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REVIEW

Comparison of three current *Clostridioides difficile* infection guidelines: IDSA/SHEA, ESCMID, and ACG guidelines

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Abstract

Purpose *Clostridioides difficile* infection (CDI) is a widely recognized condition associated with comorbidity and decreased patient quality of life. Certain professional medical organizations develop clinical practice guidelines for major diseases. This is done in an effort to streamline the universal clinical practice and ensure that a more accurate diagnosis and better treatments are offered to respective patients for optimal outcomes. However, as new data evolve, constant update of these guidelines becomes essential. While these guidelines provide up-to-date recommendations, they are not published around the same time; thus, their recommendations may vary depending on evidence available prior to guidelines preparation and publication.

Methods Recommendations and corresponding justifications from three major CDI guidelines between 2013 and 2017 were pooled and compared, and notable differences were highlighted while providing an insight and a final recommendation from a clinical standpoint.

Results Most recommendations were consistent among all three guidelines. One notable difference was in the specification of candidates for CDI diagnosis, where it would be recommended to mainly test patients with three or more diarrheal episodes over 24 h, if they had no other clear reason for the diarrhea. Another conflicting point was regarding the treatment of non-severe CDI where vancomycin can be considered for older or sicker patients; however, metronidazole still remains a reasonable option based on recent data, some of which were not cited in the most recent guidelines of IDSA/SHEA.

Conclusion Overall, it is prudent to follow these guidelines with critical appraisal to fulfill the goal of achieving optimum patient outcomes.

Keywords *Clostridioides difficile* · Guidelines · IDSA · ESCMID · ACG · Vancomycin

Introduction

Clostridioides difficile infection (CDI) has been associated with increased morbidity and decreased patients' quality of life. While mortality rates due to CDI remain low, it has been associated with hospital outbreaks and an economic burden. Appropriate management starts with appropriate diagnosis, followed by antimicrobial therapy tailored to the severity of the disease. As treating CDI is crucial, preventing its recurrence in the individual patient, as well as preventing and controlling its spread to other patients, is of utmost importance.

Medical guidelines provide summary of recommendations or suggestions on the diagnosis, treatment, or prevention of the diseases while evaluating the quality of evidence with each statement of recommendation or suggestion [1]. These guidelines are developed by a panel of experts in the field who incorporate results from the published studies along with their experience to generate the final clinical judgment [1].

Due to the serious nature of CDI, several medical societies or organizations have published guidelines to help clinicians to appropriately manage the disease and control it. CDI guidelines generally share the same outline which includes diagnosis, classification based on CDI severity, treatment (which is further divided into treatment of initial episode and treatment of recurrence), and infection control and

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prevention. Some guidelines also added an additional section on the role of prophylaxis against CDI in high-risk patients.

More than one CDI guidelines have been published in the medical literature. Therefore, to simplify the task of the health-care provider, this review aimed to combine the recommendations of three major CDI guidelines in each of the aforementioned sections of the outline, summarize them, as well as compare and contrast each recommendation backed up with studies from the literature that were either cited or not cited in the respective guidelines. The three guidelines discussed in this review include those published by the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) of 2017, the American College of Gastroenterology (ACG) of 2013, and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) of 2014. Since a similar comparison of older CDI guidelines was previously published [2], this review provides an updated comparison of the most recently published guidelines.

Diagnosis of CDI

Individual recommendations for diagnosis from the three guidelines are summarized in Table 1.

Candidates for CDI diagnosis

IDSA/SHEA and ACG guidelines specified that only patients presenting with unexplained diarrhea (defined per the World Health Organization as three or more unformed stools within 24-h duration or more frequently than is normal for the individual) should be tested for CDI [3–5]. ESCMID guidelines also included the same definition for diarrhea, though it was not stated in the context of defining CDI diagnosis candidates [6]. Notably, the recommendation of ACG in this regard was rated strong, whereas that of IDSA/SHEA was rated weak. This is possibly because the latter guidelines reported that the number of diarrheal episodes used to define clinical diarrhea has changed over the years and that clinicians should look for other conditions to which diarrhea can be attributed, such as inflammatory bowel disease (IBD), cancer chemotherapy, or use of laxatives within the past 48 h [4]. Conversely, since the ACG guidelines were developed by a panel of gastroenterology experts, the list of CDI diagnosis candidates was extended to include patients with certain gastrointestinal problems, including IBD (Table 1) [3]. From a clinical standpoint, a patient with diarrhea should be typically assessed for the presence of CDI risk factors, namely the use of antimicrobial agents (which is also emphasized in the extended list of candidates provided by ACG), potential transmission from another CDI patient, as well as other factors listed in both guidelines. However, a recent study found no difference in the rate of CDI occurrence between patients with and patients without underlying gastrointestinal conditions [7]. As a result, it would be more prudent to follow IDSA/SHEA guidelines to test patients with diarrhea that is clearly not linked to causes other than a potential infection with *C. difficile*.

