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Review Article

Updated Guidance on Treatment and Diversity of *Clostridioides* (*Clostridium*) *difficile* Infections

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ABSTRACT

Infectious hospital-associated diarrhea linked to *Clostridioides difficile*, a gram-positive anaerobic that forms spores. In North America and Europe, it is the most frequent infection associated with hospitals, and it is likely to be just as widespread elsewhere in the world. *C. difficile* has the ability to produce both TcdA and TcdB toxins, certain strains of *C. difficile* produces a binary toxin. The aim of our article is to show the importance of this bacterial species, its pathogenesis, virulence factors, and modern guidelines for treating the infection caused by this anaerobic bacterial species. It was also pointed out that it is difficult to isolate and deal with it.

Keywords: *Clostridioides difficile*, anaerobe, binary toxin, ESCMID.

INTRODUCTION

In 1976, clindamycin colitis in hamsters was found to be caused by *Clostridium difficile* (Jarmo *et al.*, 2020). In 2016 it was reclassified as *Clostridioides difficile*. It is a gram-positive, anaerobic, spore-forming bacterium which is common in nature, particularly in soil, and can spread from person to person by direct contact with contaminated environments or by the fecal-oral route (Gnocchi *et al.*, 2020). The most frequent cause of infectious diarrhea acquired in hospitals was *C. difficile*, which had a close correlation with antibiotic use. 1. Self-limiting mild diarrhea. 2. Toxic megacolon and fulminant colitis (pseudomembranous), which can result in sepsis, intestinal perforation and multiple organ failure are clinical signs linked to *C. difficile* infection (CDI) (Smits *et al.*, 2016). Studies indicate a high prevalence of CDI in both the community and hospitals, with varying rates based on demographics and clinical factors (Biswas *et al.*, 2023). For example, a 14-year study in China found a CDI detection rate of 13.6% among patients with diarrhea (Jiang *et al.*, 2024). About 20% of cases of recurring CDI showed that the majority of these cases are linked to a persistent dysbiosis of the gastrointestinal tract's microbiota and inadequate antibody levels in the serum against *C. difficile* toxins. Toxin A (TcdA) and toxin B (TcdB) which are two clostridial toxins with large molecular weights, were the primary virulence agents of *C. difficile*. The toxins A and B attach to and penetrate the epithelium of the colon, producing pro-inflammatory chemokines and cytokines, disruption of tight junctions, neutrophil infiltration, fluid secretion and the death of epithelial cells (Ooijevaar *et al.*, 2018). Certain strains, referred to as hyper-virulent strains, also develop a binary toxin, the exact purpose which is still unknown (Deshpande *et al.*, 2015). CDI which is community-acquired can be accounted for 30 percent of all the CDI cases, *C. difficile* is the 8th most commonly reported microbe in illnesses associated with health care, and its occurrence has been increasing (Jarmo *et al.*, 2020). The laboratory and clinical results were used to group CDI as severe, fulminant or mild to moderate.

The main classification characteristics used for the CDI considers as severe if serum creatinine is rising at a rate greater than 1.5 times baseline or more than 1.5 mg/dl, or if the white blood cell count is more than 15,000*106/l. If the patient was in shock, had a colectomy because of CDI hypotension, needed treatment in an intensive care unit, developed sepsis, developed a megacolon or had a gut perforation, the CDI was fulminant. When the requirements for fulminant or severe illness was not met, CDI is considered as mild-to-moderate (Saha and Khanna, 2019). A guideline on CDI treatment published in 2014, and the European society of clinical microbiology and infectious diseases gave it their approval (ESCMID). Vancomycin, metronidazole and fidaxomicin were considered to be the main drugs for CDI antibiotic treatment. The American college of gastroenterology and the infectious diseases society of America both recommended that metronidazole be used as the first line of treatment for mild CDI, and this is supported by the European advice statement, but CDI treatments and novel agents was also studied and developed, involving faecal microbiota transplantation (FMT) (Smits *et al.*, 2016).

