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Clostridioides difficile Infection: Updates on Epidemiologic Patterns, Diagnostic Tools, and Treatment Modalities

Clostridioides difficile Enfeksiyonu: Epidemiyolojik Paternler, Teşhis Araçları ve Tedavi Yöntemlerine İlişkin Güncellemeler

Lamiaa Abd El-Fattah MADKOUR

Cairo University Faculty of Medicine, Department of Microbiology and Immunology, Egypt

Abstract

Clostridioides difficile is the predominant worldwide etiology of healthcare-associated diarrhea. Furthermore, *C. difficile* infections (CDIs) have been designated by the Centers for Disease Control and Prevention as an urgent threat, which is the highest of all threat levels. Throughout the years, epidemiologic surveillance efforts and infection prevention measures have been focused on combating healthcare-associated CDIs. Nonetheless, the incidence of community-associated infection is currently witnessing an upsurge. In the meantime, insufficient clinicians' awareness, inadequate frequency of testing, or a suboptimal diagnostic scheme can result in underdiagnosis with the subsequent pervasion of CDIs. Another factor contributing to the escalating morbidities is the scarcity of anti-clostridial therapeutics that can tackle notorious re-infections and relapses. Altogether, these factors warrant raising awareness about epidemiologic patterns, diagnostic algorithms, and the updated treatment regimens for CDI.
Keywords: Auranofin, bezlotoxumab, *Clostridioides difficile*, fidaxomicin, NAAT

Öz

Clostridioides difficile, sağlık hizmetleriyle ilişkili ishalin dünya çapında en sık etiyolojik nedenidir. Ayrıca, *C. difficile* enfeksiyonu (CDE), Hastalık Kontrol ve Önleme Merkezleri tarafından tüm tehdit düzeylerinin en yükseği olan acil bir tehdit olarak belirlenmiştir. Son yıllarda, epidemiyolojik sürveyans çabaları ve enfeksiyon önleme tedbirleri, sağlık hizmetleriyle ilişkili *C. difficile* ile mücadeleye odaklanmıştır. Bununla birlikte, toplumla ilişkili enfeksiyon insidansının günümüzde artışına tanıklık etmekteyiz. Bu arada, klinisyenlerin yetersiz farkındalığı, yetersiz test sıklığı veya optimal olmayan bir tanı şeması tanı sürecinde eksikliğe ve sonuç olarak CDE'nin yaygınlaşmasına neden olabilir. Artan morbiditelere katkıda bulunan bir diğer faktör, tekrarlayan enfeksiyonlar ve nükslerle mücadele edebilecek anti-clostridial ilaçların azlığıdır. Tüm bu faktörler, CDE için güncellenmiş tedavi rejimlerinin yanı sıra epidemiyolojik paternler ve teşhis algoritmaları hakkında farkındalığı artırmayı gerekli kılar.
Anahtar Kelimeler: Auranofin, bezlotoxumab, *Clostridioides difficile*, fidaksomisin, NAAT

Introduction

Clostridioides difficile infection (CDI) is a cardinal cause of infectious diarrhea and one of the most prevalent healthcare-associated infections globally[1]. It inflicts approximately 8 in 100,000 individuals annually; in the hospital setting, it inflicts 4-8 of 1000 patients[2]. In the United States, the financial toll of CDIs hits up to 7 billion dollars annually, as CDIs prolong the hospital stay by 2.8-10.4 days[3,4], with a burden exceeding $42,000 for each patient[3].

The disease is caused by the activity of three toxins produced by *C. difficile* (enterotoxin A, cytotoxin B, and binary toxin)[5]. Through glucosyltransferase action, toxins A and B inactivate

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Address for Correspondence/Yazışma Adresi: Lamiaa Abd El-Fattah Madkour MD, Cairo University Faculty of Medicine, Department of Microbiology and Immunology, Egypt
E-mail: m_l@kasralainy.edu.eg **ORCID ID:** orcid.org/0000-0002-7849-3904
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GTPases, the regulators of cytoplasmic F-actin. Meanwhile, the binary toxin is an ADP-ribosyltransferase that catalyzes actin depolymerization[6]. Together, the toxins disrupt the cytoskeleton and tight junctions between gut epithelial cells[7]. Such a disruption provokes an inflammatory response with the liberation of cytokines and leukotrienes, eventually triggering diarrhea and pseudomembranous colitis[8,9]. Additionally, *C. difficile* spores are extremely resistant structures that promote feco-oral transmission and cause relapses in those who temporarily recover[10].

