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REVIEW

A Comparison of Current Guidelines of Five International Societies on *Clostridium difficile* Infection Management

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ABSTRACT

Clostridium difficile infection (CDI) is increasingly recognized as an emerging healthcare problem of elevated importance. Prevention and treatment strategies are constantly evolving along with the apperance of new scientific evidence and novel treatment methods, which is well-reflected in the differences among consecutive international guidelines. In this article, we summarize and compare current guidelines of five international medical societies on CDI management, and discuss some of the controversial and currently unresolved aspects which should be addressed by future research.

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INTRODUCTION

The worldwide increasing burden of *Clostridium difficile* infection (CDI) has converted the quest for optimal treatment strategies into one of the hottest topics in the field of nosocomial infectious diseases. The incidence of CDI have been steadily growing in the past decades [1], partially due to an increasing awareness of the disease, but mainly because of an important increase in the susceptible population during this period, such as the elderly or the immunocompromised [2], the appearance of BI/NAP1/027 [3] and other hypervirulent *C. difficile* strains and a growing prevalence of asymptomatic *C. difficile* carriage [4]. Patients with CDI have increased length of hospital stay, higher readmission rates, more elevated inpatient costs and higher mortality than patients without CDI [5–7].

Boards of experts approving clinical guidelines constantly have to cope with the lack of sound scientific evidence on important

aspects of CDI management, such as the precise definition of CDI severity [8–11], duration of contact isolation measures [12], or the indications and optimal time of surgical intervention [13]. The consequence of this situation is the coexistence of guidelines with certain differences in their recommendations that may raise doubts in the minds of treating physicians at the time of clinical decision making [14]. This insecurity, in turn, may also contribute to the low adherence to existing guidelines observed in various studies [15–17]. Indeed, an elevated proportion of clinicians agree on the main points where current CDI management practices could and should be improved [18].

In the following, we present a critical summary and comparison of the latest international guidelines published by five international societies on the management of CDI, and briefly discuss some of the most controversial and currently unresolved questions in this field in the light of the most up-to-date available evidence. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

CURRENT GUIDELINES ON CDI MANAGEMENT

There are a number of guidelines and recommendations on the prevention and treatment of CDI approved by national expert boards in various countries [19–25]. In this article, however, we will center our attention on seven international guidelines published in the last 6 years, reviewing and comparing their recommendations on three fundamental aspects of CDI management: contact isolation measures, pharmacological therapy, and surgical treatment.

Five of these guidelines offer guidance on the treatment of CDI: the 2010 guidelines of the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) 2010 [26]—whose updated version is under progress at the publication of this article; the 2013 guidelines of the American College of Gastroenterology (ACG) [27]; the 2014 guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [28]; the 2015 guidelines of the World Society of Emergency Surgery (WSES) [29]; and the most recent 2016 update of the 2011 guidelines of the Australasian Society for Infectious Diseases (ASID) [30, 31]. This last document also deals with CDI treatment in children, but we will focus exclusively on the recommendations made for adult patients.

Three of the above guidelines (IDSA/SHEA, ACG and WSES) include direct recommendations on contact isolation measures, whereas the ESCMID guidance document makes reference to separate guidelines approved by the same society on CDI spread control [32]. The new ASID guidelines pay only marginal attention to this issue, but there is a position statement on infection control measures in CDI published by the same society (in collaboration with the Australian Infection Control Association, AICA) in 2011 [33] which is referred to by the previous, 2011 treatment guidelines as the one recommended to follow. The recommendations of these two guidelines supported by the ESCMID and the ASID will also be taken into consideration in the following analysis.

The ASID document on CDI management [31] does not indicate recommendation strength and evidence quality, whereas the ASID/AICA guidelines on CDI prevention [33]

use the same grading system as the IDSA/SHEA guidelines. On the other hand, the two documents backed by the ESCMID [28, 32] use different grading systems. Supplementary Table 1 compares the different criteria utilized by these documents for the strength of each individual recommendation and the quality of evidence on which it is based.

CONTACT ISOLATION MEASURES

Human-to-human transmission of *C. difficile* was first suspected in the early 1980s [34], and today there is wide consensus on the importance of applying contact isolation measures in diagnosed CDI cases. The examined guidelines, however, differ in certain details in their recommendations in this respect which are worth mentioning.

Whereas hand washing with soap and water is only recommended in the outbreak setting or in cases of elevated CDI rate according to the IDSA/SHEA guidelines, and the ASID/AICA recommend it only in cases of not having used gloves and directly soiled hands, the rest of the societies strongly recommend the use of soap and water after being in contact with CDI patients.

The duration of contact precautions until at least 48 h after diarrhea resolution is a point emphasized by the non-US guidelines, whereas the IDSA/SHEA and ACG guidelines do not make clear recommendations on the exact time of discontinuation of contact precautions They refer instead to "the resolution of diarrhea" as a necessary condition for this, without further specifications, although the 48-hour-rule is mentioned as a possible strategy by the ACG guidelines.