Genetically, *C. difficile* regarded as a diverse species, and strains with effective typing are crucial for epidemiological study. The three main typing techniques used to distinguish between *C. difficile* strains was pulsed field gel electrophoresis (PFGE), PCR ribotyping and restriction endonuclease analysis (REA). The application of these techniques has shown that the identified *C. difficile* strains were emerging and predominating during the previous ten years, leading to epidemics in lots of countries (Awad *et al.*, 2014).

Definitions by European Society of Clinical Microbiology and Infectious Diseases ESCMID:

Defining CDI as an ileus, toxic megacolon, and diarrhea that are consistent with CDI, in addition to microbiologic proof of free toxins in the stool or the toxic *C. difficile* in the stool in the absence of a plausible cause for the diarrhea; or pseudomembranous colitis identified at autopsy, upon colectomy, or during endoscopy. The rCDI (recurrent CDI) was determined as the return of the CDI symptoms in eight weeks after an earlier episode's beginning, as long as the prior episode's symptoms subsided following the conclusion of the initial course of treatment. There are no particular clinical or microbiologic specifications within this definition. One or more specific signs

and symptoms of complex disease progression coupled with major systemic shock and toxin effects necessitating admission to an ICU or a surgical colectomy and even mortality were classified as severe CDI. The initial sign of recovery was the absence of diarrhea for two days following the end of antibiotic treatment (Fig. 1). The baseline's first clinical recovery regarding CDI and no infection recurrence after a twelve week follow up were considered indicators of a global (or sustained) cure (Shields *et al.*, 2015).

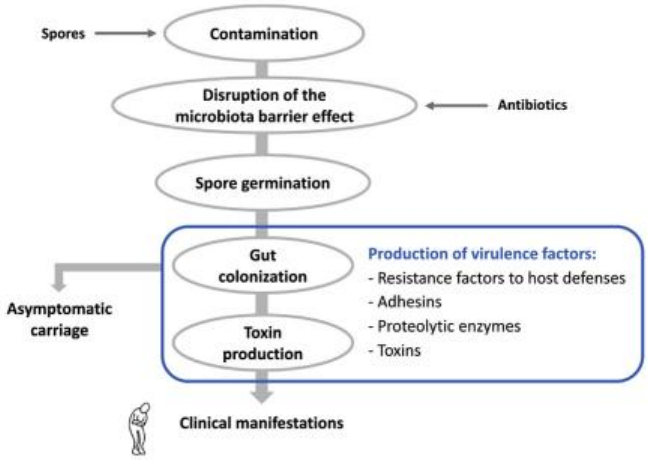

Fig. 1: Key steps of *C. difficile* infection (Janoir, 2016).

C. difficile biofilm

The 'biofilm' term is described as a microbial population enclosed in a self-produced matrix and attached to surfaces. Biofilm is common in nature and has benefits depending on the environment and biofilm composition. There is mounting evidence that the microbiota found in the human gastrointestinal tract (GI tract) could manifest as either luminal planktonic bacteria or mucosal sessile bacteria, with the formation of biofilms potentially influencing the microbiome intestine's functionality and interactions with the host. Unknown genetic processes were responsible for the transition from planktonic motile cells to sessile non-motile cells. A variety of cell-surface features, including S-layer, Type IV pili and flagella, play a role in the formation of biofilm (Buckley *et al.*, 2021).