In recent years, massive worldwide efforts have been conducted to curb healthcare-associated CDIs. However, one of the hurdles has been the emergence of hypervirulent strains including ribotype 027 that produce exceedingly large amounts of toxins[11]. Moreover, CDIs are no longer restricted to healthcare settings. Although initially believed to be a nosocomial pathogen, increasing proof reveals that CDI is acquired in the community[12], where it accounts for 37% of all CDIs[13].

Despite numerous attempts at competent prevention and effective treatments, only a few drugs are approved for the treatment of CDIs, mainly fidaxomicin, vancomycin, and metronidazole. A challenge in employing either vancomycin or metronidazole is that both agents perturb the colonic microflora. Concerning metronidazole, a further restraint is that it is totally absorbed from the intestine, leaving only trace amounts at the infection site. These shortcomings contribute to the high rate of treatment failure and relapse[14]. Fidaxomicin, approved by the Food and Drug Administration (FDA) in 2011, has an enhanced profile of its narrow spectrum and oral bioavailability[15]. Nonetheless, the treatment outcome is still far from satisfactory[16].

Consequently, in the 2019 report on antimicrobial resistance, the Centers for Disease Control and Prevention continued to designate CDIs as an urgent health threat, the highest of threat levels, with nearly 13,000 deaths in US hospitals annually[17].

Considering the previous data, the purpose of this article is to spotlight the updates in the epidemiologic features of *C. difficile* as well as to delineate the diagnostic approaches and novel treatment algorithms for CDIs.

Epidemiology of CDIs

C. difficile colonizes the intestinal tract mainly through feco-oral transmission and contact with contaminated surfaces[18]. The spectrum of CDIs comprises asymptomatic carriage, mild diarrhea, and life-threatening fulminant disease with sepsis, toxic megacolon, and pancolitis that may end in colectomy[12]. Even after recovery from initial CDI, patients remain at risk of recurrence. Approximately 18-35% of individuals treated for CDI experience one or more episodes within 2-8 weeks of initial CDI[19]. The subsequent episode can be classified as either a "relapse" with the same strain or a "reinfection" with a new *C. difficile* strain[20].

Of note, the mortality rate of CDIs reaches 12.6%[21] and is remarkably higher in patients with inflammatory bowel disease and those residing in intensive care units (ICUs)[22].

1. Healthcare-associated CDIs (HA-CDIs)

In US hospitals, *C. difficile* represents the most frequently reported healthcare-associated pathogen (15% of all infections with a reported pathogen)[23], at an estimated burden of 462,000 cases of CDIs in 2017[24]. Moreover, data from 28 hospitals in the US imply that CDIs have replaced methicillin-resistant *Staphylococcus aureus* as the most frequent etiology of healthcare-associated infections, ranking third behind urinary catheter-related infections and surgical site infections[25].

Compared with hospitalized individuals without CDIs, those with CDIs as a secondary diagnosis experience a threefold longer hospital stay, have a 3.5-fold rise in hospital expenditure, and are six times as likely to die[26].

On the contrary, a meta-analysis of data from 111 studies demonstrated that the pooled CDI prevalence rate in the Middle East is 10.2% among patients with diarrhea[27]. Another meta-analysis of 85 studies from developing countries revealed a 15% prevalence of CDIs among patients with diarrhea[28]. Meanwhile, data from Egypt demonstrated the prevalence of *C. difficile* in 13.7% of inpatients suffering from diarrhea[29]. Another Egyptian study revealed that *C. difficile* was isolated from pediatric and adult inpatients with diarrhea at a rate of 17.9% and 27%, respectively[30].

In low- and medium-income populations, CDIs are likely underreported owing to inadequate awareness and limited diagnostic resources[31]. Available data indicate that CDIs are, nonetheless, a significant etiology of diarrhea in low-resource settings[28,32].

