The management of *Clostridioides difficile* infection: from empirism to evidence

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Abstract

Clostridioides difficile infection (CDI) in clinical practice represents a challenge for its management and also prevention of recurrence. Even though there are updated guidelines for infection prevention, control and treatment, CDI remains a leading cause of healthcare acquired diarrhea with increasing incidence in the community. We present here a synthesis of the most recent international guidelines on the management of CDI.

In 2021 updated guidelines on the treatment of CDI in adults were published by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA), American College of Gastroenterology (ACG) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). These guidelines focused on CDI management in adults, including new data on the clinical efficacy of Fidaxomicin (FDX) and Bezlotoxumab. The 2017 publication of IDSA and SHEA - Clinical Practice Guidelines for *Clostridium difficile* infection also included pediatric treatment recommendations that are not a part of the 2021 update. Vancomycin (VAN) treatment for an initial CDI episode remains an acceptable alternative to FDX, considering the monetary and logistical challenge of acquiring FDX.

There is growing literature on fecal microbiota transplantation (FMT) and the 2021 guidelines describe its role in severe complicated refractory CDI cases and for which surgical management is not feasible. Moreover, there are new data on the secondary prophylaxis with VAN in refractory CDI in patients with risk factors who receive broad spectrum antibiotics.

Keywords: Bezlotoxumab, *Clostridioides difficile*, Fidaxomicin, pseudomembranous colitis, Vancomycin

Introduction

Clostridioides difficile is a spore forming anaerobic, Gram-positive bacterium that can cause pseudomembranous colitis in susceptible patients, representing a major nosocomial concern [1]. *Clostridioides difficile* infection (CDI) is a common cause of healthcare associated diarrhea. In Europe there are 189,526 cases annually of healthcare-associated CDI [2]. In America there are 223,900 *Clostridioides difficile* infections per year [3]. CDI is an important nosocomial infection that can cause severe enterocolitis and requires sanitary measures to reduce the infectious risk for other susceptible patients and adequate treatment to prevent life threatening infection.

Practitioners should bear in mind the fact that *Clostridioides Difficile* can be detected in asymptomatic patients. Therefore, testing for CDI is recommended in a patient that develops ≥3 type 7 Bristol scale stools within 24 hours [4]. For the diagnosis of CDI, a multistep algorithm testing should be used to avoid over-diagnosis by confirming the presence of a toxigenic strain of *Clostridioides difficile*. In consequence, a positive glutamate

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dehydrogenase (GDH) antigen test must be followed by a nucleic acid amplification test (NAAT) or enzyme immunoassay (EIA) test [4].

The severity of an initial CDI episode can be assessed by using clinical parameters, laboratory and imaging findings such as: fever at presentation, elevated leucocyte count, elevated serum creatinine value, distension of large intestine, pericolonic fat stranding or colonic wall thickening at imaging [5]. Using those parameters an initial CDI episode can be considered as non-severe, severe or fulminant.

Considering the severity classification of CDI there are different treatment options. The international guidelines include the Fidaxomicin, Vancomycin and Metronidazole use and promote the use of fecal microbiota transplantation (FMT) and Bezlotoxumab for recurrent episodes of CDI [4-6].

Treatment of an initial CDI episode

In 2021 updated clinical practice guidelines focused on the management of CDI were published by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), American College of Gastroenterology (ACG). the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA). There is a consensus between the three guidelines regarding the treatment of an initial non-severe CDI episode. It should be treated with Fidaxomicin or Vancomycin administered orally, depending on the availability of Fidaxomicin. If those are not available, then Metronidazole in oral administration should be considered [4-6]. Fidaxomicin is a better alternative to Vancomycin treatment because it reduces the recurrence risk of CDI [7,8].

