Current and future approaches in Clostridioides Difficile management

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ABSTRACT

Clostridioides Difficile is considered one of the main causes of the healthcare associated infections worldwide and the main cause of antibiotic-associated diarrhea, with forms of clinical disease ranging from mild to deadly. Both 2021 IDSA and ESCMID guidelines recommend that for the first episode of CDI Fidaxomicin should be considered as the preferred regimen of treatment and Vancomycin becomes 2nd Standard of Care (SOC) line, an alternative to fidaxomicin. Monoclonal antibodies, fecal microbiota transplantation and surgery remain other recommendations in the guidelines.

New means of management of Clostridioides Difficile Infection are under development, these including prevention measures (vaccination, population with non-toxigenic strains of the colon, standardized fecal microbiota products) and new antibiotics.

Keywords: Clostridioides

INTRODUCTION

Pseudomembranous colitis was first described in 1893 [1], before the occurrence of the antibiotics, but it was not until the antibiotics era when this disease knew a substantial increase in cases. Lincosamides (of which clindamycin was the most prominent representative) seemed to be especially linked with this situation and therefore, in 1974, FJ Tedesco started a prospective study that led to the identification of Clostridium Difficile and its toxins as the cause of the “Clindamycin associated colitis” [2]. No signs indicated at that time the magnitude this pandemic was about to achieve in the years after 2000. Today, Clostridioides Difficile is considered one of the main causes of the healthcare associated infections worldwide and the main cause of antibiotic-associated diarrhea, with forms of clinical disease ranging from mild to deadly. It is worthy to mention that up to 3% percent of the patients can be colonized, and they develop no signs of illness [3].

DEFINITIONS

The European Society of Clinical Microbiology and Infectious Diseases (ESCMID) released in 2021 an update of the previous (2014) guidelines for the treatment of Clostridioides Difficile infection (CDI) in adults [4]. The following definitions were set:

An episode of CDI is defined as clinical findings compatible with CDI and microbiological evidence of C. difficile free toxins by enzyme immunoassay without reasonable evidence of another cause of diarrhoea OR a clinical picture compatible with CDI and a positive nucleic acid amplification test (NAAT) preferably with a low cycle threshold (Ct) value, or positive toxigenic C. difficile culture OR pseudomembranous colitis as diagnosed during endos-
copy, after colectomy or on autopsy, in combination with a positive test for the presence of toxigenic C. difficile [4].

**Treatment response** is present when the patient has resolution of diarrhoea and has had a normal stool for that patient, with maintenance of resolution for the duration of therapy and at least 48 hours after the end of treatment, and no further requirement for CDI therapy, AND parameters of disease severity (clinical, laboratory, radiological) have improved.

**Refractory CDI** is CDI not responding to recommended CDI antibiotic treatment after 3-5 days of therapy.

**Recurrence** is present when CDI recurs within 8 weeks after a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment

**Severe CDI** is characterized by one of the following factors at presentation: fever, marked leukocytosis and rise in serum creatinine.

**Current approach:**
Both IDSA and ESCMID guidelines recommend that for the first episode of CDI Fidaxomicin should be considered as the preferred regimen of treatment (200 mg orally bid 10 days) and Vancomycin becomes 2nd Standard of Care (SOC) line, an alternative to fidaxomicin (at a dose of 125 mg orally qid for 10 days) [4,5]. This recommendation is based on the fact that fidaxomicin, as well as vancomycin is orally administered, has low systemic absorption and a narrower spectrum. Recurrences are fewer with fidaxomicin. For non-severe CDI, if fidaxomicin and/or vancomycin are not available, metronidazole can be used (500 mg orally tid for 10-14 days). Other general measures should be considered:

- Stopping any other antibiotic therapy if not necessary
- Stopping proton pump inhibitors
- Avoiding the use of anti-motility treatment
- Treating adequately the hidro-electrolitic disbalances.

In cases of recurrence, for the first recurrence, Fidaxomicin (200 mg orally bid 10 days) plus bezlotoxumab should be used if fidaxomicin was used as first line, and if Vancomycin was used, then fidaxomicin alone (200 mg orally bid 10 days). For the second recurrence, and further episodes, fecal microbiota transplantation (FMT) should be considered or Fidaxomicin (200 mg orally bid 10 days) plus bezlotoxumab. Vancomycin taper and pulse is still recommended if the above alternatives for recurrences are not available: 2 weeks 125 mg qid, 1 week 125 mg bid, 1 week 125 mg qd, then 1 week 125 mg q48h, and finally 125 mg q72h. Vancomycin in higher doses than 125 mg qid (e.g. 500 mg qid) is no longer recommended. i.v. metronidazole or i.v. tigecycline are recommended as adjunctive therapies in severe and/or complicated cases [4,5]. Prolonged administration of fidaxomicin (extended fidaxomicin), i.e. 200 mg twice daily on days 1-5, and 200 mg once daily on alternate days on days 7-25 can be considered for an episode of CDI with increased risk of recurrence, especially in elderly hospitalized patients.