On the contrary, certain factors increase the risk of HA-CDIs. Prior intake of antimicrobials, namely, cephalosporins, clindamycin, and less commonly fluoroquinolones, is a frequent risk factor[33]. CDIs are also more encountered in older patients and those with comorbid events, e.g., inflammatory bowel disease[34] and low vitamin D levels[35]. Diminished CD4 cell counts in HIV infection is an additional risk determinant[36]. Patients with a long stay in healthcare facilities are also at risk, probably because of excessive exposure to *C. difficile* via contact with those who are colonized[37]. Finally, the consumption of gastric acid suppressants[38] and certain nonsteroidal anti-inflammatory agents have been linked to CDIs[39,40].

Consequently, many countries have endeavored to launch protocols and guidelines to constrain CDIs in the acute care setting. These protocols included environmental cleaning, contact precautions, case detection, and antibiotic stewardship[41,42].

2. Community-associated CDIs (CA-CDIs)

According to the 2018 guidelines by the Society for Healthcare Epidemiology of America, CDIs are considered CA-CDIs if the patient had diarrhea onset in the community or within 48 h after hospitalization and had not been discharged from a healthcare facility in the previous three months[43].

Although formerly categorized as exclusively nosocomial, growing evidence shows that person-to-person transmission causes only <25% of CDIs, advocating the hypothesis that food might be a source of spore ingestion in humans[44].

A study proposed that *C. difficile* exists in various animals including livestock (cows, pigs, sheep, goats, and chickens), domestic animals (dogs and cats), and horses[45]. Furthermore, *C. difficile* has been recovered from retail meat products (beef, pork, and turkey), seafood (salmon and shrimp), and vegetables (lettuce, ginger, onions, carrots, potatoes, and spinach). Spores can be propagated among humans and food via the airborne route, direct contact, rodents, birds, arthropods, or fecal contamination during slaughtering[46].

Interestingly, CA-CDIs exhibit a predilection to younger people, with a substantial percentage of them (36%) reporting no antibiotic intake three months before diagnosis[47].

Khanna et al.[48] reported that patients with CA-CDIs were younger than those with HA-CDIs (median age of 50 versus 72). Other studies have revealed 21-38% of patients with CA-CDIs without antibiotic intake compared with 6-20.3% in those with HA-CDIs[49,50].

Additionally, patients with CA-CDIs have lower mortality rates than those with HA-CDIs[24,51]. Contrarily, a retrospective study from France revealed that CA-CDIs were weakly associated with more severe disease than HA-CDIs; however, no difference in mortality was found[52].

3. Epidemic Ribotypes

Different typing approaches have been used to study the epidemiology of CDIs. While serotyping was used previously, polymerase chain reaction (PCR) ribotyping is now considered the gold standard typing method. Of note, *C. difficile* ribotypes display diversity in their regional prevalence and epidemic potential. The most commonly identified ribotypes are depicted in Table 1[53].

4. Coronavirus Disease-2019 and CDIs

Efforts have been ongoing to assess CDI trends during the coronavirus disease-2019 pandemic. Published data so far revealed no rise in the rate of CDIs despite the upsurge in antibiotic consumption throughout the pandemic[54,55]. Some centers have even reported a decline in HA-CDIs[56,57].

A group of factors have plausibly contributed to such a decline. Among them has been the commitment to infection control approaches, such as higher compliance to hand hygiene and isolation precautions[57,58].

Diagnosis

An accurate and timely diagnosis of CDIs necessitates both clinical manifestations and a positive laboratory test[59]. A fundamental clinical manifestation is diarrhea, which is defined as loose stools plus a frequency of ≥3 stools over 24 or fewer hours[60]. Severe ileus, where diarrhea comes to a halt, leukocytosis, and high creatinine are significant and should draw ample attention[61].

When a patient suffers from loose stools and has other risk factors for CDIs in the absence of another possibility, e.g., diarrheagenic agents, a fecal specimen should be procured for laboratory testing to assess the possibility of CDIs[59]. At present, no single stool test represents a reference standard for CDI diagnoses[62].