Although guidelines recommend CDI testing of only unformed/loose stools (types 5–7 on Bristol stool chart) and recommend against testing of formed stools (types 1–3 on Bristol stool chart), no specific recommendation was made regarding testing of semiformed stools (type 4 on Bristol stool chart). In this regard, one study that quantified *C. difficile* in stool samples with varying degrees of consistency according to Bristol stool chart found absence of direct correlation between *C. difficile* quantity and the degree of stool consistency [8]. As such, the authors concluded that semiformed stools should be sought for CDI testing in patients presenting with the clinical picture of the disease.

Laboratory testing of CDI

Both ACG and IDSA recommend using nucleic acid amplification tests (NAATs) as the single standard diagnostic test [3, 4]. Alternatively, a multistep algorithm using glutamate dehydrogenase (GDH) (for screening) followed by toxin enzyme immunoassay (EIA) can be performed [3, 4]. In this regard, ESCMID elaborated on its recommendation about the multistep algorithm testing where a positive first test should be confirmed with one or two confirmatory tests (GDH, Toxin A and B, or NAAT) [6]. CDI testing in patients receiving laxative was addressed only in IDSA guidelines, where they recommend using a stool toxin test as part of a multistep algorithm [4].

All three guidelines recommend against the repeat of CDI testing if the first result returned negative [3, 4, 6]. While ACG also discourages testing for cure, IDSA recommends against testing stool from asymptomatic patients [3, 4].

Severity classification of CDI

The degree of CDI severity should be determined for initial CDI episodes to tailor the treatment accordingly. Table 2 provides a comprehensive summary on how each guideline classified CDI patients according to disease severity.

Treatment of CDI

The recommendations provided by each of the three guidelines for the treatment of initial and recurrent episodes of CDI are listed in Table 3. Stopping unnecessary (potentially inciting) antibiotics is a universal recommendation made by all three guidelines [3, 4, 6].

Table 1 Recommendations for diagnosis of *Clostridioides difficile* infection by the three guidelines

	IDSA/SHEA 2017	ESCMID 2014	ACG 2013
Candidate patients for CDI testing	Patients with unexplained and new-onset ≥ 3 unformed stools in 24 h. *(Weak recommendation, very low-quality evidence)*	Not specified	Only stools from patients with diarrhea. (*Strong recommendation, high-quality evidence*) The following comorbid situations are recommended to have CDI testing All patients with IBD hospitalized with a disease flare. (*strong recommendation, high-quality evidence)* Ambulatory patients with IBD who develop diarrhea in the setting of previously quiescent disease or in the presence of risk factors such as recent hospitalization or antibiotic use. (s*Strong recommendation, moderate quality evidence)* Patients with IBD who have a surgically created pouch after colectomy if they have CDI symptoms. (*Strong recommendation, moderate quality evidence*) Patients with underlying immunosuppression (including malignancy, chemotherapy, corticosteroid therapy, organ transplantation,and cirrhosis) if they have a diarrheal illness. (*Strong recommendation, moderate quality evidence)* Any diarrheal illness in women who are pregnant or periparturient. (*Conditional recommendation, low-quality evidence)*
Laboratory testing of CDI	NAAT alone or a multistep algorithm: GDH EIA + toxin EIA (may or may not be arbitrated by NAAT) or NAAT + toxin EIA rather than a toxin test alone when there are pre-agreed institutional criteria for patient stool submission. *(Weak recommendation, low quality evidence)*	Two- or three-stage algorithm, in which a positive first test is confirmed with one or two confirmatory tests or a reference method such as GDH, toxins A and B, or NAAT detecting Toxin B (TcdB)	NAAT is superior to toxins A + B EIA. (*Strong recommendation, moderate quality evidence*) Alternatively, two- or three-step algorithm: GDH EIA followed by a confirmatory test. (*Strong recommendation, moderate quality evidence).* Rectal swabs can be used for PCR and thus, may be useful in timely diagnosis of patients with ileus[a]
Diarrheal specimen from patients receiving laxatives	Use a stool toxin test as part of a multistep algorithm: GDH EIA + toxin EIA (may or may not be arbitrated by NAAT) or NAAT + toxin EIA rather than a NAAT when there are no pre-agreed institutional criteria for patient stool submission. (*Weak recommendation, low quality evidence)*	Not specified	Not specified