Bezlotoxumab is a monoclonal antibody directed against C. difficile toxin B. His addition to SOC CDI antibiotics resulted in 10% reduced risk of recurrences in the MODIFY-I and II trials and similar rates of cure. Most patients received treatment with vancomycin; if fidaxomicin is used for treatment of initial or recurrent CDI, the utility of bezlotoxumab is unknown [6]. Bezlotoxumab received US Food and Drug Administration approval in 2016 [7]. Bezlotoxumab is given as a one-time infusion, during administration of a standard treatment regimen and caution is recommended in patients with congestive heart failure [6]. Bezlotoxumab seems to be more efficient when 3 risk factors of age ≥65 years, history of severe CDI, immunocompromise, and infection with ribotype 027/078/244 are present, reducing the risk of recurrence by 25%, compared to 1 or 2 risk factors from the above, when the risk is reduced by 15% [8]. Therefore, the ESCMID guidelines recommend the addition of bezlotoxumab to SOC for an episode of CDI with increased risk of recurrence when fidaxomicin is not available or feasible [4].

Surgery is part of the treatment of C. Difficile infection, in severe - complicated cases. Surgical consultation is recommended in patients with signs of severity like hypotension, high fever, ileus, peritonitis, high number of white blood cells (over 20,000/ mmc), altered mental status, acidosis, MSOF, no longer improving after 5 days of maximal therapy [4,9,10]. Total abdominal colectomy (TAC) is the standard when surgery is needed [4]. If possible, some authors recommend partial colectomy or loop ileostomy if the situation permits as mortality seems to be significantly low in these cases [11,12]. Discordantly, others favor open total abdominal colectomy with end ileostomy rather than another procedure [13].

Fecal microbiota transplantation (FMT) refers to instillation of processed stool collected from a healthy donor into the intestinal tract of a patient with CDI. FMT has been made under various protocols that may differ largely from center to center [5,14] In general, FMT protocols utilize donor stool suspended in normal saline prior to administration (via colonoscopy, enema, or nasoduodenal/nasojugal tube). Stool is homogenized (using blender, manual effort, or other method) to liquid consistency and filtered (eg, gauze, coffee filter, strainer) to
remove particulate matter. This processed specimen is then either directly infused into the GI tract or further centrifuged and capsulized in gelatin capsules that can be administered orally. FMT has become an accepted treatment for multiple recurrent CDI [4,5]. FMT has a clear role in severe refractory CDI and its main virtue is that frequently can lead to avoidance of surgery in these cases [4,15].

Primary prophylaxis of a first episode of CDI is mainly based on the minimization of the use of antibiotics and proton pump inhibitors or other medication that lowers gastric acidity. Using oral vancomycin may be of benefit in patients at high risk for CDI [16]. The use of probiotics is not recommended by guidelines [4,5,14] and instead the risk of complications and delay in microbiome restitution are highlighted [17,18]. There are multiple studies of various probiotics for CDI prevention and the data are highly inconsistent. Secondary prevention can be obtained by the above measures or by using SOC for CDI antibiotics in patients that require other courses of antibiotics.

**Future approaches for the prevention of CDI:**

Vaccine studies in CDI domain were mainly based on toxin-based formulations until recent [19]. Unfortunately, the concept did not seem to function as these vaccines, even if they showed an effect in reducing disease episode as well as good safety profile, they did not prevent the infection. These vaccines promote toxin-neutralising serum antibodies but fail to confer protection from infection in the gut. Some studies showed even a non-favorable safety profile with reactions at the site of administration that led to early stop of the programs [20, 21]. Another proposed mechanism for the vaccination is via oral administration of an antigen (the colonization factor CD0873 and a fragment of toxin B (TcdB)) in order to produce mucosal IgA and systemic IgG. This approach seems promising, but data are still needed to conclude [22]. Colonization with non-toxigenic strains of C. Difficile may prevent infection acting like an active vaccine or by substituting the toxin-producing strains. One of the most studied non-toxigenic strain is CCUG37785 that was engineered to express immunogenic fragments of TcdA and TcdB [23]. No vaccine is still available, but many researches are in progress and there is hope that in the future an effective vaccine can be produced.

