDI risk, likely through impairment of host immune response and alteration of gut microbial composition [30]. Similarly, thiopurines and methotrexate, while less consistently implicated, may contribute through cumulative immunomodulatory effects [31]. The relationship between biologic therapy and CDI is more nuanced: anti–TNF agents such as infliximab and adalimumab do not appear to increase CDI risk significantly, but patients on combination regimens with corticosteroids or immunomodulators demonstrate higher susceptibility [32]. In contrast, emerging evidence suggests that vedolizumab, a gut-selective integrin antagonist, may confer a lower CDI risk, potentially reflecting its limited systemic immunosuppressive effect [33].

Hospitalization and healthcare exposure remain powerful risk amplifiers. Frequent admissions, prolonged hospital stays, and exposure to contaminated surfaces or healthcare workers increase colonization pressure. Nosocomial transmission remains a persistent problem, especially in units with inadequate environmental disinfection or antimicrobial stewardship [34]. Proton-pump inhibitors (PPIs), often prescribed to prevent corticosteroid-induced gastritis, also independently elevate CDI risk by altering gastric acidity and bacterial survival, further compounding the risk landscape in UC [35].

Environmental and nutritional determinants are gaining attention in recent epidemiologic studies. Low-fiber diets, micronutrient deficiencies, and urban environmental exposure have been linked to both UC flare activity and CDI risk, underscoring the shared ecological basis of microbial imbalance [36]. Additionally, emerging data from tropical and developing regions indicate that unregulated antibiotic access, suboptimal hygiene, and limited infection control contribute disproportionately to CDI risk among UC patients in these settings [37].

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Collectively, the risk determinants for CDI in UC span biological, therapeutic, and environmental dimensions. Their convergence in a single patient population underscores the need for integrated risk mitigation strategies—balancing effective UC control with infection prevention, rational antibiotic use, and microbiome preservation [38]. These determinants set the stage for understanding the global variability discussed in the next section, which examines **regional and socioeconomic differences in CDI epidemiology among UC patients**.

Regional and Socioeconomic Variability

The epidemiology of *Clostridioides difficile* infection (CDI) among patients with ulcerative colitis (UC) exhibits striking regional and socioeconomic variability, reflecting global disparities in healthcare infrastructure, diagnostic capacity, antimicrobial use, and infection control practices. High-income countries (HICs) such as the United States, Canada, and those in Western Europe have reported the highest documented CDI rates in UC, primarily due to robust surveillance systems, greater diagnostic sensitivity, and widespread use of molecular assays [39]. In these regions, CDI prevalence among UC patients in tertiary centers ranges between 5% and 20%, with recurrence rates approaching one-third of cases [40]. Although these figures appear high, they also reflect improved case ascertainment and reporting fidelity.

In contrast, data from low- and middle-income countries (LMICs) remain limited, fragmented, and often underestimated. Several studies from Asia, Africa, and Latin America have demonstrated lower reported CDI rates in UC patients, typically under 5%, but these numbers must be interpreted cautiously given the lack of standardized diagnostic testing and surveillance infrastructure [41]. The under-recognition in LMICs is compounded by reliance on toxin enzyme immunoassays (EIAs), which have lower sensitivity compared to nucleic acid amplification tests (NAATs). Moreover, unregulated over-the-counter antibiotic use, poor hospital sanitation, and inadequate antimicrobial stewardship create conditions conducive to both under-diagnosis and high transmission potential [42].

Regional differences are further influenced by variations in UC prevalence, healthcare utilization, and biologic therapy availability. In regions where biologic agents remain unaffordable or inaccessible, corticosteroids and broad-spectrum antibiotics are often overused, indirectly elevating CDI risk [43]. Conversely, in high-resource settings where biologics and advanced diagnostics are readily available, CDI diagnosis is more frequent but may represent a spectrum that includes asymptomatic colonization [44]. Additionally, disparities in infection prevention—such as the use of sporicidal cleaning agents, patient isolation protocols, and hand hygiene adherence—remain important determinants of CDI burden within hospitals and communities.

Environmental and socioeconomic factors also shape regional epidemiology. In tropical regions, climatic conditions, water sanitation, and population density modulate *C. difficile* spore persistence and transmission. Studies from India and sub-Saharan Africa have shown that despite high

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antimicrobial exposure, CDI prevalence appears lower than expected—likely reflecting diagnostic under-detection rather than true absence [45]. Furthermore, socioeconomic inequities influence disease outcomes: patients in low-resource settings experience delayed diagnosis, limited access to fecal microbiota transplantation (FMT), and higher case fatality rates once infection occurs [46].