Table 1 (continued)

	IDSA/SHEA 2017	ESCMID 2014	ACG 2013
Role of repeat testing including symptomatic, asymptomatic patients and cure test	No repeat testing (within 7 days) during the same episode of diarrhea and no stool testing from asymptomatic patients, except for epidemiological studies. (*Strong recommendation, moderate quality evidence*)	Samples with the first negative test result can be reported as negative (i.e., no repeat testing)	Repeat testing and testing for cure should be discouraged. (*Strong recommendation, moderate quality evidence*)

CDI, *Clostridioides difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction

[a]No specification of recommendation strength

Initial CDI episode

Similar to the older IDSA/SHEA guidelines of 2010 [9], both ESCMID and ACG guidelines agreed on recommending metronidazole for patients with mild-to-moderate CDI as the first-line treatment. This recommendation was based on two old randomized control trials (RCTs) with a total of 213 patients comparing metronidazole with vancomycin. Both studies concluded that the difference between metronidazole and vancomycin was not significantly different and that metronidazole was more economical [10, 11]. Moreover, both metronidazole and vancomycin adversely promote the overgrowth of vancomycin-resistant *Enterococci* (VRE) [12]. On the other hand, the new IDSA/SHEA guidelines favored vancomycin over metronidazole for the treatment of non-severe CDI based on a new evidence from two RCTs that demonstrated the superiority of vancomycin to metronidazole in terms of clinical cure [13, 14]. While the guidelines cite the study by Zar et al. under this recommendation, the study showed the superiority only in severe CDI, whereas similar findings were seen in mild CDI [13]. Similarly, a large retrospective study of 47,147 patients by Stevens and colleagues demonstrated lack of difference in CDI recurrence and 30-day mortality between the metronidazole and vancomycin groups in those who initially experienced mild-to-moderate CDI [15]. However, significantly lower 30-day mortality was observed in the vancomycin group in patients with initial severe episode of the disease [15]. Interestingly, while the new IDSA/SHEA guidelines were ready to be published in late 2017, Crowell et al. published a study in the same year showed that appropriate adherence to the older IDSA/SHEA guidelines of 2010 (that recommended metronidazole prior to vancomycin as first-line for non-severe CDI) was significantly associated with lower mortality and shorter length of stay [16]. Due to the conflicting evidence in this area, the use of metronidazole for non-severe cases may continue to remain a reasonable option, particularly in less endemic areas, as well as for younger, less sick patients (e.g., non-immunocompromised).

Both ESCMID and ACG included a recommendation on the use of fidaxomicin but only for severe cases of CDI, whereas IDSA/SHEA guidelines included this recommendation as an alternative to vancomycin and preferable over metronidazole for non-severe CDI episodes. IDSA/SHEA justified this recommendation based on two studies that compared vancomycin with fidaxomicin showing non-inferiority results [17, 18]. Furthermore, four more studies showed potential benefits associated with the use of fidaxomicin over vancomycin. The first study by Housman et al. assessed the microbiological effect of either agent on *C. difficile* colony counts using quantitative culturing of stool samples collected at different time points before, during, and after completion of therapy from CDI patients given

Table 2 Severity classification of *Clostridioides difficile* infection according to the three guidelines

