REVIEW ARTICLE

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Clostridioides difficile infection in adults – review of current knowledge (2020–2025)

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

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Abstract

Introduction and Objective. Clostridioides difficile infection (CDI) remains one of the leading causes of antibiotic-associated diarrhea and healthcare-associated infectious diarrhea in adults. The clinical spectrum ranges from mild diarrhea to fulminant colitis, toxic megacolon, sepsis, and death. In recent years, substantial progress has been made in understanding the epidemiology, pathogenesis, diagnostics, treatment, and prevention of recurrent CDI.

Review Methods. This study was prepared as a narrative literature review. The literature search included publications from 2020–2025 available in PubMed, Scopus, Web of Science, and Google Scholar. The search strategy was based on the following key words: Clostridioides difficile, Clostridioides difficile infection, CDI, epidemiology, diagnostics, treatment, recurrence, fidaxomicin, bezlotoxumab, fecal/faecal microbiota transplantation, microbiota restoration therapy, prevention, and probiotics.

Brief description of the state of knowledge. The number of community-associated cases among Clostridioides difficile infections is increasing, which is related to its natural reservoirs. Diagnostic methods consist in multistage algorithms (GDH + toxin + NAAT). Fidaxomicin and vancomycin offer effective treatment, while bezlotoxumab and FMT, including standardized microbiota products, prevent CDI recurrence. Promising new therapies are emerging, such as ridinilazole, toxoid vaccine, mRNA vaccine, and microbial interventions.

Summary. CDI remains a serious clinical problem in adult patients and continues to require improvement in diagnostics, treatment, and prevention. Further well-designed clinical trials and real-world studies are needed to optimize recurrence prevention strategies and improve long-term treatment outcomes in adult patients with CDI.

Key words

diagnostics, mRNA vaccines, fecal microbiota transplantation (FMT), *Clostridioides difficile,* ridinilazole, bezlotoxumab

Abbreviations

CDI – *Clostridioides difficile* infection; **ELISA** – enzyme-linked immunosorbent assay; **ESCMID** – European Society of Clinical Microbiology and Infectious Diseases; **FMT** – fecal microbiota transplantation; **GDH** – glutamate dehydrogenase; **IDSA** – Infectious Diseases Society of America; **NAAT** – nucleic acid amplification tests; **NPOA** – National Programme for the Protection of Antibiotics; **SHEA** – Society for Healthcare Epidemiology of America

INTRODUCTION

Clostridioides difficile (CDI) is a Gram-positive, spore-forming anaerobic bacterium and one of the major causes of antibiotic-associated diarrhea and healthcare-associated infectious diarrhea in adults [1, 2]. The clinical course of CDI ranges from mild, self-limiting diarrhea to severe colitis, toxic megacolon, intestinal perforation, sepsis, and death [1, 3, 4].

Over the past five years, the scientific literature has provided important new data regarding the epidemiology, pathogenesis, diagnostics, treatment, and prevention of recurrent CDI [1, 5–7]. At the same time, therapeutic recommendations have also undergone substantial changes, with increasing emphasis on recurrence prevention, restoration of the gut microbiota, and individualization of treatment strategies [8, 9].

The aim of the review is to provide up-to-date information on CDI in adults, with particular emphasis on epidemiology, diagnostics, treatment, recurrence prevention, and emerging therapeutic strategies.

MATERIALS AND METHOD

This study was prepared as a narrative literature review. The literature search included publications from 2020–2025 available in PubMed, Scopus, Web of Science, and Google Scholar. The search strategy was based on the following key words: *Clostridioides difficile*, *Clostridioides difficile infection*, CDI, epidemiology, diagnostics, treatment, recurrence, fidaxomicin, bezlotoxumab, fecal microbiota transplantation, microbiota restoration therapy, prevention, and probiotics.

The review focused primarily on peer-reviewed journals, clinical practice guidelines, systematic reviews, meta-analyses, and randomized clinical trials. Initial selection of the literature was based on title screening, followed by abstract assessment, and subsequently by full-text analysis of relevant publications.