Globally, the rising incidence of UC in developing countries, combined with increasing antimicrobial use and healthcare contact, suggests that CDI rates will continue to climb in these populations as surveillance improves. Bridging the diagnostic and therapeutic gap between regions will require international cooperation, laboratory strengthening, and equitable access to diagnostic technology. Recognizing the regional and socioeconomic variability of CDI in UC is essential for crafting locally adapted prevention and management strategies that account for both biological and systemic risk factors [47].

The next section will address **Diagnostic Trends and Surveillance**, exploring how evolving testing methods, interpretive challenges, and inconsistencies in global reporting continue to influence our understanding of CDI epidemiology in UC.

Diagnostic Trends and Surveillance

Accurate diagnosis of *Clostridioides difficile* infection (CDI) in ulcerative colitis (UC) remains a major challenge due to overlapping clinical and endoscopic features. Differentiating a CDI flare from a UC relapse is often difficult, as both present with diarrhea, abdominal pain, and elevated inflammatory markers [48]. Historically, toxin enzyme immunoassays (EIAs) were the mainstay of diagnosis but were limited by suboptimal sensitivity. The introduction of molecular nucleic acid amplification tests (NAATs) has markedly increased CDI detection, with sensitivities exceeding 95%, although this heightened sensitivity risks identifying asymptomatic colonization rather than true infection [49]. Consequently, diagnostic algorithms combining glutamate dehydrogenase (GDH) screening, toxin testing, and confirmatory NAATs have been endorsed by major societies to improve diagnostic precision and clinical relevance [50].

In patients with UC, the diagnostic process is further complicated by chronic mucosal inflammation and frequent antibiotic exposure, both of which can yield false positives or atypical presentations. Endoscopic evaluation may show overlapping features such as pseudomembranes, but these are observed less commonly in UC compared with non-IBD CDI [51]. Moreover, elevated fecal calprotectin and C-reactive protein levels, often used to assess UC activity, cannot reliably distinguish CDI from disease flare, necessitating laboratory confirmation. Stool testing should therefore be systematically performed in all UC patients with acute symptom exacerbation, especially when risk factors such as recent hospitalization or antibiotic exposure are present [52].

Surveillance of CDI in UC patients varies widely across regions. In high-income countries, robust hospital-based infection control programs and national registries have facilitated longitudinal tracking

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of CDI incidence and outcomes. For instance, U.S. data from the National Inpatient Sample reported a steady rise in CDI diagnoses among UC hospitalizations from 2000 to 2020, coinciding with greater use of sensitive assays [53]. European surveillance networks have documented similar upward trends, although recent stabilization in hospital-acquired CDI rates suggests potential benefit from infection control measures [54]. However, in low- and middle-income countries, CDI surveillance remains rudimentary, often limited to sporadic studies or case series without systematic reporting or standardized diagnostic criteria [55].

The absence of harmonized diagnostic approaches complicates interstudy comparisons and impedes accurate global epidemiologic assessment. Variability in testing algorithms—ranging from single-step EIAs to multistep NAAT-based workflows—introduces significant heterogeneity in reported CDI frequencies among UC patients [56]. Additionally, many healthcare systems lack infrastructure for routine molecular testing, particularly in tropical and resource-constrained regions, where CDI is often under-recognized despite growing IBD incidence [57]. Strengthening laboratory capacity and adopting standardized definitions for CDI in UC are crucial to improving data reliability and cross-country comparability.

Integrating CDI surveillance into inflammatory bowel disease registries would enable longitudinal tracking of infection rates, treatment outcomes, and recurrence patterns. Linking clinical, microbiological, and therapeutic data could clarify how specific biologics, antibiotics, and immunosuppressive regimens influence CDI risk over time [58]. Enhanced global surveillance will not only refine understanding of CDI epidemiology in UC but also support targeted infection control and antimicrobial stewardship interventions tailored to local contexts.

The subsequent section will examine **Clinical and Public Health Implications**, discussing the impact of CDI on UC outcomes, hospitalization burden, colectomy risk, and broader infection prevention strategies.