Depending on the clinical presentation and laboratory parameters of the patient, the initial CDI episode can be considered a severe one. The ESCMID guideline defines as a severe CDI a patient that has at presentation fever >38.5º C, leucocyte count >15 x 10^9/L and serum creatinine >50% above the baseline. Additional factors are provided by imaging: distension of large intestine, pericolonic fat stranding or colonic wall thickening [5]. The ACG guideline classifies a severe CDI by the leucocyte value >15,000 cells/mm^3 and value of serum creatinine >1.5 mg/dL [4]. In this case both the ACG and the ESCMID guideline recommend Vancomycin or Fidaxomicin, but the ESCMID guideline includes the possibility of associating Metronidazole i.v. or Tigecycline i.v. to the standard of care (SOC) treatment [4,5].

Fulminant CDI is defined by the ESCMID guideline as a patient with hypotension, septic shock, elevated serum lactate, ileus, toxic megacolon, bowel perforation [5]. The ACG guideline regards fulminant CDI as severe CDI plus hypotension, shock, ileus, or megacolon [4]. Both guidelines recommend use of Vancomycin in association with Metronidazole. Fulminant CDI not responding to antibiotic treatment can be treated with Tigecycline i.v. 50 mg b.i.d. according to the ESCMID guideline [5].

Surgical treatment for fulminant CDI according to the ACG and ESCMID guideline is recommended when medical treatment does not result in an improvement of the patient with CDI. Total abdominal colectomy is considered the standard surgical approach. It can be avoided by partial colectomy or loop ileostomy with intraoperative colonic lavage and postoperative instillation of Vancomycin [4,5].

The IDSA and SHEA 2021 and ACG guidelines recommend for an initial CDI episode in which the patient presents ileus, megacolon, hypotension or shock, Vancomycin administered orally together with Vancomycin enema [4,6]. The IDSA and SHEA 2021 guideline recommends in this case to add Metronidazole iv to the SOC treatment [6].

Treatment of recurrences

First CDI recurrence

A recurrence of CDI is defined by the ACG guideline as the recurrence of diarrhea and a positive NAAT or EIA test within 8 weeks after the treatment of a first CDI episode [4]. The treatment chosen in this case is different between the 3 guidelines. The IDSA and SHEA 2021 guideline recommends Fidaxomicin as a first line of treatment while the ACG guideline recommends Vancomycin in a tapered and pulsed regimen and Fidaxomicin as a second line treatment [4,6]. The ESCMID guideline recommends Vancomycin or Fidaxomicin in association with Bezlotoxumab [5]. Tapered and pulsed regimens of Vancomycin mean a 10-to-14-day course of oral Vancomycin at a dose of 125 mg q.i.d., followed by reduced doses of Vancomycin over 2 weeks (b.i.d. for a week and then q.d. for the next week), followed by a Vancomycin dose of 125 mg every 2 or 3 days for 2 to 8 weeks [9].

According to the IDSA and SHEA 2021 guideline, Bezlotoxumab can be associated with the SOC antibiotics in case of a CDI recurrence within the first 6 months of the previous CDI episode [6]. Bezlotoxumab is a human monoclonal antitoxin antibody that binds to *Clostridioides difficile* toxin B and neutralizes its activity. Bezlotoxumab 10 mg/kg is given i.v. once during SOC regimen [10]. Another treatment indication for Bezlotoxumab is an initial CDI episode in a patient with CDI recurrence risk factors such as immunosuppression, severe initial CDI or ≥65 years of age according to the IDSA and SHEA 2021 guideline [6].

Treatment of a second or more CDI recurrence(s)

According to the IDSA and SHEA 2021 guideline, the first line of treatment in second CDI recurrence is Fidaxomicin 200 mg administered b.i.d. for 10 days. Another way of administration is b.i.d. for 5 days followed by once a day every other day for a duration of 20 days.

If Fidaxomicin isn't available, Vancomycin by mouth in a tapered and pulsed regimen is a good alternative. For a longer period of administration, Vancomycin by mouth 125 mg q.i.d. for 10 days followed by Rifaximin 400 mg t.i.d. for 20 days can be used especially in a patient with multiple recurrences [6]. Rifaximin is a non-absorbable antibiotic, rifamycin derivative that has a broad spectrum which includes *Clostridioides difficile*. Its effect on CDI was studied, showing a decrease of recurrent diarrhea in patients with CDI [11,12].