There is consensus among the five guidelines in the preference of chlorine-containing disinfection agents for the cleaning of patient rooms and the equipment used in CDI cases. The minimum allowed chlorine concentration of these solutions, however, is higher in the ACG guidelines than the other documents (5000 vs. 1000 ppm). The ASID/AICA and the ESCMID guidelines also emphasize the importance of thorough terminal room cleaning after discharge or transfer of a CDI patient, and the ESCMID also recommends additional immediate cleaning to take place in cases of environmental fecal contamination. The details of the individual recommendations are summarized in Table 1.

Unresolved Issues

According to recent evidence, stool, skin, and environmental contamination after a resolved CDI episode persist in a considerable proportion of cases, and *C. difficile* shedding by cured patients may be as high as 50% 1–4 weeks after the end of treatment [12]. This phenomenon can lead to a higher hand contamination rate of healthcare personnel caring for these patients that, in turn, may increase the risk of in-ward *C. difficile* transmission [35]. In light of these data, maintaining contact precautions after a treated CDI episode until discharge may be of potential benefit in terms of CDI spread control.

Related to this problem is the screening of asymptomatic *C. difficile* carriers at hospital admission, which has recently also been in the focus of attention. Apart from a series of mathematical models that demonstrate the cost-effectiveness of this practice [36–38], a recent quasi-experimental study reported a significant decrease in CDI incidence after the implementation of this measure [39]. If the screening of potential *C. difficile* carriers in the hospital will ever form part of guideline recommendations depends on the results of future studies addressing this issue.

Table 1 Recommendations on contact isolation precautions in CDI by 5 current international guidelines

	IDSA/SHEA 2010 [26]	ASID/AICA 2011 [33]	ACG 2013 [27]	ESCMID 2008 [32]	WSES 2015 [29]
Hand hygiene	Emphasize compliance with the practice of hand hygiene (A-II). Hand wash with soap and water in an outbreak or an increased CDI rate (B-III)	Emphasize compliance with hand hygiene (A-II). Alcohol-based hand rub is the agent of choice for hand hygiene. If hands become soiled or gloves have not been used, then hands must be washed with soap and water	Hand hygiene should be used by all healthcare workers and visitors entering the room of any patient with known or suspected CDI. Hand washing with soap and water is recommended (strong recommendation, moderate-quality evidence)	Meticulous hand washing with soap and water is recommended for all staff after contact with CDI patients, also after the removal of gloves or aprons used during this contact (IB, 2a)	Hand hygiene with soap and water should be used by all healthcare workers contacting any patient with known or suspected CDI. The most effective way to remove *C. difficile* spores from hands is through hand washing with soap and water (1B)
Glove and gown use	Healthcare workers and visitors must use gloves (A-I) and gowns (B-III) on entry to a room of a CDI patient	Gloves should be used during the care of patients with CDI (A-I) and use of gowns/aprons is recommended (B-III)	Gloves and gowns should be used by all healthcare workers and visitors entering the room of any patient with known or suspected CDI (strong recommendation, moderate-quality evidence)	Healthcare workers should wear gloves for contact with a CDI patient; this includes contact with body substances and/or potentially contaminated environment (IB, 1b). Gowns or aprons should always be used for managing patients who have diarrhea (IB, 1a)	Disposable glove use during care of a patient with CDI may be effective in preventing transmission; these must be removed at the point of use and hands thoroughly decontaminated afterwards through soap and water hand washing (1B)

Table 1 continued

	IDSA/SHEA 2010 [26]	ASID/AICA 2011 [33]	ACG 2013 [27]	ESCMID 2008 [32]	WSES 2015 [29]
Private rooms or cohorting	Accommodate CDI patients in private room (B-III) or cohort patients providing dedicated commode for each patient (C-III)	Patients with ≥3 loose stools/24 h should be placed in a single room with dedicated toilet facilities (B-III), or cohorted with other patients with the same cause of diarrhea (C-III)	Patients with known or suspected CDI should be placed in a private room or in a room with another patient with documented CDI (strong recommendation, high-quality evidence)	Patients with CDI should be isolated in single rooms whenever possible (IB, 1b). A designated toilet or commode should be provided (IB 1b). If isolation in single rooms is not possible, isolation in cohorts should be undertaken (IB, 1b). Cohorted patients should be managed by designated staff (IB, 1b)	Patients with suspected or proven CDI should be placed in contact (enteric) precautions (1B), ideally placed in private rooms with en-suite hand washing and toilet facilities. If a private room is not available, known CDI patients may be cohort-nursed in the same area
Duration of precautions	Maintain contact precautions for the duration of the diarrhea (C-III)	Contact precautions should be continued until at least 48 h after diarrhea has ceased (C-III)	Contact precautions should be maintained at a minimum until the resolution of diarrhea (strong recommendation, high-quality evidence)	Isolation precautions may be discontinued 48 h after symptomatic CDI has resolved and bowel movements have returned to normal (II, 4)	Contact (enteric) precautions should be maintained until the resolution of diarrhea, which is demonstrated by passage of formed stool for at least 48 h