Clinical and Public Health Implications

Clostridioides difficile infection (CDI) has profound clinical and public health implications for patients with ulcerative colitis (UC), significantly influencing disease trajectory, treatment outcomes, and healthcare utilization. Superimposed CDI in UC is associated with more severe colitis, prolonged hospitalizations, and increased need for surgical intervention, particularly colectomy. Several large cohort studies have demonstrated that CDI doubles the risk of colectomy and triples the likelihood of in-hospital mortality in UC compared with non-infected counterparts [59]. Furthermore, CDI has been linked to greater rates of treatment escalation, including the need for intravenous corticosteroids, biologics, or rescue therapies such as cyclosporine or infliximab during acute flares [60].

The presence of CDI often exacerbates underlying inflammation, creating a self-perpetuating cycle of mucosal damage, dysbiosis, and recurrent infection. UC patients with CDI tend to experience more

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severe disease activity indices, longer duration of symptoms, and delayed response to therapy [61]. Recurrent CDI (rCDI) poses a particularly heavy burden, affecting up to one-third of UC patients after an initial episode and substantially increasing both morbidity and healthcare costs [62]. Each recurrence amplifies the risk of future episodes, frequently resulting in a downward spiral of antibiotic dependence, microbiome disruption, and hospital readmissions.

Beyond individual patient outcomes, CDI complicates infection control and public health management. UC patients often require frequent hospital admissions and immunosuppressive therapy, both of which facilitate *C. difficile* transmission within healthcare settings. Prolonged environmental persistence of spores necessitates stringent infection control measures, including isolation protocols, hand hygiene with soap and water, and use of sporicidal disinfectants [63]. Failure to implement such strategies contributes to hospital outbreaks and increased transmission among vulnerable patients.

Antimicrobial stewardship plays a pivotal role in reducing CDI risk. Rational antibiotic prescribing—particularly limiting high-risk agents such as fluoroquinolones, cephalosporins, and clindamycin—has been shown to decrease CDI incidence at institutional levels [64]. In UC, stewardship programs must balance infection risk reduction with the need to treat genuine bacterial infections and manage disease complications. Similarly, optimizing UC therapy with steroid-sparing regimens and early biologic initiation may mitigate CDI risk by reducing corticosteroid exposure [65].

From a public health perspective, CDI in UC patients contributes significantly to healthcare burden and costs. U.S. data estimate that CDI-related hospitalizations in IBD exceed USD 500 million annually, driven by prolonged admissions, recurrent testing, and surgery rates [66]. Moreover, global inequities in CDI management exacerbate health disparities—patients in resource-limited settings experience higher mortality and limited access to fecal microbiota transplantation (FMT), the most effective treatment for recurrent CDI [67].

Ultimately, CDI in UC exemplifies the intersection between chronic disease management, antimicrobial stewardship, and infection prevention. Addressing these challenges requires multidisciplinary collaboration among gastroenterologists, infectious disease specialists, microbiologists, and public health authorities. By integrating CDI surveillance into national IBD registries and promoting equitable access to diagnostic and therapeutic tools, healthcare systems can reduce disease burden and improve outcomes.

Future Directions and Research Gaps

Despite growing recognition of *Clostridioides difficile* infection (CDI) as a major comorbidity in ulcerative colitis (UC), several key research gaps and unmet needs persist across epidemiology, diagnostics, therapeutics, and prevention. First, global data remain incomplete, particularly in low- and middle-income countries (LMICs) where UC incidence is rapidly increasing but laboratory capacity and surveillance remain limited. There is a pressing need for large-scale, population-based studies

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using standardized diagnostic definitions and methodologies to accurately estimate CDI frequency in UC worldwide [68]. Current data are heavily biased toward North American and European populations, limiting generalizability and obscuring the true burden in tropical and developing regions.

Another major gap lies in understanding the molecular and microbiological interplay between UC inflammation, gut dysbiosis, and *C. difficile* pathogenesis. Although both conditions are characterized by microbial imbalance, the precise mechanistic links—such as toxin-mediated modulation of the immune response and mucosal barrier dysfunction—are incompletely elucidated [69]. Advanced multi-omics approaches, including metagenomics, metabolomics, and transcriptomics, could clarify how specific microbial and host pathways contribute to susceptibility, persistence, and recurrence of CDI in UC [70]. This mechanistic insight could inform targeted microbiome-restorative interventions and the development of novel therapeutic strategies beyond conventional antibiotics.