	IDSA/SHEA 2017	ESCMID 2014[a]	ACG 2013
Physical examination			
Fever ≥ 38.5 °C		√	*
Rigors		√	
Abdominal tenderness			√
Abdominal distention			*
Ileus	*	√	*
Signs and symptoms of peritonitis		√	
Hemodynamic instability	*	√	*
Respiratory failure		√	*
Mental status change			*
Intensive care unit admission		√	*
Laboratory alterations			
Leukocyte count	≥ 15,000 cells/mm^3	> 15,000 cells/mm^3 (band neutrophils > 20% of leukocytes)	≥ 15,000 cells/mm^3 (≥ 35,000 or < 2000 cells/mm^3)*
Creatinine	> 1.5 mg/dL	> 50% above the baseline or ≥ 133 μM	Renal failure*
Albumin		< 30 g/L	< 30 g/L
Lactate		≥ 5 mM	> 2.2 mmol/L*
Colonoscopy and imaging			
Pseudomembranous colitis		√	
Megacolon/large intestine distension	*	√	
Colonic wall thickening		√	
Pericolonic fat stranding		√	
Unexplained ascites		√	

√Factors indicating severe CDI

*Additional criteria for increased risk of severe CDI: serious comorbidity, immunodeficiency, and age ≥ 65 years

[a]Factors indicating complicated (or fulminant) CDI

the antibiotics [19]. The study found no significant difference between the colony counts of vegetative *C. difficile* in samples from patients who received fidaxomicin or vancomycin. Nonetheless, fidaxomicin resulted in a significant reduction in spore counts by ≥ 2 $\log_{10}$ CFU/g compared with vancomycin at the 9–19 days follow-up visit ($P = 0.02$). The second study was a pilot study comparing *C. difficile* toxin concentrations between patients who received vancomycin vs. fidaxomicin, where only the latter was associated with sustained levels of both toxins for up to 30 days post-therapy [20]. The third study by Gallagher and colleagues showed the economic advantage of fidaxomicin, where a significantly lower number of patients who received the agent were readmitted to the hospital with CDI within 90 days compared with those who received vancomycin ($P = 0.03$) [21]. Moreover, those who received fidaxomicin also experienced a shorter total length of hospital stay vs. the vancomycin group (87 vs. 183 days) on the basis of actual total costs of $196,200 and $454,800 in the fidaxomicin and vancomycin groups, respectively. Similar results with fidaxomicin were demonstrated in the fourth study by Goldenberg et al., where implementing the use of fidaxomicin resulted in significantly lower rate of CDI recurrence and 28-day mortality compared with the period prior to fidaxomicin use ($P < 0.05$ for both comparisons) [22]. It is presumed that such effects of fidaxomicin can help mitigate CDI symptoms, as demonstrated by the decrease in toxin concentrations which might have been translated into the shortened length of stay seen in the two latter studies. Additionally, fidaxomicin is also presumed to be linked to decreased probability of CDI recurrence within the same patient or transmission between patients given its effects on spore reduction, which showed reduced rates of readmission in the two latter studies. All four studies were published in or after 2015, though none was cited in the IDSA/SHEA guidelines of 2017 to support recommending fidaxomicin, perhaps over vancomycin. Overall, fidaxomicin seems to be a very attractive option for clinicians given its clinical, microbiological, and economical value in CDI treatment. Hence, it was presented as a favorable option in IDSA/SHEA guidelines and is presumed to receive an equal level of favorability in the upcoming ESCMID and ACG guidelines.

Table 3 Pharmacological treatment recommendations for *Clostridioides difficile* infection of the three guidelines