Table 1 continued

	IDSA/SHEA 2010 [26]	ASID/AICA 2011 [33]	ACG 2013 [27]	ESCMID 2008 [32]	WSES 2015 [29]
Room and equipment disinfection	Disinfection of patient rooms and environmental surfaces (B-II) as well as equipment between uses for different patients (C-III) Use of (at least 1000 ppm) chlorine-containing or other sporicidal cleaning agents is recommended (B-II)	Daily cleaning of all horizontal surfaces and frequently touched items within patient reach with neutral detergent and at least 1000 ppm chlorine-containing solution is recommended, as well as thorough terminal cleaning after patient discharge/transfer (B-II)	Disinfection of environmental surfaces is recommended using EPA-registered disinfectant with *C. difficile* sporicidal label claim, or 5000 ppm chlorine-containing cleaning agents (strong recommendation, high-quality evidence)	Regular disinfection of rooms of CDI patients should be done using sporocidal agents, ideally at least 1000 ppm chlorine-containing agents (IB, 2b). When environmental fecal soiling occurs, cleaning needs to be done as soon as possible (IB, 1b). After discharge of a CDI patient, rooms must be cleaned and disinfected thoroughly (IB, 2b). All equipment should carefully be cleaned and disinfected using a sporocidal agent immediately after use on a CDI case (IB, 1b)	For environmental cleaning, hypochlorite disinfection such as sodium hypochlorite solutions are suggested for regular use in patient areas where *C. difficile* transmission is ongoing
Use of dedicated and/or disposable material	Removal of environmental sources of *C. difficile* including replacement of electronic rectal thermometers with disposables (B-II)	Dedicated equipment should be provided for each patient. Rectal thermometers should be disposable (B-II)	Disposable equipment should be used. Non-disposable equipment should be dedicated to the patient's room (strong recommendation, moderate-quality evidence)	Medical devices should be dedicated to a single patient (IB, 1b). Thermometers should not be shared (IA, 1b). The use of disposable material should be considered whenever possible (IB, 1b)	–

PHARMACOLOGICAL THERAPY

The summary of pharmacological treatment recommendations of the five CDI guidelines can be found in Table 2.

Initiation of Pharmacological Treatment

All five expert boards lay special emphasis in their recommendations on the withdrawal of unnecessary systemic antibiotic treatment upon CDI diagnosis (recommendation strengths IDSA/SHEA: A-II; WSES: 1-C; ACG: strong/high-quality; ESCMID and ASID: no strength of recommendation indicated). There are, however, greater differences among these documents in the recommendations on the when and how of the initiation of specific anticlostridial treatment. The ESCMID guidelines advocate a 48-h "wait-and-see" policy after stopping all systemic antibiotics for the initial management of a first non-severe episode of CDI (recommendation C-II). In contrast, the IDSA/SHEA guidelines and the WSES guidelines recommend initiating empiric antibiotic treatment in all cases of strong suspicion of CDI even before microbiological confirmation is available (recommendation C-III and 1B, respectively), whereas the ACG guidelines recommend full treatment in this scenario even in cases of negative microbiological results (strong recommendation, moderate-quality evidence). This last document also suggests the prompt initiation of empiric therapy in the particular case of severe colitis in a patient with inflammatory bowel disease (conditional recommendation, low-quality evidence). The ASID guidelines chose a different approach to this problem, advising laboratories to perform automatic tests for the presence of toxigenic *C. difficile* on *every* unformed stool sample they receive from hospitalized patients, even in the absence of the specific request form.

Unresolved Issues

Empirical treatment of CDI before the collection of stool specimens may be inevitable in certain cases, as recommended by three of the five analyzed guidelines. It has to be borne in mind, however, that the proportion of a false negative microbiological test may reach 14% after 1 day, and up to 45% after 3 days, of treatment, independently from the detection method used [40]. These same three guidelines accept the use of PCR on rectal swab specimens for CDI diagnosis in patients with ileus, but there are no recommendations about the use of this method in the case of an anticipated delay in stool specimen collection for other reasons.

On the other hand, PCR tests without the direct detection of *C. difficile* toxins may lead to overdiagnosis of CDI, as it cannot differentiate between infection and colonization [41], and an erroneous diagnosis of CDI may lead to unnecessary treatment and to the delay in some cases of further efforts to find the real cause of the symptoms.

Treatment Choice According to CDI Severity

The appearance of life-threatening complications, such as shock, bowel perforation or peritonitis, are clear signs of a severe CDI, but there is considerably less consensus on other patient and/or disease parameters that would predict an unfavorable disease course and warrant a more aggressive initial therapy. Although all examined guidelines differentiate between mild-moderate and severe CDI, there are great differences among the exact criteria they use to define these categories.