Risk factors

Antibiotics were the major risk factor used to disrupt fecal microbiota. Severe illness, advanced age and hospitalizations is considered as other risk factors. Early cases were attributed to Clindamycin. Nevertheless, the wide spreading of fluoroquinolone and penicillin usage was coupled with most antibiotic usage. Antibiotics "such as metronidazole" could reduce the disease and offer sufficient therapy. The senior ages (more than65 years) had a greater risk of developing the disease. Prevalence is more than ten times greater than the lower age group for an unknown etiology. It is assumed that this has to do with the host's compromised immune system. It is still unknown if using proton pump inhibitors or acid suppressive drugs increases the risk of contracting *C. difficile* infection. The *C. difficile* spores represent a vector of infection, also spores were acid resistant. Additional risk factors were the chemotherapy use, transplantation of organs, exposure to an infected person or a carrier and presence of an intestinal inflammation (Adhikari, 2018).

Diagnosis

Various diagnostic methods for *C. difficile* infections (CDI) have been studied extensively. Current laboratory diagnostic methods involve an enzyme immunoassay for glutamate

dehydrogenase tests, cytotoxicity neutralization tests of cell cultures, nucleic acid amplification tests NAATs, enzyme immunoassays for toxins A & B (EIAs) and toxigenic cultures (Chung *et al.,* 2021). The non severe infections include watery diarrhea which was the major symptom. The remaining symptoms associated were cramps (pain in lower abdomen), mild fever, vomiting and nausea. In addition, blood and mucus could be found in the stool and hematochezia was rarely noticeable. At the same time severe *C. difficile* infections is when the serum creatinine >1.5 mg/dl or the count of white blood cells >15,000 cells/ml. It involves fever, lactic acidosis, hypovolemia, sepsis and distension of the abdomen. A fulminant colitis can happen with a very low blood and many organ failures. Ileus and toxic megacolon also can be present (Czepiel *et al.,* 2019). The presence of a toxin gene of the *C. difficile* or *C. difficile* toxin in stool depended on laboratory evaluation diagnosis. Laboratory methods do not rely on distinguishing *C. difficile* asymptomatic carriage and infection. A positive stool study and clinical suspicion is considered a diagnosis. Depending on the radiographic and colonoscopic evaluations, could see the Pseudo-membranes. Endoscopic evaluation is not recommended for routine evaluations. During the infection of *C. difficile*, not all patient cases have pseudomembranes. In addition, the pseudomembranes presence does not validate the infection diagnosis. The presence of *C. difficile* toxins A & B and GDH antigen is currently detected either via (NAATs) or by enzyme-linked immunoassay (EIA) (Koo *et al.,* 2014). Although the GDH produced by the isolates of *C. difficile* has a high sensitivity, this test cannot have the ability to distinguish between toxigenic and non-toxigenic strains. The EIA for the toxins A & B has an increased rate of false negative because bacteria does not always have the ability for toxin production. The (NAATs) method is considered a DNA-based test, involving the PCR (polymerase chain reaction). This test has a high specificity and sensitivity. In addition, this test has ability to identify the toxigenic strains. Cell culture cytotoxic assay and anaerobic culture required both intensive and time consuming (Mada and Alam, 2024).

For the prompt handling and therapy of this growing epidemic spread of infection, molecular diagnosis of *C. difficile* is essential. From sophisticated molecular assays to conventional culture procedures, a variety of diagnosis approaches have been established, each with unique benefits and drawbacks.

The most reliable method for detecting toxin genes (TcdA, TcdB) in stool samples is the use of polymerase chain reaction (PCR), which offers great accuracy as well as specificity (Camargo *et al.,* 2021). Isothermal amplification is a rapid isothermal technique, which includes recombination polymerase amplification (RPA). RPA has improved healthcare diagnosis in the past few years by detecting genes encoding toxin in around 15 minutes (Bachmann *et al.,* 2024). When in comparison with molecular approaches, enzyme immunoassays may not be as sensitive in detecting toxins A and B (Chamgordani *et al.,* 2024).

The high cost of PCR and the requirement for quick and affordable methods for diagnosis are two obstacles that still exist despite advancements. These problems might be resolved and CDI management enhanced by using emerging technologies like biosensors and microfluidic systems (Camargo *et al.,* 2021; Chamgordani *et al.,* 2024). Although molecular approaches have transformed the diagnosis of CDI, numerous settings still rely on conventional procedures, underscoring the requirement for more widespread availability of cutting-edge diagnostics.