Definition of CDI. According to the recommendations of the National Programme for the Protection of Antibiotics (NPOA),

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CDI is diagnosed in a patient with clinical symptoms consistent with infection, most commonly diarrhea, together with at least one of the following criteria: detection of toxins A and/or B in stool, identification of a toxigenic *Clostridioides difficile* strain in stool samples, or endoscopic and/or histopathological findings characteristic of pseudomembranous colitis [10]. In clinical practice, the diagnosis should always take into account both laboratory results and the patient's symptoms and risk factors, as asymptomatic carriage without active infection is also possible [8, 10, 11].

Epidemiology and risk factors of *Clostridioides difficile* infection in adults. In recent years, a sustained increase in the burden of CDI has been observed in both hospital and community settings [1, 2, 12]. Although healthcare-associated cases remain a major clinical problem, community-acquired CDI is increasingly recognized as an important issue for public health [1, 12, 13]. This shift is significant because it indicates that CDI is no longer restricted exclusively to hospitalized patients with classic healthcare-associated risk factors.

The most important risk factors for CDI in adults include recent or prolonged antibiotic therapy, hospitalization, advanced age, chronic comorbidities, immunosuppression, and disturbances of the gut microbiota [1, 14, 15]. Antibiotics most strongly associated with CDI include clindamycin, fluoroquinolones, and cephalosporins [1, 14]. Prolonged hospitalization, invasive procedures, and exposure to a contaminated healthcare environment also increase the risk of infection [1, 16, 17].

Disruption of the gut microbiota is a key predisposing factor. Dysbiosis reduces colonization resistance and facilitates germination of *Clostridioides difficile* spores and proliferation of vegetative forms in the colon [1, 15]. Because spores are highly resistant to environmental conditions and to many disinfectants, they may persist for prolonged periods on dry surfaces, thereby promoting transmission in hospitals, long-term care facilities, and other public environments [1, 10, 16, 18].

Environmental reservoirs may also contribute to community-acquired CDI. Spores have been identified in water, soil, food, and public spaces [1, 10, 13]. Epidemiological studies suggest that a substantial proportion of primary CDI cases may originate outside the hospital setting, particularly among younger adults without classic healthcare-related risk factors [1, 2, 13]. These findings indicate the need for broader preventive strategies encompassing not only hospital infection control but also environmental awareness and prudent antibiotic use in outpatient care.

Pathogenesis of *Clostridioides difficile* infection. The pathogenesis of CDI is closely linked to intestinal dysbiosis, bacterial colonization, and toxin-mediated epithelial injury. In most patients, antibiotic-induced disruption of the gut microbiota reduces colonization resistance and allows *Clostridioides difficile* spores to germinate in the colon [1, 15]. The vegetative bacterial forms then produce toxins that damage the intestinal mucosa and trigger an inflammatory response.

The major virulence factors are toxin A (TcdA) and toxin B (TcdB), which inactivate Rho family GTPases, disrupt the cellular cytoskeleton, impair intercellular junctions, and increase epithelial permeability [6]. These effects promote mucosal injury, neutrophil recruitment, cytokine release, and pseudomembrane formation [1, 6]. Binary toxin CDT may further enhance bacterial adhesion and colonization [6].

Hypervirulent strains, particularly ribotypes 027 and 078, have been associated with increased toxin production, enhanced sporulation, biofilm formation, and more severe clinical disease [1, 12, 19]. Resistance to fluoroquinolones has also contributed to the dissemination of epidemic strains in some settings [1, 19].

Biofilm formation plays an important role in persistence of infection and recurrences. Biofilm protects bacteria against antibiotics and host defence mechanisms, creates a reservoir of spores, and may contribute to disease recurrence after apparently successful treatment [1, 15]. Recent genomic and molecular studies have also identified additional virulence-related mechanisms, including sporulation, epigenetic regulation, nutrient acquisition, and host–pathogen interactions, which may become potential therapeutic targets in the future [6, 7].

Diagnosis of *Clostridioides difficile* infection in adults. The diagnosis of CDI in adults should be based on the presence of compatible clinical symptoms, especially unexplained diarrhea, together with appropriate laboratory testing [8, 10, 11]. Diagnostic testing should be performed only in symptomatic patients, because asymptomatic colonization is relatively common and may lead to over-diagnosis if laboratory results are interpreted without correlation with the clinical picture [8, 11, 20].