However, historically, the laboratory gold standard for diagnosing CDI was toxigenic culture (TC)[63]. This entailed the culture of *C. difficile* from the stool and then testing the retrieved isolates to demonstrate their ability to produce toxins. Although TC exhibited >95% sensitivity, its utility has been hindered by

Table 1. Characteristic features of common epidemic ribotypes of *C. difficile*[53]

Ribotype	Toxin genes	Resistant to	Regions
001/072	Genes of toxins A and B	MXF, LEV, ERY, CTX, CLI	Germany, Spain, Sweden, Scotland, Korea
002	Genes of toxins A and B	MXF, CIP	UK, Japan, Hong Kong
012	Genes of toxins A and B	MXF, CLI, ERY, RIF, TET	China, Sweden, Chile, Czech Republic
027/176	Genes of toxin A, toxin B and binary toxin	MXF, ERY, CLI	Japan, China, Korea, Singapore, Austria, Denmark, Finland, France, Germany, Hungary, Ireland, Luxembourg, The Netherlands, Norway, Spain, Sweden, UK, Chile, Panama, Costa Rica, Mexico

CIP: Ciprofloxacin, CLI: Clindamycin, CTX: Cefotaxime, ERY: Erythromycin, LEV: Levofloxacin, MXF: Moxifloxacin, RIF: Rifampicin, TET: Tetracycline

the lengthy turnaround duration (3-5 days), rendering it inconvenient for routine diagnosis. In addition, TC alone often yields false-positive results because of nontoxigenic strains[64]. Owing to these limitations, TC is traditionally employed as a reference method rather than a diagnostic tool.

Before 2009, laboratory identification of *C. difficile* was performed by a two-step process through the detection of glutamate dehydrogenase (GDH) by enzyme immunoassay (EIA) followed by EIA for toxins A and B. While GDH EIAs have a high sensitivity reaching >90%, they cannot distinguish active infection from asymptomatic colonization, resulting in a relatively low specificity[59,65]. To account for this limitation, positive GDH EIA can be a screening tool to be ensued by toxin A/B EIA, which has a lower sensitivity (51-63%) but higher specificity (91-100%)[59]. In combination, GDH EIA screening ensued by toxin A/B EIA permits a sensitive, specific, and practical method for CDI diagnosis.

Subsequently, in 2009, the US FDA approved the first nucleic acid amplification test (NAAT) for *C. difficile*[59,63]. The amplification of *C. difficile* DNA is carried out via PCR, which detects the genes encoding A and B toxins; however, it cannot distinguish between pathogen presence versus toxin production. Although NAAT cost is higher than those of other approaches, it has been widely allocated as the preferred diagnostic tool owing to its high sensitivity (Table 2), rapid turnaround time, and single-step strategy[59].

After many centers accredited NAAT as the sole method of diagnosing CDIs, US hospitals began to witness remarkable uptrends in CDIs, with a concomitant uptick in the consumption of anticlostridial therapeutics. Retrospective studies comparing the incidence of CDIs before and after NAAT implementation demonstrated a >50% leap in HA-CDIs[67]. Further evaluation of NAAT elucidated that despite being highly sensitive, it lacks sufficient specificity to distinguish colonization from active infection. Hence, the use of NAAT alone carries the potential of overdiagnosing CDIs by detecting asymptomatic carriers. Furthermore, NAAT can remain positive in >50% of patients after completing their treatment, compounding the challenge of interpreting results in those with prior infection[68].

Approaches to Mitigate Overdiagnosis

Several key strategies can be employed to improve the appropriate testing of CDIs and distinguish colonization from clinical disease. One of the fundamental interventions is diagnostic stewardship. Patients should not be tested for *C. difficile* unless they present with clinical features of actual infection, such as an unexplainable and new-onset watery diarrhea (≥3 loose stools in 24 h) in the absence of other causes, e.g., laxative intake or antibacterial/chemotherapy-related diarrhea[69].

At present, the recommended diagnostic algorithm comprises a 2-3-step approach to augment sensitivity and specificity. Acceptable approaches include either GDH detection or NAAT, followed by toxin A/B EIA. Patients are eligible for treatment only if toxin EIA yields a positive result, inferring that they have clinical CDIs rather than mere colonization. In general, employing NAAT alone is not recommended owing to its low positive predictive value[59].