The ESCMID guidelines recognize the difficulty of precisely defining CDI severity,

Table 2 Recommendations on pharmacological treatment of CDI according to five current international guidelines

	IDSA/SHEA 2010 [26]	ACG 2013 [27]	ESCMID 2014 [28]	WSES 2015 [29]	ASID 2016 [31]
First episode					
Mild-moderate	Metronidazole 500 mg/8 h p.o. 10–14 days (A-I)	Metronidazole 500 mg/8 h p.o. 10 days (strong/moderate) Vancomycin 125 mg/6 h p.o. 10 days in case of no response after 5–7 days of metronidazole therapy (strong/moderate), metronidazole intolerance/allergy, or pregnant/breastfeeding women (strong/high) Add vancomycin 500 mg (in 100–500 mL of normal saline)/6 h via enemas if oral antibiotics cannot reach a segment of the colon (conditional/low)	Metronidazole 500 mg/8 h p.o. 10 days (A-I) Vancomycin 125 mg/6 h p.o. 10 days (B-I) (preferred over metronidazole if risk of recurrence) Fidaxomicin 200 mg/12 h p.o. 10 days (B-I) (preferred over metronidazole if risk of recurrence) Metronidazole 500 mg/8 h i.v. 10 days if intolerance of oral treatment (A-II) Stop systemic antibiotics + 48 h clinical observation (C-II) Immunotherapy with human monoclonal antibodies (C-I) or immune whey (C-II)	Metronidazole 500 mg/8 h p.o. 10 days (1-A) Vancomycin 125 mg/6 h p.o. 10 days in case of no response to metronidazole (1-A) Fidaxomicin 200 mg/12 h p.o. 10 days in case of high risk of recurrence (1-A)	Metronidazole 400 mg/8 h p.o. 10 days Vancomycin 125 mg/6 h p.o. 10 days in case of refractory CDI

Table 2 continued

	IDSA/SHEA 2010 [26]	ACG 2013 [27]	ESCMID 2014 [28]	WSES 2015 [29]	ASID 2016 [31]
Severe	Vancomycin 125 mg/6 h p.o. 10–14 days (B-I)	Vancomycin 125 mg/6 h p.o. 10 days (conditional/moderate) Add vancomycin 500 mg (in 100–500 mL of normal saline)/6 h via enemas if oral antibiotics cannot reach a segment of the colon (conditional/low)	Vancomycin 125 mg/6 h p.o. 10 days (A-I) Fidaxomicin 200 mg/12 h p.o. 10 days (B-I) Metronidazole 500 mg/8 h i.v. 10 days (A-II) + vancomycin 500 mg (en 100 mL normal saline)/6 h via enemas or via NGT 10 days if oral treatment not possible (B-III) Tigecycline 50 mg/12 h i.v. 14 days if oral treatment not possible (C-III) DO NOT use metronidazole in monotherapy (D-I)	Vancomycin 125 mg/6 h p.o. 10 days (1-A) Vancomycin 500 mg/6 h via enemas + metronidazole 500 mg/8 h i.v. when oral antibiotics cannot reach the colon (1-B) or in case of fulminant colitis (1-C)	Vancomycin 125 mg/6 h p.o. 10 days (first-line therapy) Metronidazole 500 mg/8 h i.v. + vancomycin 125 mg/6 h via NGT ± vancomycin 500 mg (in 100 mL normal saline)/6–8 h via enemas in refractory CDI or when unable to tolerate oral therapy (second-line therapy) Intestinal microbiota transplantation after 3–5 days of vancomycin or fidaxomicin treatment (third line therapy) Fidaxomicin 200 mg/12 h p.o. 10 days (third-line therapy) Tigecycline 50 mg/12 h i.v. 14 days if oral therapy not possible (third line therapy)
Severe complicated	Vancomycin 500 mg/6 h p.o. or via NGT + Metronidazole 500 mg/8 h i.v. Consider adding Vancomycin 500 mg (in 100 mL normal saline)/6 h via enemas if ileus is present (C-III)	Vancomycin 125 mg/6 h p.o. + metronidazole 500 mg/8 h i.v. (strong/low) Vancomycin 500 mg/6 h v.o. + 500 mg (in 500 mL of normal saline) via enemas + metronidazole 500 mg/8 h i.v. if ileus or significant abdominal distension is present (strong/low)			
First recurrence	Same treatment as for initial episode (A-II) stratified according to disease severity (C-III)	Same treatment as for initial episode, according to disease severity	Vancomycin 125 mg/6 h p.o. 10 days (B-I) Fidaxomicin 200 mg/12 h p.o. 10 days (B-I) Metronidazole 500 mg/8 h p.o. 10 days (C-I)	Same treatment as for initial episode according to disease severity (1-B) Fidaxomicin 200 mg/12 h p.o. 10 days (1-B)	Vancomycin 125 mg/6 h p.o. 10 days