	IDSA/SHEA 2017	ESCMID 2014	ACG 2013
Initial episode, non-severe (mild-to-moderate)	Vancomycin 125 mg PO every 6 h or fidaxomicin 200 mg PO every 12 h for 10 days. *(Strong recommendation, high-quality evidence)* If above agents are unavailable, metronidazole 500 mg PO every 8 h for 10 days. *(Weak recommendation, high-quality evidence)*	Metronidazole 500 mg PO every 8 h for 10 days. *(Strong recommendation, high-quality evidence)* Vancomycin 125 mg PO every 6 h or fidaxomicin 200 mg PO every 12 h for 10 days. *(Moderate recommendation, high-quality evidence)* Vancomycin 500 mg PO every 6 h for 10 days. *(Weak recommendation, high-quality evidence)* Stop inducing antibiotics and observe for 48 h. *(Weak recommendation, moderate quality evidence)*	Metronidazole 500 mg PO every 8 h for 10 days. *(Strong recommendation, high-quality evidence)* Failure to respond to metronidazole within 5–7 days should prompt consideration of a change to vancomycin 125 mg every 6 h for 10 days. *(Strong recommendation, moderate quality evidence)* Patients in whom oral antibiotics cannot reach a segment of the colon (i.e., ileus), vancomycin enema should be added as 500 mg in 100–500 mL of normal saline every 6 h. *(Conditional recommendation, low quality evidence).*
Initial episode, severe	Vancomycin 125 mg PO every 6 h or fidaxomicin 200 mg PO every 12 h for 10 days. *(Strong recommendation, high-quality evidence)*	Vancomycin 125 mg PO every 6 h for 10 days. *(Strong recommendation, high-quality evidence)* Vancomycin 500 mg PO every 6 h for 10 days. *(Moderate recommendation, moderate quality evidence)* Fidaxomicin 200 mg PO every 12 h for 10 days. *(Moderate recommendation, high-quality evidence)*	Vancomycin 125 mg PO every 6 h for 10 days. *(Conditional recommendation, moderate quality evidence)* Patients in whom oral antibiotics cannot reach a segment of the colon (i.e., ileus), vancomycin enema should be added as 500 mg in 100–500 mL of normal saline every 6 h. *(Conditional recommendation, low quality evidence)*

Table 3 (continued)

	IDSA/SHEA 2017	ESCMID 2014	ACG 2013
Initial episode, fulminant (severe complicated)	Vancomycin 500 mg PO or NG every 6 h. *(Strong recommendation, moderate quality evidence)* If ileus, consider adding vancomycin 500 mg in 100 mL of normal saline PR every 6 h. (*Weak recommendation, low quality evidence)* + IV metronidazole 500 mg every 8 h. *(Strong recommendation, moderate quality evidence)*	Surgery if failed antibiotic therapy with systemic toxicity, peritonitis, or toxic colonic dilatation and bowel perforation[a]	If no significant abdominal distention, vancomycin 125 mg PO every 6 h + metronidazole 500 mg IV every 8 h. (*Strong recommendation, low-quality evidence)* If ileus or toxic colitis and/or significant abdominal distention, vancomycin 500 mg PO every 6 h + 500 mg PR in 500 mL normal saline every 6 h + metronidazole 500 mg IV every 8 h. (*Strong recommendation, low-quality evidence)* Surgical therapy should be considered in patients with any one of the following conditions attributed to CDI Hypotension requiring vasopressor therapy Clinical signs of sepsis Organ dysfunction Mental status changes WBC count ≥ 50,000 cells/mm^3 Lactate ≥ 5 mmol/L Complicated CDI with failure to improve on medical therapy after 5 days (*Strong recommendation, moderate quality evidence)*
First recurrence	If a standard regimen was used for the initial episode, vancomycin PO tapered and pulsed regimen (125 mg PO every 6 h for 10–14 days, every 12 h for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks). *(Weak recommendation, low quality evidence)* If vancomycin was used for the initial episode, fidaxomicin 200 mg PO every 12 h for 10 days. *(Weak recommendation, moderate quality evidence)* If metronidazole was used for the primary episode, vancomycin 125 mg PO every 6 h for 10 days rather than a second course of metronidazole. *(Weak recommendation, low quality evidence)*	Vancomycin 125 mg PO every 6 h or fidaxomicin 200 mg PO every 12 h for 10 days. (*Moderate recommendation, high-quality evidence)* Metronidazole 500 mg PO every 8 h for 10 days. (*Weak recommendation, high-quality evidence)* Vancomycin 500 mg PO every 6 h for 10 days. *(Weak recommendation, low quality evidence)*	Same as initial episode. *(Conditional recommendation, low quality evidence)*

Table 3 (continued)