A novel approach for primary prevention of CDI is coadministration of a poorly absorbed beta-lactamase (ribaxamase, SYN004) when administering broad-spectrum antibiotics [24, 25].

Alternatives to classic FMT are also in development. RBX2660 - developed by Rebiotix MRT™ - is a formulation composed of filtered and cryopreserved stool derived from healthy donors. In phase III studies already, RBX2660 has already shown efficacy and safety in preventing recurrences [26]. In order to avoid the lack of regulation and uniformity in the domain of FMT, a group of researchers proposed a microbial consortium called RePOOPulate or Microbial Ecosystem Therapeutic 1 (MET – 1) formed of 33 bacterial strains from the stool of a healthy donor cultivated using a bioreactor and selected based on antimicrobial resistance profiles. MET – 1 showed that enhances barrier function in T84 human intestinal epithelial cells and protects against the disruption of F-actin by purified TcdA in T84 and Caco2 cells [27]. SER-109, developed by Seres Therapeutics is another formulation of almost 50 species of Firmicutes, that showed a promising result, with 29 of 30 patients achieving clinical improvement in a study, and also a phase 3 study showed a good effect on recurrence [28].

**Future approaches for the treatment of CDI:**

Some of the antibiotics already on the market have been used off-label for the treatment of CDI and showed efficacy. Nitazoxanide, an antiparasitic medication already commercialized has shown results comparable with vancomycin [29]. It showed comparable results with metronidazole also [30]. Fusidic acid, an anti-staphylococcal medication excerpt also some effects on CDI [31]. The tetracyclines, have an increasing amount of evidence emerging to support their use for CDI. From this class, tigecycline is recommended by the guidelines as an additive in severe complicated forms of CDI. Other compounds have already been tested and showed activity against C. Difficile in in vivo or in vitro studies: eradycycline, omadacycline and aminomethycycline [32,33]. Because these tetracyclines have a broad spectrum, their use in CDI will be probably limited in the future as they can cause collateral damage.

A systematic review that included 8 studies on rifaximin in the treatment of CDI concluded that in the treatment of mild-moderate CDI, rifaximin is a viable alternative to existing therapies, but large rates of resistance and the risk of selecting more resistant strains are discouraging [34]. Clofazimine was approved by FDA in 1986 and is currently tested for CDI.

New antibiotics are being developed for the treatment of CDI, some of them with quite promising results.

Ridinilazole is an orally administered antibiotic whose mechanism of action is incompletely understood [35]. Phase III studies are currently ongoing and results are promising, with results superior to vancomycin (sustained clinical response 66.7% versus 42.4%) and no significant adverse events that led to discontinuation of the therapy [36].

Nisin is a bacteriocin produced by a group of Gram-positive bacteria that belongs to Lactococcus
and Streptococcus species. Nisin Z and A inhibit the growth of C. difficile in vitro. Nisin A also affects C. difficile spores, decreasing the spore viability by 40–50% [37].

LFF571 inhibits bacterial growth by binding to protein synthesis elongation factor Tu (EF-Tu) [38]. Novartis has finished phase II studies in 2015 and promising results were published, the substance showing high potency with narrow spectrum against CDI, still no news regarding phase III studies have occurred yet [39].

Ramoplanin is a glycolipodepsipeptide antibiotic. Like LFF571, finished phase 1 and 2 studies with good resuts, but are no sign of continuation of the development [39]. It affects gut flora at the same extent as vancomycin, but what seemed promising was the fact that it affected spores of C. Difficile [40].

DNV3837 is an intravenously administered oxazolidinone–quinolone hybrid prodrug as well as cadazoloid [39]. It decreases populations of C. Diff, Bifido-

dobacterium spp., Lactobacillus spp., and Enterococcus spp. and increases Escherichia coli while not affecting Bacteroides spp. Counts [39].

Other drugs in more incipient phases of development are Ibezapolstat an oral antibiotic that inhibits the DNA polymerase IIIIC of C. difficile, CRS3123, a fully synthetic diaryl diamine antibiotic that acts by inhibiting type 1 methionyl tRNA synthetase, a factor involved in bacterial protein synthesis, DS-2969b, that acts by inhibiting DNA gyrase B and can be administered orally or intravenously [39].

Gold nanoclusters developed with the help of nanotechnology are a solution under development [41].

As seen above, because of the existence of refractory forms, of severe and complicated forms, of relatively frequent recurrences, the need for new treatments in CDI is still high and therefore many researchers are currently in development with promising compounds in the pipeline.

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REFERENCES