The ESCMID guideline recommends FMT as a first line of treatment for a second CDI recurrence. A second line of treatment is represented by Vancomycin or Fidaxomicin in association with Bezlotoxumab and if those two lines of treatment are not available, Vancomycin in a tapered and pulsed regimen is recommended [5].

According to the IDSA and SHEA 2021 guideline, FMT is recommended for patients who had at least 2 recurrent CDI episodes and no clinical response to the SOC antibiotic treatment [6]. Another course of treatment is Bezlotoxumab 10mg/kg given i.v. once during SOC regimen [6].

A recurrence of CDI is particularly challenging to treat and FMT has a higher success rate in comparison to broad spectrum antibiotics in this case. The source of stool should be vigorously screened. The age of an FMT donor should be less than 60 years, with a body mass index between ≥18 and ≤30 kg/m^2. When it is possible, FMT should be sourced from a centralized stool bank from an unrelated donor, but another possible choice for FMT donor is a family member or significant other [13,14]. Fresh stool (processed within 6 hours of defecation) or frozen fecal material (used within 6 hours from thawing) can be used for FMT. It may be delivered through the upper gastrointestinal tract using nasogastric or nasoenteric tubes, upper gastrointestinal endoscopy and capsules. Another way of administering FMT is via the lower gastrointestinal tract using enema or lower gastrointestinal endoscopy. The colonoscopy approach is the preferred route of FMT administration because it allows the delivery of FMT and the evaluation of the severity of the colon inflammation, including the presence of pseudomembranes [15].

Antibiotic resistance in CDI

For many years Metronidazole was considered an optimal treatment choice for CDI. The latest guidelines for CDI management removed Metronidazole as a first line treatment based on recent randomized controlled trials that demonstrated high rates of treatment failure in patients treated with Metronidazole [16,17]. A reason for these findings is the pharmacokinetic limitations of Metronidazole after oral administration [16,17]. Another reason is the presence of *Clostridioides difficile* strains such as polymerase chain reaction ribotype 027 (RT027) that possesses Metronidazole, Rifampicin, Moxifloxacin, Clindamycin, Imipenem and Chloramphenicol resistance [18,19]. In Europe the RT027 was identified predominantly in Denmark, Hungary, Italy and Poland [18,19]. RT027 was also reported in Romania causing outbreaks [20]. In the United States a decline in RT027 prevalence was observed in the last decade [21].

Vancomycin is increasingly used due to the updated CDI guidelines, but the clinical treatment response has decreased over time. The existing literature on Vancomycin resistance focuses on the *Clostridioides difficile* genes associated with Vancomycin resistance as a tool for obtaining the best treatment outcome [22,23]. There is no consensus on *Clostridioides difficile* culture and susceptibility testing in clinical practice, making it difficult to evaluate the degree of Vancomycin resistance. *Clostridioides difficile* strains with reduced susceptibility to Vancomycin represent a therapeutic challenge. Hypervirulent strains of *Clostridioides difficile* with reduced susceptibility to Vancomycin have been reported in Israel [24].

Prophylaxis of CDI

Primary prophylaxis

Primary prophylaxis of CDI represents the prevention of an initial CDI episode in a patient that has no previous history of CDI. The 2017 publication of IDSA and SHEA- Clinical Practice Guidelines for *Clostridium difficile* infection includes the importance of primary prophylaxis in CDI. The patient with CDI should be isolated from other patients without CDI to prevent spore transmission. Medical personnel should wear protective gowns and gloves when they interact with the stool of the infected patient or *Clostridioides difficile* spore contaminated objects. Moreover, hand hygiene with either soap and water or an alcohol-based hand hygiene product prevents the transmission of *Clostridioides* difficile spores [25]. These aspects are described in the 2021 publication of ACG as well [4].