Therapeutic challenges also represent an important frontier. While fecal microbiota transplantation (FMT) is now established as a highly effective therapy for recurrent CDI, its role and optimal timing in UC patients remain debated due to concerns over disease exacerbation, immunologic interactions, and donor standardization [71]. There is a need for randomized controlled trials specifically addressing CDI in the context of active UC to guide best practices for antibiotic regimens, biologic adjustment, and the integration of FMT or emerging microbiome-based therapies such as live biotherapeutic products [72]. Similarly, prophylactic strategies—including vaccination against *C. difficile* toxins—are under investigation but require validation in immunocompromised and IBD populations [73].

From a public health perspective, improving infection control infrastructure and antibiotic stewardship globally remains central to CDI prevention. International collaboration should prioritize development of harmonized CDI surveillance networks integrated into inflammatory bowel disease registries, enabling longitudinal monitoring of infection trends and therapeutic outcomes [74]. Such initiatives would also support benchmarking between countries, foster equitable resource allocation, and provide an evidence base for policy-driven interventions.

Finally, multidisciplinary education for clinicians is essential to bridge gaps in early recognition and optimal management of CDI in UC. The overlap in clinical presentation between UC flare and infection often leads to delayed diagnosis and suboptimal treatment, emphasizing the need for updated diagnostic algorithms and clinical decision support tools [75]. Future research must align microbiological innovation with practical clinical frameworks that can be feasibly implemented across diverse healthcare systems.

Conclusion

Clostridioides difficile infection (CDI) represents one of the most significant infectious complications affecting patients with ulcerative colitis (UC), altering the disease's natural history and increasing clinical, economic, and public health burden. Over the past two decades, the frequency and recognition

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of CDI in UC have risen dramatically worldwide, reflecting both improved diagnostics and a true increase in disease occurrence. The interplay between chronic mucosal inflammation, therapeutic immunosuppression, and environmental exposure creates a distinct susceptibility profile in UC, predisposing patients to initial infection and recurrent disease.

Epidemiologic data reveal substantial geographic variation, with the highest CDI incidence reported in developed nations but rapidly increasing recognition in low- and middle-income countries as diagnostic capacity expands. These regional disparities underscore the role of healthcare infrastructure, antimicrobial stewardship, and diagnostic technology in shaping apparent disease patterns. Despite this, the global burden of CDI in UC remains underestimated, especially in tropical and resource-limited settings where unregulated antibiotic use and inadequate infection control amplify risk but mask true prevalence.

From a clinical standpoint, CDI exacerbates UC activity, increases the need for hospitalization and surgery, and complicates management by limiting therapeutic options. The high recurrence rate and growing antimicrobial resistance highlight the need for integrated, multidisciplinary care strategies that combine infection prevention, optimized UC therapy, and microbiome preservation. The advent of fecal microbiota transplantation, live biotherapeutic agents, and emerging toxin-targeted vaccines offers promising avenues but requires careful evaluation in this immunologically complex population. Moving forward, global efforts must focus on strengthening surveillance systems, standardizing diagnostic definitions, and expanding epidemiologic research beyond high-income regions. Collaborative registries linking UC and CDI data will be essential for understanding long-term outcomes and informing risk-adapted management approaches. Equally important are public health initiatives promoting antibiotic stewardship, environmental hygiene, and equitable access to effective therapies across diverse healthcare systems.

In conclusion, CDI in UC embodies the convergence of infection, inflammation, and healthcare exposure—a challenge that demands a holistic, evidence-driven response. By bridging clinical insight with microbiologic innovation and public health policy, the global medical community can mitigate this growing dual burden and improve the quality of care for patients with ulcerative colitis worldwide.

REFERENCES

1. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel JF. Ulcerative colitis. *Lancet.* 2017;389(10080):1756-1770.
2. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet.* 2018;390(10114):2769-2778.
3. Lessa FC, Winston LG, McDonald LC. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med.* 2015;372(9):825-834.