	IDSA/SHEA 2017	ESCMID 2014	ACG 2013
Second recurrence	Vancomycin PO tapered and pulsed regimen. *(Weak recommendation, low quality evidence)* Vancomycin 125 mg PO every 6 h for 10 days followed by rifaximin 400 mg PO every 8 h for 20 days. *(Weak recommendation, low quality evidence)* Fidaxomicin 200 mg PO every 12 h for 10 days. *(Weak recommendation, low quality evidence)*	Vancomycin 125 mg PO every 6 h for 10 days followed by pulsed regimen (125–500 mg per day every 2–3 days for at least 3 weeks, vancomycin orally 125 mg PO every 6 h for 10 days followed by taper regimen (gradually decreasing the dose to 125 mg per day), or fidaxomicin 200 mg PO every 12 h for 10 days. *(Moderate recommendation, moderate quality evidence)* Vancomycin 500 mg PO every 6 h for 10 days. *(Weak recommendation, moderate quality evidence)*	Pulsed vancomycin regimen (*Conditional recommendation, low quality evidence)*
Multiple (≥ 3 recurrences) who have failed appropriate antibiotic treatments	Fecal microbiota transplantation. *(Strong recommendation, moderate quality evidence)*	Same as second recurrence Fecal microbiota transplantation + vancomycin 500 mg PO every 6 h for 4–14 days + bowel lavage. *(Strong recommendation, high-quality evidence)*	Fecal microbiota transplantation (*Conditional recommendation, moderate quality evidence).*

CDI, *Clostridioides difficile* infection; IV, intravenous; NG, nasogastric; PO, by mouth; PR, per rectum

[a]No specification of recommendation strength

The ACG guidelines rank vancomycin second to metronidazole in case the latter did not result in satisfactory response. This was based on an observational study of 207 patients who received 500 mg of metronidazole every 8 h and continued to be symptomatic after completing 10 days of therapy [23]. The authors concluded that the lack of response despite receiving the full course is an indication of a severe disease, warranting additional treatment approaches. In patients where oral antibiotics cannot reach a segment of the colon, ACG recommends that vancomycin enema be added relying on data from two studies [24, 25]. In contrast, IDSA/SHEA suggests metronidazole only if vancomycin and fidaxomicin are unavailable because of the inferior results reported in four studies [14, 23, 26, 27].

For severe CDI, all three guidelines recommend vancomycin for first-line treatment. In addition, IDSA/SHEA and ESCMID guidelines also include fidaxomicin as an alternative to vancomycin, based on several clinical trials demonstrating the superiority of both vancomycin and fidaxomicin to metronidazole in severe CDI cases [13, 14, 28]. Rectal administration of vancomycin is also recommended by ACG in the presence of conditions halting delivery of oral antibiotics [3]. In addition, ESCMID moderately recommend (and weekly recommend for mild-to-moderate CDI) a higher dose of vancomycin at 500 mg based on four studies [10, 11, 29, 30]. Nevertheless, one cited study reported equal response with 125 mg and 500 mg of vancomycin [31]. Interestingly, a study that assessed the correlation between fecal vancomycin concentrations resulting from 125 mg dose and clinical outcomes did not find that higher concentrations were associated with better outcomes [32].

ACG and IDSA/SHEA guidelines recommend adding intravenous (IV) metronidazole and rectal vancomycin (in case of ileus) to oral vancomycin in patients with fulminant (severe complicated) CDI based on a study by Rokas et al. that showed mortality advantage when IV metronidazole was added to the regimen ($P=0.03$) [33]. The only difference between the two guidelines is that ACG keeps the recommended vancomycin dose at 125 mg, while IDSA/SHEA recommend the 500 mg dose. The high dose recommendation by IDSA/SHEA seems to stem from an expert opinion, and a statement recommending monitoring trough concentrations of vancomycin has been added to the guidelines, as such high doses were associated with prolonged exposure and renal failure [4, 34].

Recurrent CDI

CDI recurrence is defined by the three guidelines as the reappearance of documented CDI within 8 weeks after the onset of the previous episode, provided that symptoms have resolved after completing therapy [3, 4, 6].

For the treatment of the first CDI recurrence, the three guidelines did not have a consensus on the choice of antibiotics. Repeating the same regimen used in the initial episode was the recommendation made by ACG [3]. ESCMID provided a recommendation similar to its recommendation for the treatment of severe CDI (vancomycin or fidaxomicin) [6]. IDSA/SHEA preferred tailoring the treatment according to the choice made for treating the initial episode and including a recommendation for the use of tapered and pulsed regimen of vancomycin [4]. In this regard, a regimen comprising tapered or pulsed dosing of vancomycin resulted in a significantly lower recurrence rate compared with metronidazole ($P=0.01$ and 0.02 for tapered and pulsed regimens, respectively) [35]. Moreover, the use of fidaxomicin was associated with fewer secondary recurrences compared with vancomycin after using it for the treatment of a first CDI recurrence per a study by Cornely et al. (recurrence rate = 35.5% vs. 19.7%; $P=0.0003$) [36]. A recommendation for the use of fidaxomicin for the first recurrence of CDI was made by IDSA/SHEA and ESCMID [4, 6].