The 2021 publications of ACG and ESCMID mention the importance of evaluating risk factors for developing CDI and tackling them [4,5]. The risk factors can be divided in exogenous and endogenous risk factors. The exogenous risk factors are represented by pharmacological agents such as antibiotics, proton pump inhibitors (PPIs), H2 receptor antagonists, nonsteroidal anti-inflammatory drugs (NSAIDs) and by invasive procedures such as recent abdominal surgery and invasive mechanical ventilations [26].

Endogenous risk factors are patient related, regarding patient comorbidities, for example: immunosuppression or neutropenia, diabetes, inflammatory bowel disease (IBD), chronic kidney disease, solid cancer, hypoalbuminemia, or age over 65 years old [26]. For such patients with endogenous risk factors repeated hospital admissions

should be avoided, as they increase the risk of CDI [5].

Broad-spectrum antibiotic treatment represents a major risk factor by disrupting the gut microbiome. Use of Clindamycin and Fluoroquinolones represent the highest risk for CDI in community-acquired CDI. In hospital-acquired CDI the antibiotic use risk factors are third generation Cephalosporins followed by Clindamycin, fourth generation Cephalosporins, Carbapenems, Fluoroquinolones and Piperacillin in combination with a beta-lactamase inhibitor [27,28].

The use of probiotics has not been considered beneficial in primary or secondary CDI prophylaxis [5,6,29]. The use of PPIs as a risk factor for CDI was debated in published articles. Although some studies reveal an epidemiological association between PPIs and CDI [30,31], others do not find an association between them [32]. Unnecessary proton pump inhibitor treatment should be discontinued considering the fact that in some studies the use of PPIs is related to CDI or CDI recurrence [4,5,25,30].

Secondary prophylaxis of CDI

Secondary prophylaxis represents the prevention of CDI recurrence [33]. Exposure to antimicrobials is one of the risk factors for developing community acquired CDI because of the disruption of the gut microbiome and facilitating the proliferation of *Clostridioides difficile* [34].

When facing a patient that must take antibiotic therapy, the physician should take into consideration other risk factors for developing CDI and if the patient had a previous CDI episode. Oral Vancomycin prophylaxis with a dose of 125 mg b.i.d. is recommended in these carefully selected patients [33].

Table I. Severity classification and treatment of CDI presented by the three guidelines.