Table 2 continued

	IDSA/SHEA 2010 [26]	ACG 2013 [27]	ESCMID 2014 [28]	WSES 2015 [29]	ASID 2016 [31]
Multiple recurrences	Vancomycin 125 mg/6 h p.o. 10–14 days, followed by a tapering and/or pulsed regimen of oral vancomycin (B-III)	2nd recurrence: Vancomycin 125 mg/6 h p.o. 10 days, followed by a pulsed regimen of oral vancomycin (conditional/low) ≥3rd recurrence: Consider intestinal microbiota transplant (conditional/moderate)	Intestinal microbiota transplantation after 4 days of vancomycin 500 mg/6 h p.o. (A-I) Vancomycin 125 mg/6 h p.o. 10 days, followed by a tapering or pulsed regimen of oral vancomycin (B-II) Fidaxomicin 200 mg/12 h p.o. 10 days (B-II) Vancomycin 500 mg/6 h p.o. 10 days (C-II) DO NOT use metronidazole in monotherapy (D-II)	Vancomycin 125 mg/6 h p.o. (optionally followed by a tapering and/or pulsed regimen of oral vancomycin) (1-B) Fidaxomicin 200 mg/12 h p.o. 10 days (1-B)	Vancomycin 125 mg/6 h p.o. 14 days, ± a tapering regimen of oral vancomycin Fidaxomicin 200 mg/12 h p.o. 10 days (especially in high-risk of relapse population) Intestinal microbiota transplantation after 3-5 days of vancomycin or fidaxomicin treatment (if the first two options failed and in the absence of contraindications) Rifaximin "chaser" therapy (if the first two options failed and intestinal microbiota transplantation is contraindicated or not available)

p.o. per os, *NGT* nasogastric tube

but offers an extensive list of clinical and laboratory markers in the presence of which severe CDI may be established, and mentions older age, serious comorbidity, immunodeficiency and ICU admission as additional criteria for an increased risk of a severe disease. Similarly, the WSES guidelines also refer to the absence of consensus on the definition of severe CDI, and make its recommendations based on risk factors for an unfavorable disease course. The ASID document defines severe CDI as two or more signs or symptoms from a list similar to the one found in the ESCMID guidelines, and names toxic megacolon, ICU admission, need of surgery and death due to CDI as determinants of a complicated disease course. In the US-based guidelines (IDSA/SHEA and ACG), severe-complicated CDI is specified as an additional disease severity grade, again with important differences between the ways it is defined by the two expert boards. The individual criteria to define severe CDI or an elevated risk for severe CDI according to the five guidelines are summarized in Table 3.

All five guidelines agree on recommending oral metronidazole as the first choice of antibiotic in case of mild-moderate CDI in the absence of risk factors for recurrence and oral vancomycin in the presence of severe CDI. The ACG, WSES and ASID documents also recommend changing metronidazole for vancomycin when no improvement is observed after 3–7 days of treatment (ACG: strong recommendation and moderate-quality evidence; WSES: 1-A recommendation).

The recommended therapy for severe-complicated disease according to the IDSA/SHEA and ACG guidelines should be based on the combination of vancomycin administered orally or via nasogastric tube and intravenous metronidazole, with the addition of rectal vancomycin in the presence of ileus (recommendation C-III and strong/low-quality evidence, respectively). The other three boards of experts, however, recommend the combination of enteric vancomycin and intravenous metronidazole to be reserved for severe cases when oral intake is impossible or contraindicated (ESCMID, WSES and ASID), or as second-line therapy in case of non-responders to vancomycin monotherapy (ASID). In cases of oral intolerance, the ESCMID document also supports the use of intravenous tigecycline, although only with a recommendation grade of C-III, a treatment option also mentioned in the ASID guidelines, as a 3rd line therapy for severe CDI refractory to the combination of vancomycin and metronidazole.

Unresolved Issues

It is remarkable that only one of the guidelines [28] mention older age as a factor associated with CDI severity, despite its notoriously being reported as an important predictor of unfavorable outcome [8, 42]. Different studies suggest different age cut-off values to predict a severe disease course [43–48]. This makes sense, because a single, well-definable cut-off most probably does not exist, as it is suggested by results showing a linear or quasi-linear relationship between these factors and disease severity or mortality [49–52]. The threshold of 65 years as proposed by the ESCMID guidelines may be an acceptable choice [28], but curiously none of the three studies referred to by the authors to support this choice use this exact age cut-off [8, 44, 47]. It seems evident that the precise impact of age on CDI severity needs further clarification.

The burden of comorbid conditions is also known to be associated with a severe course of CDI [8, 42], and yet it is only mentioned in

Table 3 Criteria for (the risk of) severe CDI according to currently used international guidelines

	IDSA/SHEA 2010 [26]	ACG 2013 [27]	ESCMID 2014 [28][b]	WSES 2015 [29]	ASID 2016 [31][c]
Physical examination					
Fever ≥38.5 °C		+[a]	+	+	+
Rigors			+		
Abdominal tenderness		+			
Ileus	+[a]	+[a]	+	+	+
Signs and symptoms of peritonitis/perforation			+	+	+
Hemodynamic instability	+[a]	+[a]	+	+	+
Respiratory failure		+	+		
Mental status change		+			
ICU admission		+	+		+[a]
Laboratory alterations					
Leukocyte count	≥15,000 cells/mm^3	≥15,000 cells/mm^3	≥15,000 cells/mm^3 >20% band neutrophils	≥15,000 cells/mm^3	≥15,000 cells/mm^3 >20% band neutrophils
		≥35,000 or <2000 cells/mm^3[a]			
Creatinine	≥1.5× baseline value	Renal failure[a]	≥1.5× baseline value or >133 uM/L	Acutely rising serum creatinine	≥1.5× baseline value
Albumin		<30 g/L	<30 g/L	<25 g/L	<25 g/L
Lactate		>2.2 mmol/L[a]	≥5 mmol/L	Increased serum lactate	Elevated lactate level
Imaging and colonoscopy					
Pseudomembranous colitis			+		+
Megacolon/large intestine distension	+[a]		+		+[a]/+
Colonic wall thickening			+		+
Pericolonic fat stranding			+		+