Further, repeating the test for CDIs should be avoided within a week of a negative test result because of the low diagnostic yield. Likewise, patients successfully treated should not undergo a test of cure because the tests remain positive in >60% of patients[47].

In the same context, antimicrobial stewardship is a crucial approach to combat CDIs. To reduce overall antibiotic exposure, prescribers are encouraged to specify the duration of antibacterial therapy. Alternatively, antibacterial therapeutics prescribed for >7 days should be assessed by the antimicrobial stewardship program to evaluate the appropriateness and value of continued therapy. Furthermore, according to the regional epidemiology and *C. difficile* prevalence, restricting the use of clindamycin, cephalosporins, carbapenems, and fluoroquinolones can be advised to ensure the judicious usage of broad-spectrum antibacterial agents[69].

Specific Prophylaxis Against CDIs

Although a Cochrane review has found that probiotics are effective in preventing CDIs[70], such a result may be insufficient for routine clinical implementation. This in part is due to the use of different probiotic formulations in the trials included in the

Table 2. Performance of the available tests for the diagnosis of *C. difficile* infections[59,64,66]

Test	Sensitivity	Specificity
Toxigenic culture (TC, reference test)	Over 95%	80-90%
Nucleic acid amplification test (NAAT)	92-97%	83-100%
Glutamate dehydrogenase (GDH) detection	86-99%	70-88%
Toxin A and B enzyme immunoassay (EIA)	51-63%	91-100%
Glutamate dehydrogenase detection + toxin A/B immunoassay (GDH + Toxin EIA)	83-100%	91-100%
Nucleic acid amplification + toxin immunoassay (NAAT + Toxin EIA)	92-100%	91-100%

Cochrane review. In addition, probiotics may delay microbiome reconstitution following antibiotic therapy in addition to concerns about the associated adverse effects[71]. Another prophylactic approach against CDIs is antibiotic administration, where retrospective studies have revealed a 5-30% decrease in CDI occurrence with oral vancomycin prophylaxis in patients on broad-spectrum antibiotics[72,73]. Another regimen is the co-administration of ribaxamase (a poorly absorbed β-lactamase) when administering broad-spectrum antibiotics. Of note, a phase 2b trial revealed a 2.4% risk reduction of CDI occurrence when administering ribaxamase along with ceftriaxone[74].

Treatment of CDIs

Based on the 2021 guidelines of the Infectious Diseases Society of America, CDIs are best treated with fidaxomicin, while vancomycin is an alternative[75].

In 2021, the European Society of Clinical Microbiology and Infectious Diseases updated its 2014 guidelines for CDI management. An important modification stated that metronidazole is no longer recommended for CDIs if fidaxomicin or vancomycin is available and that fidaxomicin is the preferred agent for both initial CDIs and first recurrence of CDIs[71].

Based on these guidelines, severe CDIs are marked by one of the following criteria at the time of presentation: fever (>38.5 °C), marked leukocytosis (>15×10^9/L), and high creatinine (>50% above the baseline). Meanwhile, severe complicated CDIs (or fulminant CDIs) occur when one of the following signs is present that needs to be attributed to CDIs: hypotension, septic shock, high lactate levels, ileus, toxic megacolon, perforated bowel, or any fulminant disease course. On the contrary, refractory CDIs are irresponsive CDIs after 3-5 days of the recommended therapy[71].

A summary of the treatment recommendations is depicted in Figure 1. In addition to these–interventions, the following measures were recommended in the 2014 treatment guideline[60,76]:

- Cessation of unnecessary antimicrobials,

- Replacing deficient fluids and electrolytes,

- Avoiding antimotility agents,

- Re-assessment of the use of proton-pump inhibitors.

1. Fidaxomicin and Vancomycin as the Standard of Care

A phase three randomized controlled trial compared fidaxomicin with vancomycin and reported no difference in the cure rates; however, the study revealed a 9.9% reduction in the recurrence risk at four weeks in favor of fidaxomicin (15% vs. 25% reduction)[77].