		IDSA and SHEA 2021	ACG 2021	ESCMID 2021
First CDI episode	Non-severe WBC ≤ 15,000 cells/mL Crea < 1.5 mg/dL	I. FDX 200 mg b.i.d. for 10 days	I. VAN 125 mg po q.i.d.	I. FDX 200 mg b.i.d. for 10 days
		II . VAN 125 mg po q.i.d. for 10 days	II. FDX 200 mg b.i.d. for 10 days	II. VAN 125 mg po q.i.d.
		III. Metronidazole 500 mg po t.i.d. for 10-14 days	III. Metronidazole 500 mg po t.i.d. for 10-14 days	III. Metronidazole 500 mg po t.i.d. for 10 days
	Severe WBC ≥ 15,000 cells/mL Crea > 1.5 mg/dL		I. VAN 125 mg po q.i.d. for 10 days	VAN or FDX +/- Metronidazole iv or Tigecycline iv
			II. FDX 200 mg b.i.d. for 10 days	
	Fulminant	VAN 500 mg po q.i.d. + Metronidazole 500 mg iv t.i.d.	VAN 500 mg po q.i.d. for 48-72 h	VAN or FDX
			VAN + Metronidazole 500 mg iv t.i.d.	Surgical consultation
			FMT when Fulminant CDI is refractory to AB therapy	Tigecycline 50 mg iv b.i.d.
				FMT
	Ileus	add VAN enemas + VAN po + Metronidazole 500 mg iv t.i.d.	add VAN 500 mg enemas t.i.d.	
First recurrence		I. FDX 200 mg b.i.d. for 10 days	I. Tapered and pulsed dose VAN	I. VAN or FDX + Bezlotoxumab
		II. FDX 200 mg b.i.d. for 5 days then once every other day for 20 days	II. FDX	II. FDX 200 mg b.i.d. for 5 days then q.d. every other day for 20 days
		III . VAN 125 mg po tapered and pulsed regimen		III. VAN tapered and pulsed
		IV . VAN 125 mg po q.i.d. for 10 days		
		V. Bezlotoxumab 10 mg/kg iv once during SOC AB		
Second recurrence		I. FDX 200 mg b.i.d. for 10 days	I. FMT through colonoscopy or capsules	I. FMT
		II. FDX 200 mg b.i.d. for 5 days then once every other day for 20 days	II. Repeat FMT in case of CDI recurrence in the first 8 weeks of initial FMT	II. VAN or FDX + Bezlotoxumab
		III . VAN 125 mg po tapered and pulsed regimen	III. VAN po for recurrent CDI in patients who relapsed after FMT	III. VAN tapered and pulsed
		IV. VAN 125 mg po q.i.d. for 10 days followed by Rifaximin 400 mg t.i.d. for 20 days	IV. Bezlotoxumab for patients at risk of recurrence	
		V. FMT after at least 3 CDI episodes		
		VI. Bezlotoxumab 10 mg/kg iv once during SOC AB		
IBD + CDI			VAN po q.i.d. for at least 14 days	
			FMT for recurrent CDI in patients with IBD	

Abbreviations: **CDI**- *Clostridoides difficile* infection; **WBC**- white blood cells; **Crea**- creatinine; **FDX**- Fidaxomicin; **VAN**- Vancomycin; **q.d.**- once a day; **b.i.d.**- twice daily; **t.i.d.**- three times a day; **q.i.d.**- four times a day; **po**- oral; **iv**- intravenous; **SOC**- standard of care; **FMT**- fecal microbiota transplantation, **AB**- antibiotic, **IBD**- inflammatory bowel disease.

Evaluating the need for testing and choosing a diagnostic test for CDI

CDI should be suspected in a patient with ≥ 3 watery stools within 24 hours especially when that patient was recently exposed to the healthcare environment, took antibiotic treatment or is over 65 years old [4]. It is important to evaluate the risk factors for developing CDI before choosing a diagnostic test.

CDI diagnostic tests

Available diagnostic tests for CDI are NAAT, GDH antigen test and EIA test. All those tests should be used for testing unformed stool. EIA test detects toxin A and B produced by the organism in the infected patient. NAAT detects the gene encoding toxin but it does not indicate if the organism is producing the toxin. Therefore, a positive NAAT can appear in an asymptomatic patient. GDH is produced both by toxigenic and nontoxigenic strain of *Clostridioides difficile.* A positive GDH tests must be followed by NAAT or EIA test to confirm the presence of a toxigenic strain [4,35]. By using a multistep algorithm in testing for CDI, overdiagnosis by applying only NAAT is avoided [25].

According to the IDSA and SHEA 2017 and ACG guidelines, practitioners should evaluate the clinical presentation of the patient before choosing a diagnostic test. If the stool of the patient is unformed, the patient is not using laxatives and has an unexplained onset of over 3 unformed stools in 24 h he should be tested for CDI [4,25]. When there are institutional criteria for patient stool submission for CDI testing, a good diagnostic method is NAAT or one of the following: stool toxin test and GDH test; toxin test and GDH test arbitrated by NAAT; NAAT plus toxin test. It is not recommended to repeat the testing within 7 days during the same episode of unformed stool [25].