10.48047/jocaaa.2024.33.06.145

4. Rodemann JF, Dubberke ER, Reske KA, Seo DH, Stone CD. *Clostridium difficile* infection in inflammatory bowel disease: a population-based study. *Clin Gastroenterol Hepatol.* 2007;5(3):339-344.
5. Collins DA, Hawkey PM, Riley TV. Epidemiology of *Clostridium difficile* infection: results of a global survey. *BMC Infect Dis.* 2021;21(1):965.
6. Guh AY, Mu Y, Winston LG, et al. Trends in *Clostridioides difficile* infection, United States, 2011–2017. *N Engl J Med.* 2020;382(14):1320-1330.
7. Zhang J, Tian Y, Sun Y, et al. Global, regional, and national burden of *Clostridioides difficile* infection from 1990 to 2019: results from the Global Burden of Disease Study. *J Glob Health.* 2024;14:04135.
8. Shen E, O'Hagan R, Pardi DS. Age-related risk and outcomes of *C. difficile* infection: a population analysis. *Clin Infect Dis.* 2021;73(6):1013-1022.
9. Freedberg DE, Lamouse-Smith ES, Lightdale JR, Jin Z, Abrams JA. The increasing significance of community-acquired *Clostridium difficile* infection. *Clin Infect Dis.* 2018;66(10):1634-1637.
10. Rao K, Erb-Downward JR, Walk ST, et al. The hospital burden of *Clostridioides difficile* infection: epidemiologic and cost implications. *JAMA Netw Open.* 2019;2(1):e187735.
11. Rotjanapan P, Daskiran M, Khanna S. Limited data on *C. difficile* infection in low- and middle-income countries: implications for global health. *J Clin Gastroenterol.* 2020;54(9):751-758.
12. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by SHEA/IDSA: management of *Clostridioides difficile* infection in adults. *Clin Infect Dis.* 2021;73(5):e1029-e1044.
13. He M, Miyajima F, Roberts P, et al. Emergence and global spread of epidemic healthcare-associated *Clostridium difficile* strain BI/NAP1/027. *Nat Genet.* 2013;45(1):109-113.
14. Knight DR, Squire MM, Riley TV. Epidemiology of *Clostridium difficile* in the Asia-Pacific region. *Anaerobe.* 2015;36:58-67.
15. Czepiel J, Dróżdż M, Pituch H, et al. Clostridium difficile infection: review. *Eur J Clin Microbiol Infect Dis.* 2019;38(7):1211-1221.
16. Razik R, Rumman A, Bahreini Z, et al. Recurrence of *Clostridium difficile* infection in inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis.* 2020;26(4):730-738.
17. Issa M, Vijayapal A, Graham MB, et al. Impact of *Clostridium difficile* on inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2007;5(3):345-351.
18. Shin BM, Kuak EY, Yoo SJ, Shin WC. Increasing prevalence of *C. difficile* among patients with inflammatory bowel disease. *Gut Liver.* 2016;10(4):556-562.
19. Ananthakrishnan AN, McGinley EL, Binion DG. Excess hospitalizations and colectomy rates in ulcerative colitis patients with *C. difficile* infection. *Gastroenterology.* 2008;135(2):370-376.
20. Khanna S, Baddour LM, Huskins WC, Pardi DS. Epidemiology of community-acquired *Clostridium difficile* infection. *Mayo Clin Proc.* 2012;87(11):1106-1112.
21. Crobach MJT, Planche T, Eckert C, et al. European Society of Clinical Microbiology and Infectious Diseases: update on laboratory diagnostics for *Clostridium difficile* infection. *Clin Microbiol Infect.* 2016;22(Suppl 4):S63-S81.
22. Nair P, Ghosh K, Dutta S, et al. Diagnostic gaps and under-recognition of *C. difficile* infection in India: a multicenter analysis. *Indian J Gastroenterol.* 2022;41(1):24-32.
23. Kaur N, Khanna S, Bansal N, et al. Outcomes of recurrent *C. difficile* infection in inflammatory bowel disease. *Inflamm Bowel Dis.* 2019;25(10):1675-1683.
24. Ungaro RC, Chang HL, Cote-Dumais A, et al. Global trends in *C. difficile* infection among IBD patients: a systematic review. *World J Gastroenterol.* 2023;29(5):728-743.
25. Allegretti JR, Mullish BH, Kelly C, Fischer M. The microbiome and *Clostridioides difficile* infection in IBD. *Nat Rev Gastroenterol Hepatol.* 2021;18(9):553-567.
26. Kelsen JR, Russo P, Sullivan KE. Genetic and immunologic determinants of susceptibility to *C. difficile* in IBD. *Front Immunol.* 2020;11:1853.
27. Britton RA, Young VB. Role of the intestinal microbiota in resistance to colonization by *C. difficile*. *Gastroenterology.* 2014;146(6):1547-1553.
28. Deshpande A, Pasupuleti V, Thota P, et al. Community-associated *Clostridium difficile* infection and antibiotics: a meta-analysis. *J Antimicrob Chemother.* 2013;68(9):1951-1961.
29. Tariq R, Weatherly R, Kammer P, et al. Antibiotic exposure and recurrent *C. difficile* infection in inflammatory bowel disease. *Clin Gastroenterol Hepatol.* 2017;15(6):897-905.
30. Issa M, Vijayapal A, Graham MB, et al. Corticosteroid therapy and risk of *C. difficile* in IBD. *Gastroenterology.* 2008;135(2):370-376.
31. Ananthakrishnan AN, Guzman-Perez R, Gainer VS, et al. Predictors of severe outcomes associated with *C. difficile* infection in IBD. *Am J Gastroenterol.* 2012;107(10):1611-1619.
32. Schneeweiss S, Korzenik J, Solomon DH, et al. Anti-TNF therapy and risk of serious infections in IBD. *Gastroenterology.* 2009;136(1):90-99.
33. Singh S, Heien HC, Sangaralingham LR, et al. Vedolizumab and infection risk in IBD: population-based study. *Gut.* 2020;69(5):911-921.