Table 3 continued

	IDSA/SHEA 2010 [26]	ACG 2013 [27]	ESCMID 2014 [28][b]	WSES 2015 [29]	ASID 2016 [31][c]
Otherwise unexplained ascitis			+		+

+ Factors indicating (the risk of) severe CDI

[a] Factors indicating a complicated CDI course

[b] Additional criteria for increased risk of severe CDI: serious comorbidity, immunodeficiency, age >65 years

[c] Additional criteria for complicated CDI: requirement for surgery or death due to CDI

relation to CDI severity in the ESCMID guidelines [28]. A great number of individual comorbid illnesses have been related to increased CDI severity and mortality in previous studies, such as malignant diseases [47, 53, 54], chronic renal failure [47, 55], cardiopulmonary conditions [47, 52, 54, 56–58], diabetes mellitus [52, 57], inflammatory bowel disease [54, 59, 60], or liver cirrhosis [50, 54, 61]. While it may be difficult to handpick a complete and exclusive list of comorbid conditions related to severe outcome, it seems clear that a greater number of underlying illnesses and comorbid conditions of higher severity entail worse CDI prognosis. The most frequently evaluated comorbidity index that aims to embrace all these underlying diseases is the Charlson Comorbidity Index (CCI) [52, 62–65], followed by the American Society of Anesthesiologists (ASA) physical status classification system [48, 66], and Horn's index [67]. All of them have demonstrated good correlation with CDI severity and poor outcome. The superiority of any of these comorbidity scales over the rest has not been investigated in this respect, but there seems to be sufficient evidence available for their future inclusion among CDI severity risk factors.

In contrast to age and comorbidity, computer tomography (CT) findings and the presence of pseudomembranes as evidenced by colonoscopy are both included as markers of severe disease in more than one current set of guidelines [28, 31], albeit based on rather dubious scientific evidence. Although CT scan is a useful tool to diagnose toxic megacolon [68], other specific radiological findings do not seem to correlate indubitably well with CDI severity [69, 70]. Similarly, endoscopic findings with or without colon biopsy may help clarifying diarrhea etiology in cases of a high clinical suspicion and a negative *C. difficile* stool test [71], but the presence of pseudomembranous colitis seems to be a less CDI-specific finding than it is generally believed to be [72], and its relationship with severe outcome has not been demonstrated either [73].

Oral vancomycin combined with intravenous metronidazole is the treatment of choice in severe-complicated CDI according to the IDSA/SHEA and ACG guidelines. This combination was recently reported to be superior to vancomycin monotherapy in terms of mortality in a retrospective study in critically ill CDI patients [74], but a posterior animal model did not confirm these results [75], and a meta-analysis comparing the efficacy and safety of vancomycin therapy with combination regimens did not find any benefit of this combination either [76]. Moreover, this last study demonstrated a higher rate of adverse events (including higher mortality) in patients receiving combination therapy. More recent

guidelines do not give preference to combination therapy over vancomycin monotherapy in severe CDI, but randomized controlled trials evaluating this question have not yet been performed.

Recurrent CDI

CDI recurrence is defined by three of the guidelines as a reappearance of documented CDI either within 8 weeks of completion of anticlostridial treatment (ACG) or within the 8 weeks following the onset of the first episode (ESCMID and ASID), while the remaining two documents do not define an exact time-frame for recurrent CDI. Most of these guidelines mention some risk factors for recurrent CDI in a tangential manner, but the ESCMID guidance document offers the most comprehensive list of these factors: age over 65 years, continued use of antibiotics after CDI diagnosis, severe comorbidity including renal failure, more than one previous CDI episode, use of proton pump inhibitors, and a severe initial CDI.

The majority of the examined guidelines recommend using the same antibiotic in a second CDI episode that had been prescribed for the first one with reasonable adjustments according to disease severity. In the ESCMID guidelines, however, fidaxomicin and vancomycin both have a B-I recommendation for recurrent disease, whereas the use of metronidazole is only marginally supported in this setting (recommendation C-I). Moreover, the most recent ASID document directly discourages from using metronidazole in recurrent CDI.

Unresolved Issues

General consensus on the precise definition of the patient population at an elevated recurrence risk is still lacking, though the evidence available is somewhat more consistent than in the case of disease severity. The risk factors listed by the ESCMID guidelines are largely in accordance with the conclusions of two meta-analyses and a systematic review performed on this topic [42, 77, 78]. More recent studies greatly support these previous results, but also name additional risk factors for recurrent CDI not mentioned by any of the current guidelines. In a retrospective, but very extensive cohort, steroid treatment was found to be associated with recurrent CDI [79], and a very recent prospective cohort identified enteral tube nutrition as another independent predictor of recurrence [80]. In another report on a retrospective cohort of more than 750 patients, the authors found a longer hospital stay to independently predict recurrent CDI [81], and there is growing evidence that inflammatory bowel disease may also predispose to CDI recurrence [82]. It is also important to mention that proton pump inhibitor treatment, although it has been associated with CDI relapse on multiple occasions [78, 81, 83], still remains one of the most controversial recurrence risk factors, with at least two recent studies published with negative results on this supposed relationship [84, 85].