The ACG guideline recommends including highly sensitive tests and highly specific tests to distinguish between colonization and active infection. Firstly, the stool should be tested with a highly sensitive NAAT or GDH test. If it is positive, then an EIA test should follow. If both tests are positive, then CDI is confirmed. Practitioners should bear in mind that no test is perfect and the decision to treat can be made on the clinical presentation of the patient. In this case empiric treatment can be administered. Lack of response to Vancomycin treatment in nonsevere cases or an atypical course of the disease can contradict the CDI diagnosis [4].

Pediatric management recommendations

The 2017 Clinical Practice Guidelines for *Clostridioides difficile* infection included the management of CDI in pediatric patients [25]. The 2021 IDSA and SHEA guideline focuses on adult treatment recommendations and includes new data on Fidaxomicin and Bezlotoxumab use in treatment of CDI [6].

Diagnosis of CDI in pediatric patients

Testing for CDI in pediatric patients is recommended after 12 months of age in the presence of diarrhea. There is a high prevalence of asymptomatic *Clostridioides difficile* colonization in infants. Children younger than 12 months of age should be tested for *Clostridioides difficile* if there is clear evidence of pseudomembranous colitis or toxic megacolon in the presence of diarrhea and after other causes for diarrhea are excluded [25].

In pediatric patients older than 2 years of age CDI testing is recommended in case of prolonged diarrhea and additional risk factors such as IBD, immunosuppression, recent antibiotic treatment or contact with the healthcare system [25].

Treatment of CDI in pediatric patients

For an initial episode of non-severe CDI in children Metronidazole (po for 10 days, 7,5 mg/kg/dose t.i.d. or q.i.d.) or Vancomycin (po for 10 days, 10 mg/kg/dose q.i.d.) is recommended [25]. Metronidazole has been used historically in pediatric treatment of CDI as a first line treatment, but as the 2017 IDSA and SHEA guideline recommends use of Vancomycin over Metronidazole in adults with non-severe CDI, recent studies show a better outcome using Vancomycin over Metronidazole in pediatric patients [36,37]. Fidaxomicin was omitted from pediatric recommendations because of lack of evidence at the time of the 2017 IDSA and SHEA publication. Since then, new data are available and in January 2020 US Food and Drug Administration approved Fidaxomicin for the treatment of CDI in children over 6 months old [38].

For an initial episode of severe CDI in children Vancomycin (po or pr for 10 days, 10 mg/kg/dose q.i.d.) is the first treatment of choice and Metronidazole (po for 10 days, 10 mg/kg/dose t.i.d.) can be added to the Vancomycin treatment if deemed necessary [25].

In case of a first recurrence of non-severe CDI, Metronidazole (po for 10 days, 7,5 mg/kg/dose t.i.d. or q.i.d.) or Vancomycin (po for 10 days, 10 mg/kg/dose q.i.d.) is recommended [25].

In case of a second recurrence Vancomycin in a tapered and pulsed regimen is recommended. An alternative is Vancomycin (po for 10 days, 10 mg/kg/dose q.i.d.) followed by Rifaximin (no pediatric dosing available, maximum dose of 400 mg t.i.d.) for 20 days. Another course of treatment is FMT for pediatric patients with multiple recurrences of CDI following antibiotic treatment [25]. Children with IBD can also receive FMT, failed treatment among those patients may be related to clinically active IBD [39].

Conclusions

Oral Vancomycin remains an important treatment choice in clinical practice because of economic considerations and its logistical availability even though new guidelines promote Fidaxomicin use in CDI as a first line of treatment. Depending on the financial possibility of implementing Fidaxomicin use in hospitals, medical

practitioners can observe a reduction of the CDI burden in the healthcare system. Fecal microbiota transplantation use for severe CDI not responding to antibiotic treatment is recommended by both the ACG and ESCMID guidelines. Bezlotoxumab in addition to the SOC treatment is recommended for the treatment of the first CDI recurrence by the 2021 IDSA and SHEA and ESCMID guidelines. Tigecycline i.v. use is recommended by the ESCMID guideline for the treatment of severe CDI when Vancomycin or Fidaxomicin treatment is not improving the clinical state of the patient.

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