For the second recurrence of CDI, both IDSA/SHEA and ESCMID guidelines agree on the use of either fidaxomicin or tapered and pulsed vancomycin regimen [4, 6]. On the other hand, ACG only recommended the latter approach in this situation [3]. Of note, IDSA/SHEA guidelines also included a new suggestion not included in its ESCMID and ACG counterparts, that is, using oral rifaximin therapy following a 10-day course of standard oral vancomycin [4]. This novel suggestion was made on the basis of a randomized, double-blind, placebo-controlled trial showing a significantly reduced rate of recurrent diarrhea (despite of the cause) in the rifaximin arm vs. the placebo arm (21% vs. 49%; $P=0.018$); however, no significant difference between the two groups was observed in terms of CDI-associated diarrhea (15% vs. 31%; $P=0.11$) [37].

For patients with multiple recurrences (defined as three or more CDI episodes) who have failed appropriate antibiotic treatment, all three guidelines recommend fecal microbiota transplantation [3, 4, 6]. ESCMID recommends continuing oral antibiotic therapy with this treatment approach [6].

With regard to probiotics, none of the guidelines recommended their use for primary or secondary prevention of CDI due to insufficient data or controversial results [3, 4, 6].

CDI prevention

The first step to be carried out to prevent the transmission of infection is to isolate the CDI patient in a single private room. Such recommendation is provided by all three guidelines [3, 4, 6]. ACG extends this recommendation to include patients with suspected infection [3]. In case of limited room vacancy, ESCMID and IDSA suggest placing

infected patients in cohort [4, 6]. Moreover, health-care workers and visitors are strongly recommended to use personnel protective equipment, such as gown and gloves, prior to entering rooms of CDI patients followed by hand washing with soap and water (to physically eliminate *C. difficile* spores) along with hand sanitization with an antiseptic after exiting the room as recommended by all three guidelines [3, 4, 6].

After a CDI patient is discharged from the hospital room, a disinfection procedure of the room surfaces and equipment should be carried on as recommended by IDSA and ESCMID using chlorine-containing agent (of a concentration of at least 1000 ppm) or other sporicidal cleaning agents [4, 6]. ACG was more specific with regard to the disinfection agent to be used: it should be an Environmental Protective Agency (EPA) registered disinfectant with *C. difficile* sporicidal label claim, or 5000 ppm chlorine-containing cleaning agent [3].

Additional recommendations provided by the three guidelines to prevent the spread of CDI include use of dedicated and disposable materials and dedicating medical devices to a single patient or use of disposable caps as in the case of rectal electronic thermometers [3, 4, 6].

While ESCMID limits the duration of precautions to 48 h after symptomatic CDI has resolved and bowel movements have returned to normal, ACG and IDSA did not specify a duration, but recommended maintaining contact precautions for the duration of the diarrhea [3, 4, 6]. Following appropriate infection control and prevention measures in healthcare settings is crucial to limit the spread of the infection, since exposure to health care was the major significant factor associated with reinfection (rather than relapse) with new *C. difficile* ribotype (over other factors, such as age, initial infection with 027 strain, exposure to antibiotics or proton pump inhibitors, or type of antibiotic used in initial CDI therapy) [38].

Conclusion

Clinical practice guidelines get updated regularly as new evidence arise in the medical literature which may influence the change in recommendations compared with the older version of the guidelines or older guidelines published by peer organizations. The most prominent example observed here was the significant change in treatment recommendation for initial non-severe CDI episode in the 2017 guidelines by IDSA/SHEA compared with ESCMID and ACG guidelines of 2014 and 2013, respectively.

As guidelines are developed by a panel of experts in the field to include only reliable evidence to draw recommendations, compliance with these guidelines in clinical practice is deemed prudent.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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