The large toxins *TcdA* and *TcdB*

The genome of bacteria containing a toxin-encoding pathogenicity locus (PaLoc) is associated with CDI symptoms. In most strains, the PaLoc is located in the chromosome at the same site. The studies about the function and structure shed light on the action mechanisms of every toxin of *C. difficile* specifically *TcdA* and the *TcdB.* Both toxins when are produced, they bind together and then enter the epithelium of colon to induce cytokine production and inflammatory chemokine, tight junctions were disrupted and fluid secretion in addition to the death of epithelial cells (Fig. 2) (Smits *et al.,* 2016; Stofkova *et al.,* 2020).

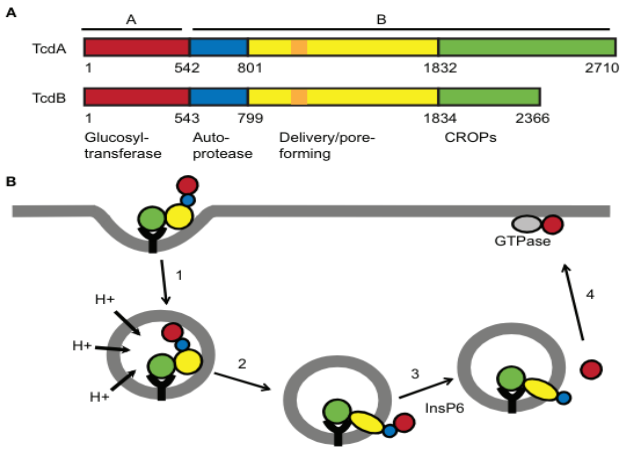

Fig. 2: The cellular intoxication mechanism and primary structure of *TcdA* and *TcdB* which are homologous AB toxins containing four domains (Pruitt and Lacy, 2012).

Binary toxin (CDT)

Certain strains of C. difficile produce C. difficile transferase (also known as a binary toxin or CDT), which is considered to be a third toxin. Recent years have seen a rise in interest in CDT because of its growing frequency in isolates originating from both humans and animals. The binary toxin locus (CdtLoc) has an operon that contains both genes cdtB and cdtA, and encodes CDT (Martínez-Meléndez *et al.*, 2022). Though its exact involvement in the pathophysiology of disease is still unknown, recent research has shed light on the CDT's action mechanisms. Two parts of the CDT was an enzymatic component (CDTa) and a binding translocation component (CDTb). CDT was a member of the family of binary ADP-ribosylating toxins. ADP ribosyltransferase activity was possessed by CDTa, while CDTb helps the enzyme component to enter the cell cytoplasm. The actin cytoskeleton was destroyed by CDTa, which ultimately resulted in cell death. (Goldsmith *et al.*, 2023).

Treatment

It primarily depends on the sickness kind, which can be broadly divided into three categories:

1. Creatinine serum is one and a half mg/dl and WBC is 15,000 cells/cumm are indicators of non-severe CDI.
2. Creatinine serum is one and a half mg/dl and WBC is more than15,000 cells/cumm indicating severe CDI.
3. Megacolon, shock, or hypotension are signs of fulminant colitis.

Non-severe CDI: It was advised to treat non-severe illnesses with oral metronidazole, fidaxomicin or vancomycin. The medicines rifaximin, nitazoxanide, ramoplanin, tigecycline and teicoplanin was also effective against this bacterium.