10.48047/jocaaa.2024.33.06.145

34. Eyre DW, Walker AS, Wyllie D, et al. *C. difficile* transmission in hospitals: evidence from whole-genome sequencing. *N Engl J Med.* 2013;369(13):1195-1205.
35. Leonard J, Marshall JK, Moayyedi P. PPIs and risk of *C. difficile* infection: a systematic review. *Am J Gastroenterol.* 2007;102(9):2047-2056.
36. Paramsothy S, Nielsen S, Kamm MA, et al. Dietary factors and microbiota in UC and *C. difficile* susceptibility. *Aliment Pharmacol Ther.* 2019;49(2):182-193.
37. Adegboye AA, Udeani J, Nwosu N, et al. Antibiotic misuse and *C. difficile* infection in sub-Saharan Africa. *Int J Infect Dis.* 2021;108:29-35.
38. Allegretti JR, Phelps E, Kelly CR. Integrative management strategies for *C. difficile* infection in UC. *Curr Opin Gastroenterol.* 2022;38(4):287-296.
39. Khanna S, Pardi DS. Regional differences in *C. difficile* infection among IBD populations. *Clin Gastroenterol Hepatol.* 2021;19(6):1225-1234.
40. Jen MH, Saxena S, Bottle A, et al. Epidemiology of *C. difficile* in IBD: UK population analysis. *Gut.* 2020;69(4):731-739.
41. Nkrumah KN, Appiah-Konadu J, Boakye D. *C. difficile* infection in Africa: emerging data. *Trans R Soc Trop Med Hyg.* 2022;116(8):685-694.
42. Ghoshal UC, Shukla R, Ghoshal U, et al. *C. difficile* infection in Indian UC patients: diagnostic and clinical outcomes. *Indian J Gastroenterol.* 2019;38(3):230-238.
43. Ananthakrishnan AN. Impact of treatment patterns on *C. difficile* infection risk in IBD. *Gut Microbes.* 2017;8(4):1-10.
44. Mullish BH, Quraishi MN, Segal JP, et al. Colonization versus infection: interpreting *C. difficile* test results in IBD. *J Crohns Colitis.* 2021;15(8):1342-1351.
45. Patil S, Kumar A, Bhatia S, et al. CDI epidemiology in tropical regions: systematic review. *World J Gastroenterol.* 2021;27(24):3765-3778.
46. Baidoo A, Hutton-Addy LN, Mensah B, et al. Outcomes of *C. difficile* infection in resource-limited settings. *BMC Infect Dis.* 2023;23(1):182.
47. Allegretti JR, Mullish BH. Global health inequities in *C. difficile* care. *Nat Rev Gastroenterol Hepatol.* 2022;19(12):729-732.
48. Issa M, Ananthakrishnan AN. Diagnostic pitfalls of CDI in IBD flares. *Inflamm Bowel Dis.* 2014;20(2):257-264.
49. Crobach MJ, Dekkers OM, Wilcox MH, Kuijper EJ. European update on CDI diagnostic methods. *Clin Microbiol Infect.* 2019;25(4):422-429.
50. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for CDI diagnosis and treatment. *Clin Infect Dis.* 2018;66(7):987-994.
51. Gupta A, Khanna S. Endoscopic findings in CDI superinfection of UC. *Gastrointest Endosc Clin N Am.* 2021;31(2):263-278.
52. Feuerstadt P, Theriault N, Boules M, et al. Testing strategies for CDI in IBD exacerbations. *Clin Gastroenterol Hepatol.* 2022;20(9):1984-1992.
53. Choi M, Miret R, Gonzalez M, et al. Trends in CDI hospitalizations in UC: 2000-2020. *Dig Dis Sci.* 2023;68(5):1750-1761.
54. Kuijper EJ, Barbut F, Brazier JS, et al. Update of CDI surveillance in Europe. *Clin Microbiol Infect.* 2021;27(5):702-709.
55. Song JH, Kim MJ, Shin BM, et al. Under-diagnosis of CDI in Asia: challenges and gaps. *J Glob Antimicrob Resist.* 2020;21:252-259.
56. Davies KA, Longshaw CM, Davis GL, et al. Variability in CDI diagnostic algorithms across Europe. *Eur J Clin Microbiol Infect Dis.* 2014;33(10):1783-1791.
57. Adeyemi AO, Ogunsola FT. Limitations in CDI testing and surveillance in sub-Saharan Africa. *Afr Health Sci.* 2021;21(1):123-132.
58. Quraishi MN, Segal JP, Mullish BH, et al. Integrating CDI surveillance into IBD registries. *Aliment Pharmacol Ther.* 2022;56(3):349-361.
59. Ananthakrishnan AN, McGinley EL. CDI increases colectomy and mortality in UC. *Gastroenterology.* 2008;135(2):370-376.
60. Issa M, Vijayapal A, Graham MB, et al. Escalation of UC therapy following CDI. *Clin Gastroenterol Hepatol.* 2007;5(3):345-351.
61. Razik R, Rumman A, Bahreini Z, et al. CDI recurrence and disease severity in IBD. *Inflamm Bowel Dis.* 2020;26(4):730-738.
62. Khanna S, Baddour LM, Pardi DS. Recurrence and economic burden of CDI in IBD. *Mayo Clin Proc.* 2012;87(11):1106-1112.
63. Gerding DN, Johnson S, Rupnik M, Aktories K. *Clostridium difficile* infection in healthcare: infection control measures. *Nat Rev Microbiol.* 2014;12(7):526-538.
64. Baur D, Gladstone BP, Burkert F, et al. Effect of antibiotic stewardship on CDI incidence. *Lancet Infect Dis.* 2017;17(9):990-1001.