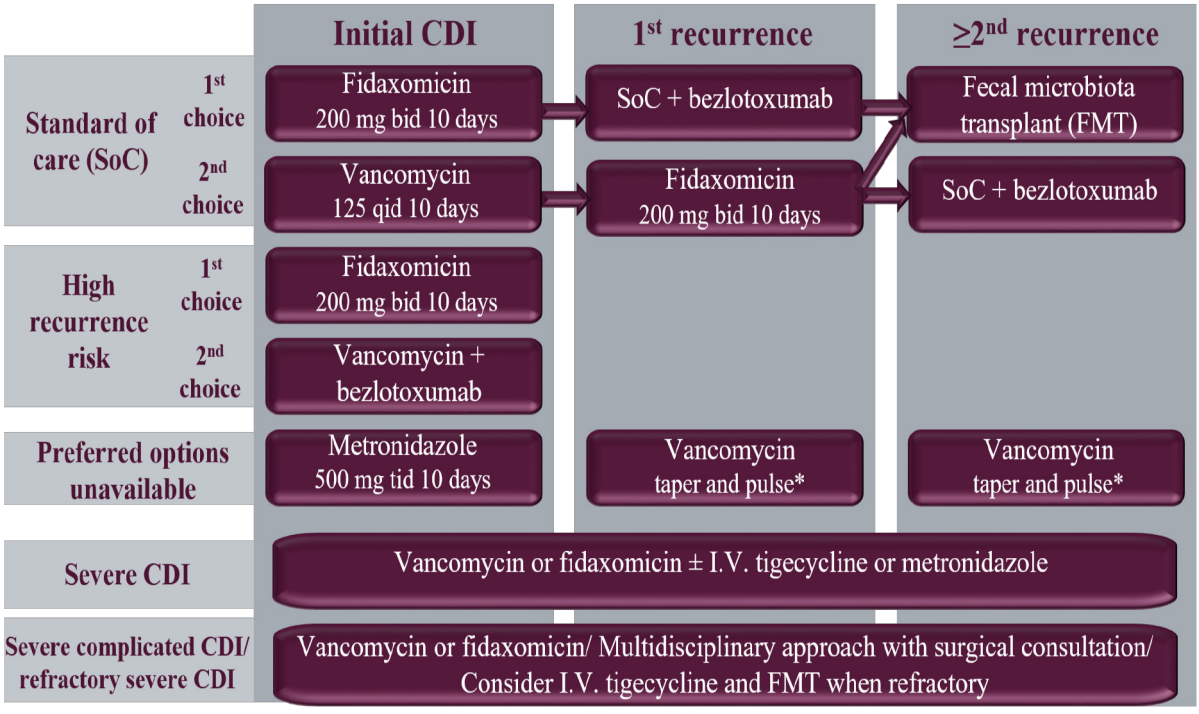

Figure 1. Suggested treatment algorithm for *C. difficile* infections[71]

*Vancomycin taper and pulse: 125 mg qid for 14 days, followed by 125 mg bid for 7 days, then 125 mg qd for 7 days, then 125 mg q48h for 7 days, then 125 mg q72h for 7 days

CDIs: *C. difficile* infections

As it possesses the narrowest activity spectrum, fidaxomicin is less likely to disrupt the gut microbiome[78], which is a merit in the case of CDIs. Of note, fidaxomicin costs much higher than vancomycin, which represents an obstacle against a widespread prescription. Nonetheless, the decreased recurrences and subsequent decline in rehospitalizations partially balance this high cost and may eventually result in cost-effectiveness[79,80].

2. Bezlotoxumab

This is a monoclonal antibody against toxin B of *C. difficile*. The addition of bezlotoxumab to the standard of care antibiotics produced the same cure rates but resulted in 10% reduced risk of recurrences in MODIFY-I and II trials[81]. In these trials, 48% of the patients were receiving vancomycin, whereas only 4% were taking fidaxomicin. Thus, the value of combining bezlotoxumab with fidaxomicin is uncertain.

For patients with a history of congestive heart failure, vigilance should be applied when prescribing bezlotoxumab. In these patients, heart failure was more commonly reported compared with the placebo group, and more deaths occurred. Hence, in these vulnerable patients, bezlotoxumab must be reserved for use only when the drug benefits outbalance the risks[71].