Faecal microbiota transplantation (FMT)

FMT involves injecting a healthy donor's stool suspension either by an upper gastrointestinal (nasoduodenal or nasojejunal tube) or a lower gastrointestinal (colonoscopy or retention enema). Primary and recurrence CDI was mostly caused by disruption and decreased diversity of intestinal microbiota. The major cause of this condition was use of antibiotics, which will further disturb the natural gut flora when utilized for the treatment of CDI. When medications used to treat CDI are stopped, any remaining spores of *C. difficile* can germinate in the existence of disturbed microbiome, which could result in rCDI. The principle of FMT was the restoration of a healthy microbiome. For the management of rCDI, it has been shown that FMT is a successful and safe treatment; the total efficacy rate is between 80 and 90%. Nevertheless, compared to open-label and observational research, randomized trials using FMT have shown lower cure rates (Figure 3). FMT

should only be administered to patients who have experienced two or more rCDI episodes, according to the ESCMID panel's consensus **(**Tariq *et al.*, 2019; Jarmo *et al.*, 2020**).**

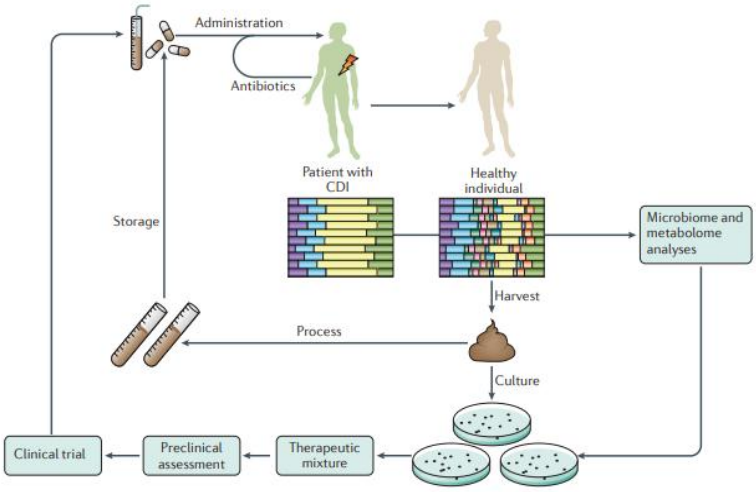

Fig. 3: Steps of faecal microbiota transplant (Smits *et al.*, 2016).

Immunizations

Vaccines against *C. difficile* toxin are currently being developed. Immunization against the toxins produced by *C. difficile* presents the prospect of a successful preventative strategy. A few encouraging findings have come from small trials (Buckley *et al.*, 2021).

Vaccines and monoclonal antibodies offer a potential future defense against CDI. Toxins A and B are the targets of the following monoclonal antibodies that have been developed: Bezlotoxumab and Actoxumab respectively. When these antibodies were examined, it was discovered that 2655 people would benefit from a decreased risk of recurrence (Posteraro *et al.*, 2018; Wilcox *et al.*, 2019).

Nontoxigenic *C. difficile* strains

A toxin's production-related genes are absent from non-toxigenic *C. difficile* (NTCD) strains. When a toxigenic strain of NTCD colonizes a patient, it can prevent CDI. M3, one of these NTCD strains, has been demonstrated to colonize healthy volunteers without risk. In some studies, it was revealed that treated subjects saw a remission of CDI following treatment with metronidazole or vancomycin at varying dosages of NTCD-M3 spores. The course of treatment seemed safe and was well tolerated. While not all treated patients became colonized, the highest dosage that was advised for fourteen days proved to be less effective than the same dose for seven days in colonizing the gastrointestinal tract and considerably reducing CDI recurrence (Ooijevaar *et al.*, 2018).

Plasmids and their role in pathogenicity

It has been widely noted that the abundance of plasmids in *C. difficile* contributes significantly to the development of antibiotic resistance in bacteria. The proliferation and survivability of pathogenic bacteria carrying plasmids, which are regarded as antibiotic-resistant strains, are facilitated by the ability of these plasmids to transmit genes that give resistance to various drugs.