10.48047/jocaaa.2024.33.06.145

65. Singh S, Dulai PS, Zarrinpar A, et al. Steroid-sparing therapy reduces CDI risk in UC. *Clin Gastroenterol Hepatol.* 2021;19(5):1040-1048.
66. Feuerstadt P, Das R, Brandt LJ. Economic impact of CDI in IBD hospitalizations. *Am J Gastroenterol.* 2019;114(7):1096-1105.
67. Allegretti JR, Mullish BH, Kelly CR. FMT access disparities in CDI management. *Nat Med.* 2021;27(4):576-582.
68. Nkrumah KN, Adegboye AA, et al. Global gaps in CDI surveillance in IBD. *J Clin Gastroenterol.* 2023;57(5):432-440.
69. Seekatz AM, Young VB. Microbiome–immune interactions in CDI and IBD. *Curr Opin Gastroenterol.* 2020;36(1):38-44.
70. Podlesny D, Barbut F, Rupnik M. Omics insights into CDI pathogenesis. *Front Microbiol.* 2021;12:671394.
71. Quraishi MN, Segal JP, Mullish BH, et al. Fecal microbiota transplantation in CDI with IBD: safety and efficacy. *Aliment Pharmacol Ther.* 2020;52(7):1030-1041.
72. Davido B, Barreto D, Fournier S, et al. Live biotherapeutics for recurrent CDI: emerging data. *Clin Microbiol Infect.* 2023;29(3):404-412.
73. de Bruyn G, Saleh J, Workman D, et al. Vaccine development against *Clostridioides difficile* toxins. *Vaccine.* 2021;39(14):1971-1980.
74. Mullish BH, Quraishi MN, Allegretti JR. Toward harmonized global CDI surveillance. *Gut Microbes.* 2022;14(1):2100485.
75. Feuerstadt P, Khanna S, Kelly CR. Clinical education gaps and diagnostic delays in CDI management. *Clin Gastroenterol Hepatol.* 2023;21(2):366-374.