Enzyme-linked immunosorbent assays (ELISA) detecting toxins A and B are widely used because of their relatively high specificity and rapid turnaround time; however, their sensitivity is limited, which may lead to false-negative results [10, 11, 20].

Nucleic acid amplification tests (NAAT), including PCR-based methods, enable detection of toxin gene fragments with high sensitivity and specificity [11, 20]. Their main limitation is that they identify the presence of toxigenic strain genes rather than active toxin production. Therefore, a positive NAAT result should always be interpreted in the clinical context, since detection of toxin genes alone does not necessarily confirm active toxin production [9, 11, 20].

Anaerobic stool culture remains a highly sensitive method; however, it is time-consuming and requires additional confirmation of strain toxigenicity [10, 11, 20]. For this reason, culture is used mainly in epidemiological studies, strain typing, and research rather than in routine first-line diagnostics [11, 19].

Current recommendations support the use of multi-step diagnostic algorithms, usually combining glutamate dehydrogenase (GDH) testing, toxin assays, and NAAT [11, 20–22]. Such strategies improve diagnostic accuracy and help distinguish active infection from colonization [11, 21, 22]. In adult clinical practice, this approach is considered the most appropriate compromise between sensitivity, specificity, and clinical relevance.

Treatment of *Clostridioides difficile* infection in adults. The therapeutic approach to CDI depends on disease severity and on whether the episode is primary or recurrent [8, 9]. Contemporary treatment strategies increasingly focus not only on resolution of acute symptoms, but also on prevention of recurrence [8, 9, 23].

Fidaxomicin and vancomycin are currently the main first-line agents used in the treatment of CDI in adults [8, 9]. Fidaxomicin is a narrow-spectrum macrocyclic antibiotic with

Table 1. Interpretation of Test Results According to the Recommendations of the National Programme for the Protection of Antibiotics 2016–2020 – *Clostridioides (Clostridium) difficile* Infections: Epidemiology, Diagnostics, Therapy, Prevention [10].

Result	Interpretation / Management
GDH(+)/Toxin A/B(+)	Active toxin production – confirmed infection with a toxigenic *Clostridioides difficile* strain. The result indicates infection requiring treatment in accordance with current guidelines. No further testing necessary.
GDH(+)/Toxin A/B(–)	Indeterminate result. NAAT or toxigenic culture (TC) should be performed.
GDH(+)/Toxin A/B(–)/NAAT(+)	Clinical assessment required – this pattern may correspond either to active CDI or colonization with a toxigenic strain; therapeutic decisions should be based on the clinical presentation and risk factors.
GDH(+)/Toxin A/B(–)/NAAT(–)	*Clostridioides difficile* infection unlikely.
GDH(–)/Toxin A/B(–)	*Clostridioides difficile* infection very unlikely. No further testing required. The result suggests an alternative etiology of diarrhea; further evaluation for other gastrointestinal pathogens should be considered.
GDH(–)/Toxin A/B(+)	Possible false-positive result or technical error. Repetition of the test and verification in the context of clinical symptoms are recommended.

limited impact on the gut microbiota, whereas vancomycin is a glycopeptide that inhibits bacterial cell wall synthesis [5, 24, 25]. The latest data indicate that fidaxomicin is associated with lower recurrence rates than vancomycin, whereas the initial clinical cure rates are generally comparable [5, 24, 25].

The 2021 IDSA/SHEA and 2021 ESCMID guidelines place greater emphasis on the use of fidaxomicin, particularly in adult patients at increased risk of recurrence [8, 9]. Vancomycin remains an acceptable alternative when fidaxomicin is unavailable or cannot be us ed [8, 9, 26]. In contrast, metronidazole, which was previously widely used as first-line treatment in mild to moderate disease, now has a limited role and is generally reserved for situations in which the preferred therapeutic options are unavailable [8, 9, 27, 28].