In intestinal graft-versus-host disease (GVHD), a potentially elevated recurrence risk is not clearly established. In this conditions, however, the clinical manifestation of a flare of the underlying disease may be confounded with CDI, and CDI may also worsen the prognosis of GVHD [86, 87]. For this reason, taking special care to optimize initial CDI treatment in this patient population in order to minimize recurrences may be beneficial. However, this underlying condition is not mentioned by any of the current international guidelines.

Given that the reason behind four-times-a-day administration of vancomycin is to be sought in the fast

elimination of the drug from the colon of a patient with severe diarrhea, maintaining this same dosing frequency after diarrhea resolution may not be absolutely necessary. In fact, decreasing vancomycin dosing frequency at this point could potentially help prevent additional unnecessary damage to the intestinal microbiota without increasing treatment failure rate or recurrence risk. In a recent in vitro study on alternative dosing regimens of fidaxomicin, a shortened fidaxomicin course followed by a pulsed or tapered regimen enhanced the recovery of intestinal bifidobacteria population without losing efficacy in terms of the resolution of simulated CDI [88]. Similar studies with vancomycin, however, have not yet been performed.

Based on a similar argument, in patients that promptly respond to antibiotic treatment with normalization of their bowel habit, completing the recommended overall treatment duration of 10–14 days may not be completely indispensible. Though one can suspect that shorter antibiotic courses could lead to higher recurrence rates, no overwhelming evidence exists about this relationship [89]. Until further research answers these intriguing questions, however, adherence to the now generally accepted dosage regimens of currently used anticlostridial drugs is recommended.

Multiple Recurrent CDI

Fidaxomicin, the newest incorporation in the antibiotic armament against *C. difficile* with a significantly greater capacity to reduce recurrence risk as compared to metronidazole or vancomycin, was first approved in 2011 in the US,and it was also introduced gradually in the European market during the three following years (first in the UK, the Nordic countries and Austria, and later in the Czech Republic, France, Hungary, Portugal, Slovakia and Spain in 2012, followed by the rest of Europe during the years 2013 and 2014). From 2012 on, fidaxomicin has also gained authorization progressively in the rest of the globe, such as in Japan, Canada, Australia, South Africa or the Middle East countries. As a consequence, the 2010 IDSA/SHEA guidelines do not make reference to this antibiotic, and in the 2013 ACG guidelines, it is mentioned, albeit not recommended for insufficient available evidence on its superiority as compared to vancomycin by that time, and for its rather elevated cost.

The recent apparition of fidaxomicin is the main reason why the most relevant differences in the examined guidelines can be found in their recommendations for the management of multiple CDI recurrences. The IDSA/SHEA guidelines—published in the pre-fidaxomicin era—recommend vancomycin treatment with taper or pulse regimens from the second recurrence on, as do the 2013 ACG guidelines (the first one that appeared after the approval of fidaxomicin in the US). In the 2014 ESCMID document, the use of vancomycin taper or pulse regimen and fidaxomicin obtained the same level of recommendation for multiple recurrences (B-II). This is also the first guidance document that overtly discourages clinicians from using metronidazole in this situation due to a higher risk of recurrences (D-II). It is to be remarked that metronidazole was already considered a bad antibiotic choice for multiple recurrences by the IDSA/SHEA ASID and ACG guidelines, but mainly because of its potential for cumulative neurotoxicity and not for its suboptimal efficacy. According to the WSES guidelines, the use of vancomycin and fidaxomicin in multiple recurrent CDI are also equally recommended (1-B). This document, as

well as the ESCMID guidelines, also advocates the use of fidaxomicin in first episodes of CDI in patients with an elevated risk of recurrence (recommendations 1-A and B-I, respectively). On the other hand, the most recent ASID guidelines do not recommend fidaxomicin in first episodes due to uncertainty about cost-effectiveness as compared to conventional treatment options, and suggests its use from the second recurrence on or as second-line treatment in refractory CDI.

The use of intestinal microbiota transplantation has also gained a more central role in multiple recurrent and refractory CDI over the past years. It is only briefly mentioned as an alternative treatment option in the oldest guidelines (IDSA/SHEA), whereas it is already included among the recommendations of the ACG guidelines, though only as a conditional recommendation supported by moderate-quality evidence. In more recent guidelines, however, its grade of recommendation for multiple CDI recurrences is equal (WSES: 1-B) or even higher (ESCMID: A-I) than that of vancomycin or fidaxomicin (1-B and B-II in the WSES and ESCMID guidelines, respectively). Intestinal microbiota transplantation is also considered by the ASID as equally valid as a treatment option for multiple recurrences as fidaxomicin or vancomycin, and further as a good second-line therapy choice after vancomycin failure in refractory CDI. This most recent guidelines also state their recommendations about the optimal transplant protocol.