3. Intravenous Metronidazole

A retrospective analysis performed on 138 patients admitted to the ICU revealed that adding intravenous metronidazole to oral vancomycin was not associated with a better clinical result in severe nonfulminant CDIs[82]. Contrarily, a retrospective study in patients admitted to the ICU reinforced the suggestion that adding intravenous metronidazole to oral CDI therapy in patients in a critical condition might be of benefit[83]. Such conflicting results necessitate weighing the benefits against the risks for each case.

4. Intravenous Tigecycline

A retrospective study performed in a single center compared intravenous tigecycline as monotherapy with oral vancomycin plus intravenous metronidazole in severe CDIs. The study demonstrated a higher cure rate (76%) with tigecycline than with vancomycin plus metronidazole (53%)[84]. On the contrary, another study revealed that combining tigecycline with vancomycin had no added benefit[85]. A recent review based on retrospective observational research deduced that tigecycline can be a potential therapeutic against severe CDIs[2].

5. Other Agents

Rifaximin is an oral antibiotic of the same class as rifampin. In the management of mild and moderate CDIs, it has demonstrated noninferiority to available therapies, with the advantages of being poorly absorbed from the intestine, having slight adverse reactions, and a surprisingly minimal effect on the colonic microbiome. Nonetheless, clinical studies have displayed a resistance rate of 29-48.9%[86].

In addition, ridinilazole is potentially an antibiotic of interest for treating CDIs. In a phase 2 randomized controlled trial, it proved its superiority over vancomycin in attaining sustained cure[87].

Interestingly, some drugs have been experimented in mice and yielded a noticeable anticlostridial activity, e.g., auranofin, an FDA-approved antirheumatic agent, exhibited a reduction in *C. difficile* sporulation and toxin secretion in mice[88]. Other therapeutics that were experimented in mice include doxapram (a breathing stimulant), amoxapine (an antidepressant), and trifluoperazine (an antipsychotic). Nonetheless, the mechanism by which they achieved anticlostridial action is obscure[89].

Meanwhile, antivirulence therapy has drawn remarkable interest in combating antibiotic-resistant infections. Such agents are neither bacteriostatic nor bactericidal; they primarily attenuate bacterial virulence rather than its growth[90,91]. Thus, there is a low tendency to provoke pathogen resistance, in addition to the advantage of minimally affecting the gut microflora[92,93]. Baicalin, a flavone glycoside in the herb *Scutellaria baicalensis,* has been investigated *in vitro* against *C. difficile* with promising results[94].

On the other hand, the development of surotomycin and cadazolid was terminated after failing to prove noninferiority in randomized controlled trials[95,96].

6. Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) has gained a foothold in treating multiple recurrent CDIs. An observational cohort study reported an 87% cure rate in one month for severe complicated refractory CDIs[97]. Considering the high mortality associated with the surgical treatment of CDIs and the fact that some patients are unfit for surgery, FMT can play an important role in patients with refractory severe complicated CDIs for whom surgery is unfeasible, provided that a cautious risk assessment is made on a case-by-case basis. The expert team should also discuss intravenous antibiotics pre- and post-FMT, depending on the patients underlying condition and follow-up parameters[71].

Conclusion

Clostridioides difficile infections still represent costly and potentially life-threatening infections, especially in older vulnerable patients. Further, CDIs are now observable in community-dwelling younger, healthier populations.

To attain the dual target of reducing infection rates and lowering the risk of resistance, it is pivotal to distinguish colonization from clinical CDIs through judicious testing algorithms. Meanwhile,

experimenting with novel treatment modalities directed against CDIs has become a worldwide priority owing to the high disease incidence, recurrence, mortality, and scarce therapeutic options. Agents that are less amenable to invoke resistance and/or alter gut microflora represent plausible approaches and can provide a novel prospect in impeding CDIs.

In summary, CDIs still pose a significant menace, and a multifaceted approach is warranted to curb this infection. Both diagnostic and antimicrobial stewardship must be accompanied by state-of-the-art education on appropriate testing and treatment modalities.

Ethics

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