Older recommendations of the Polish National Programme for the Protection of Antibiotics (NPOA) from 2018 differ from more recent international guidelines, particularly in assigning a greater role to metronidazole and in the limited inclusion of newer therapies [10]. This discrepancy reflects the need to update national recommendations in line with current scientific evidence [8, 9, 26].

Ridinilazole has emerged as a promising investigational option. Phase III clinical trial data suggest that it may preserve the gut microbiota more effectively than vancomycin while maintaining clinical efficacy; however, it has not yet been incorporated into routine clinical practice [23, 29, 30]. Other agents, such as nitazoxanide and rifaximin, have also been investigated, but the current evidence is insufficient to recommend their routine use as standard therapy in adults [3, 30, 31]. The optimal duration of therapy, as well as the feasibility of shorter treatment regimes, remains an area of active investigation [32].

Recent changes in *Guidelines for the Treatment of Clostridioides difficile Infection* in adults. A major shift in the recent approach to CDI treatment in adults has been the move away from metronidazole-based strategies toward therapies aimed at sustained cure and prevention of recurrence [8, 9]. In both the 2021 IDSA/SHEA and 2021 ESCMID guidelines, fidaxomicin has gained a preferred position in the treatment of the first CDI episode in adults [8, 9].

Another important change concerns recurrent disease. In the case of the first recurrence, fidaxomicin remains the preferred therapeutic option, both in standard and extended regimens, whereas vancomycin taper-and-pulse regimens remain an acceptable alternative [8, 9, 33]. In patients with multiple recurrences, current strategies include vancomycin taper-and-pulse regimens, fidaxomicin, bezlotoxumab, and faecal microbiota transplantation (FMT) [8, 9, 33].

Bezlotoxumab, a monoclonal antibody directed against toxin B, has become an important adjunctive option in adult patients at high risk of recurrence, including older individuals, immuno-suppressed patients, and those with previous CDI episodes [34, 35]. Its role is not to replace antibiotic therapy, but to complement it in selected high-risk patients [34–36].

These changes indicate a broader shift in clinical thinking: CDI treatment is no longer limited solely to controlling the

Table 2. Comparison of Therapeutic Recommendations for *Clostridioides difficile* Infection in the IDSA/SHEA 2021, ESCMID 2021, and NPOA (Poland) 2018 Guidelines

Aspect	IDSA/SHEA 2021	ESCMID 2021	NPOA (Poland) 2018
Treatment of the first CDI episode	Fidaxomicin preferred; vancomycin as an alternative if fidaxomicin is unavailable	Fidaxomicin preferred; vancomycin as an alternative	Metronidazole as first-line treatment in mild/moderate CDI; vancomycin in severe cases
Role of metronidazole	Limited to situations in which fidaxomicin and vancomycin are unavailable	Not recommended if preferred therapeutic options are available	Standard management in mild/moderate CDI
Treatment of first recurrence	Fidaxomicin (standard or pulsed regimen); alternatively vancomycin taper/pulse	Fidaxomicin or vancomycin; recurrence-oriented strategies	No preference for fidaxomicin; treatment based on vancomycin or metronidazole
Management of multiple recurrences	Fidaxomicin, vancomycin taper/pulse, combination regimens, FMT	Recurrence-oriented strategies including FMT	FMT acceptable, but not as first-line therapy
Bezlotoxumab	Recommended as adjunctive therapy in patients at high risk of recurrence	Included as an optional therapeutic modality	Not included (unavailable at the time of guideline development)
FMT	Recommended after ≥2 recurrences or after antibiotic treatment failure	Formally incorporated into therapeutic algorithms	Available, but not recommended as first-line treatment
Dominant therapeutic concept	Prevention of recurrence, sustained remission	Individualization of therapy and reduction of recurrence	Treatment of the acute CDI episode

acute episode but increasingly aims to restore colonization resistance and reduce the risk of future recurrences [8, 9, 23].

Scope of recommendations in the latest CDI Guidelines.

Prevention of recurrence *Clostridioides difficile* infection. Recurrence remains one of the most important clinical challenges in adult CDI [1, 31, 33]. The risk is particularly high in older patients, those with comorbidities, immunosuppression, prior CDI episodes, or ongoing antibiotic exposure [1, 34, 35].