The genes that confer resistance to the antibiotic metronidazole on the **Metro PCD** plasmid have been identified, which show high similarity of sequence through different types of isolates (Smits *et al.*, 2022). Plasmids play an essential and effective role in facilitating the horizontal transfer of resistance genes, contributing to the overall resistance landscape in *C. dificile* and other pathogens (Kartalidis *et al.*, 2021). In addition, treatment options are complicated since the emergence of multidrug-resistant bacterial isolates is directly linked to the presence of plasmids in *C. difficile* (Wickramage *et al.*, 2021). A larger concern to public health arises from *C. difficile*'s

role as a source of the genes for resistance to antibiotics that can be passed on to different bacteria (O'Grady *et al.*, 2021). It is crucial to remember that mutations in chromosomes and efflux pumps are two additional mechanisms that make significant contributions to the susceptibility characteristics of *C. difficile*, even if plasmids have a key role in the development of antibiotic resistance in this disease (Wickramage *et al.*, 2021).

One possible treatment approach for treating infections brought on by this disease is to target the *C. difficile* plasmid. Plasmid-mediated virulence genes are among the novel strategies that aim to interfere with the pathogenesis of *C. difficile* according to recent studies. Plasmids help *C. difficile* become more virulent by promoting the production of toxins and spores, both of which are essential for the establishment of an infection (Cun *et al.*, 2024). By inhibiting these plasmids, the severity of infection can be decreased by preventing the synthesis of toxins (Bratkovič *et al.*, 2024). Focusing on plasmid-encoded proteins may improve immunity and offer protection over the long term, according to studies on multi-epitope vaccines made from the *C. difficile* core genome (Aiman *et al.*, 2024).

Targeting the *C. difficile* plasmid is a novel strategy, but it is important to take into account the possibility of plasmid transfer between bacterial populations, which might make treatment plans more difficult and make other pathogens more virulent.

CONCLUSIONS

Here are the main conclusions of the article:

1. *C. difficile* infection (CDI) is the most common healthcare-associated infection, with rising global incidence.
2. Toxins A and B drive CDI pathogenesis, while binary toxin's role remains unclear.
3. Antibiotic use, hospitalization, and age are key risk factors, with proton pump inhibitors' role uncertain.
4. Diagnosis relies on NAATs, EIAs, and GDH tests, with biosensors showing promise.
5. Treatment includes vancomycin, fidaxomicin, FMT (highly effective for recurrence), and monoclonal antibodies.
6. Plasmids contribute to antibiotic resistance, making them potential therapeutic targets.
7. Future strategies focus on vaccines, plasmid-targeted therapies, and microbiome restoration.

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التوجيهات المحدثة حول علاج وتنوع عدوى *Clostridioides* (*Clostridium*) *difficile*

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الملخص

الإسهال المعدي المرتبط بالمستشفيات والذي يسببه المطثية العسيرة (كلوستريديوم ديفيسيل)، وهي بكتيريا لا هوائية موجبة لصبغة جرام تشكل الأبواغ. في أمريكا الشمالية وأوروبا، يعتبر هذا الإسهال العدوى الأكثر شيوعًا المرتبطة بالمستشفيات، ومن المرجح أن يكون منتشرًا بنفس القدر في أماكن أخرى من العالم. تمتلك المطثية العسيرة القدرة على TcdA وTcdB إنتاج السموم. وتنتج بعض سلالات المطثية العسيرة سمًا ثنائيًا.

وان الهدف من هذه الدراسة هو اظهار اهمية هذا النوع البكتيري وامراضيته وعوامل الضراوة والتوجيهات الحديثة لعلاج الاصابة الحاصلة جراء هذا النوع البكتيري اللاهوائي كذلك تمت الاشارة الى صعوبة عزلها والتعامل معها.

الكلمات المفتاحية: المطثية العسيرة، لا هوائية، السم الثنائي، الجمعية الأوروبية لعلم الأحياء الدقيقة السريري والأمراض المعدية (ESCMID).