Fidaxomicin plays a key role in recurrence prevention because of its more favorable effect on the gut microbiota and lower recurrence rates compared with vancomycin [5, 24, 25]. In selected adult patients, the addition of bezlotoxumab to standard antibacterial therapy further reduces the risk of recurrence [34, 35, 37].

Equally important is antimicrobial stewardship. Reducing inappropriate antibiotic use, especially of broad-spectrum agents associated with dysbiosis, remains one of the most effective strategies for both primary and secondary prevention [14, 17, 18]. In this context, recurrence prevention should be regarded as an integral part of CDI management rather than as a separate issue considered only after recurrence has already occurred.

Faecal microbiota transplantation and microbiota restoration therapies. FMT has become an established treatment for adult patients with multiple recurrent CDI, particularly after failure of standard antibacterial regimens [8, 9, 38, 39]. Meta-analyses and clinical studies consistently demonstrate the high efficacy of FMT in recurrent disease [38, 40, 41, 39]. Long-term follow-up data also indicate an acceptable safety profile when appropriate donor screening procedures and standardized protocols are applied [39, 42].

In recent years, an important shift has also occurred from classical donor-derived FMT toward standardized microbiota restoration therapies. In 2022 and 2023, the US Food and Drug Administration (FDA) approved two microbiota-based products for the prevention of recurrent CDI: Rebyota and Vowst [43–46]. These products represent an important step toward more standardized and reproducible microbiota-based treatment strategies.

Microbiota restoration therapies are particularly relevant because they target one of the key mechanisms responsible for recurrent CDI, namely incomplete recovery of the intestinal microbiome after antibiotic exposure [15, 45–47]. In adult patients with recurrent CDI, they may offer advantages in reproducibility, quality control, and safety compared with traditional, non-standardized FMT preparations.

In clinical practice, conventional FMT still requires careful donor selection, microbiological and virological screening, appropriate preparation of transplant material, and use of standardized administration protocols [43]. These factors remain essential for maintaining safety and therapeutic efficacy.

Emerging therapeutic and preventive strategies. Ongoing research is evaluating several novel approaches to the treatment and prevention of CDI in adults. These include bacteriophage therapy, microbiota-protective co-interventions, toxin-targeted therapies, vaccines, and next-generation microbiome interventions [30, 48, 49]. Bacteriophage therapy is of particular interest because of its theoretical ability to selectively target *Clostridioides difficile* while preserving commensal bacteria [49]. Although current evidence is mainly preclinical or early translational, this strategy may become important in future precision approaches to CDI treatment.

Vaccines against *Clostridioides difficile* toxins also remain under investigation [48]. Interest concerns not only traditional toxoid-based vaccines but also newer platforms, including mRNA-based approaches [30,48]. However, these strategies are still in the research phase and cannot yet be regarded yet as standard preventive methods.

Probiotics have been widely discussed as a potential strategy for preventing antibiotic-associated diarrhea and CDI, but the available evidence remains inconclusive [50, 51]. Some reviews suggest that selected probiotic strains may reduce the risk of CDI in high-risk populations; however, the effect appears to depend on the strain, dose, timing of administration, and baseline patient risk [50, 51]. Therefore, routine probiotic prophylaxis in all adults receiving antibiotics cannot currently be recommended.

Similarly, synbiotics, postbiotics, and other 'biotics' are being investigated as microbiota-modulating strategies [52–55]. Although biologically promising, the current clinical evidence specific to CDI remains limited. At present, these approaches should be regarded as experimental rather than standard clinical practice.

Prevention and infection control. Effective CDI prevention requires more than pharmacological therapy alone. Infection control measures remain crucial in both hospitals and long-term care facilities [16–18]. Hand hygiene, personal protective equipment, environmental decontamination, and epidemiological surveillance constitute the core elements of CDI prevention programmes [16–18].

Because *Clostridioides difficile* spores are resistant to alcohol-based hand sanitizers, hand washing with soap and water after contact with infected patients or contaminated environments is particularly important [10, 18]. Environmental decontamination should include the use of sporicidal agents, and education of healthcare personnel to ensure adherence to infection control procedures should remain a permanent component of ongoing training aimed at improving awareness and knowledge in infection prevention [10, 16, 18].

Additional hospital measures include patient isolation, the use of gloves and gowns, provision of separate toilet facilities whenever possible, and surveillance of healthcare-associated CDI cases [10, 16, 17]. Environmental interventions, such as UV-C disinfection, may further reduce the microbial burden in high-risk areas; however, they should be considered adjunctive rather than stand-alone preventive strategies [56].

Management of hospitalized patients with *Clostridioides difficile* infection. Because of the high environmental persistence of spores, adult patients with CDI treated in hospital settings should be managed with strict contact precautions [10, 16, 18]. Practical measures include:

- patient isolation whenever possible;
- use of gloves and protective gowns by staff and visitors;
- hand washing with soap and water after patient contact;
- environmental disinfection with sporicidal agents;
- limitation of unnecessary patient transport;
- education of staff and visitors regarding transmission routes;

- surveillance of CDI cases and monitoring of antibiotic use [10, 14, 16, 18].

These measures are essential not only to limit transmission but also to reduce the frequency of healthcare-associated recurrences and outbreaks.

Post-discharge management of patients with *Clostridioides difficile* infection. After hospital discharge, some adult patients may continue to shed *Clostridioides difficile* spores. Therefore, basic hygienic precautions should be continued at home, including frequent hand washing with soap and water, thorough toilet disinfection with chlorine-containing agents when indicated, and laundering of contaminated materials at appropriately high temperatures [10, 17].

Patients should also be informed about the risk of recurrence, the importance of avoiding unnecessary antibiotic therapy, and the need to seek medical advice in the event of recurrent diarrhea. Education at the time of discharge may improve early recognition of recurrence and reduce delays in treatment initiation [10, 14, 17].

Clinical and economic aspects of *Clostridioides difficile* infection treatment. Economic considerations increasingly influence CDI management. Although fidaxomicin is associated with higher direct acquisition costs than vancomycin, long-term analyses suggest that it may be cost-effective because of lower recurrence rates and fewer re-hospitalizations [25]. This is particularly relevant in adult populations at high risk of recurrence, in whom the disease is associated with substantial clinical and economic burden.

Combination treatment strategies are also being evaluated. In selected patients, combining antibacterial therapy with bezlotoxumab may improve outcomes by simultaneously targeting bacterial eradication and reducing toxin-related recurrence risk [34, 35, 37]. Such approaches are consistent with the broader trend toward individualized CDI treatment and adaptation of therapy to the patient's risk profile [8, 9, 23].

However, implementation of these strategies in routine practice may be limited by drug availability, cost, and reimbursement policies. This is particularly important in countries where access to fidaxomicin, bezlotoxumab, or microbiota restoration therapies remains restricted.

CONCLUSIONS

CDI remains a serious clinical problem in adult patients and continues to require improvement in diagnostics, treatment, and prevention [1, 2, 4]. Recent data have expanded current understanding of the role of dysbiosis, toxin-mediated injury, and recurrence risk, and have contributed to the development of new therapeutic strategies.

The most important changes in the years 2020–2025 include broader implementation of multi-step diagnostic algorithms, recommendation of fidaxomicin as the preferred agent in current international therapeutic guidelines, increased use of bezlotoxumab in adult patients at high risk of recurrence, and the growing clinical importance of faecal microbiota transplantation (FMT) and therapies aimed at restoration of the intestinal microbiota [8, 9, 34, 45, 46]. Standardized microbiota-based products represent a significant step forward in the prevention of recurrent CDI [43–46].

At the same time, infection prevention, environmental control, and antimicrobial stewardship remain indispensable [14, 16–18]. Further research, regular updating of national recommendations, and improved access to modern therapies are necessary to optimize the management of adult patients with CDI in everyday clinical practice.

Further well-designed clinical trials and real-world studies are needed to optimize recurrence prevention strategies and improve long-term treatment outcomes in adult patients with CDI.

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