Unresolved Issues

The role of fidaxomicin in multiple recurrent CDI is unquestionable today. There is growing evidence, however, demonstrating that it may be more cost-effective than vancomycin or metronidazole in recurrent CDI and also as a first-line treatment [90–93]. In a study presenting real-world data on fidaxomicin use in seven English hospitals, the most significant reduction in CDI recurrence rates after the introduction of fidaxomicin was observed in the centers where it was used as first-line treatment in all CDI cases [94]. Fidaxomicin use, moreover, seems to lead to less environmental *C. difficile* contamination, which may have a positive impact on in-hospital *C. difficile* spread [95], and since it does not significantly alters gut microbiota, its use may also reduce the risk of intestinal colonization by multiresistant bacteria in comparison with vancomycin treatment [96]. If these data are confirmed by forthcoming studies, fidaxomicin will probably gain a more central role in CDI treatment.

The administration of vancomycin via nasogastric tube is a generally accepted practice, but fidaxomicin is only recommended by current guidelines to be administered orally. According to recent data, this may be a safe and efficient treatment option when oral intake is impossible [97–99]. Future guidelines may consider this fidaxomicin administration method for CDI patients with an elevated recurrence risk and impaired oral intake.

Intestinal microbiota transplantation represents an approach that is markedly different from other current CDI therapies that may even have a deleterious collateral effect on the intestinal microbiota [100]. Despite the need of a rather complex infrastructure to perform this intervention [101–103], its advantages clearly outweigh the inconveniences. Due to the reconstitution of a healthy intestinal microbiota, this treatment method has demonstrated an excellent clinical efficacy in recurrent CDI [104], and has also been proved to be cost-effective as compared to

vancomycin and even fidaxomicin [91, 105, 106]. It is becoming available in an increasing number of centers worldwide, and the recently demonstrated efficacy of frozen and encapsulated microbiota administered orally makes it an ever more attractive treatment choice [107]. Based on these promising results, it may only be a matter of time until oral microbiota therapy becomes the backbone of the treatment of recurrent and refractory CDI.

Probiotics and Immunotherapy

The role of probiotics and immunotherapy in CDI is controversial, and this is clearly reflected in the discordant recommendations on their use among the examined guidelines.

The WSES guidelines are the only ones which do not recommend directly against the use of probiotics in CDI treatment. It suggests that probiotics may be of use as adjunctive therapy for recurrent CDI (2-B), whereas the other four guidelines consider their utilization not to be recommended in any scenario (IDSA/SHEA: C-III; ACG: moderate recommendation, moderate-quality evidence; SCMID: D-I).

Immunotherapy is only marginally mentioned by the IDSA/SHEA and the ASID guidelines without formulating concrete recommendations with respect to them, and the other guidelines make only very weak and cautious recommendations on this issue. The ACG guidelines consider the addition of intravenous immunoglobulin to the antibiotic treatment potentially helpful in patients with hypogammaglobulinemia (strong recommendation, low-quality evidence), whereas the WSES document recommends its use only in the case of multiple recurrences or fulminant CDI (2-C). The WSES guidelines suggest that monoclonal antibodies to toxins A and B may also be of some benefit in preventing CDI recurrences, especially in CDI caused by the hypervirulent strain 027 (2-C). The ESCMID guidance document assigns a C-I recommendation to the use of monoclonal antibodies combined with vancomycin or metronidazole in first episodes of CDI. Curiously, this last document supports the potential use of passive immunotherapy with immune whey after completing oral antibiotic therapy in an initial CDI episode in order to reduce the recurrence risk (C-II), while its use in multiple recurrences is advised against (D-I).

Unresolved Issues

Probiotics are currently not recommended for the treatment of CDI or for the prevention of CDI recurrence by the majority of the analyzed guidelines. A recent meta-analysis, however, demonstrated its efficacy in primary CDI prophylaxis in patients receiving systemic antibiotic treatment [108]. Hence, they may be considered for this indication by future guidelines.

The recommendations regarding immunotherapy may also change substantially in the future, given that the monoclonal antibody bezlotoxumab efficiently prevented CDI recurrence in two recent randomized controlled trials [109]. Moreover, there are also various vaccines against *C. difficile* under development, the most advanced of which [110] is currently being evaluated in a phase III clinical trial (NCT01887912).

SURGICAL TREATMENT

Different guidelines refer to the "severely ill patient" (IDSA/SHEA), patients with "systemic inflammation and deteriorating clinical condition despite maximal antibiotic therapy (with) toxic megacolon, acute abdomen, and

severe ileus" (ESCMID), or "patients with fulminant colitis" (WSES) as candidates for surgical treatment. Indications for surgery according to the ASID guidelines are toxic megacolon, bowel perforation or severe deterioration in spite of first and second line medical therapy. The ACG guidelines seem to offer the most detailed recommendations for surgical consultation, suggesting it to be solicited in all severe-complicated CDI cases with one or more of the following characteristics: hemodynamic instability requiring vasopressors, clinical sepsis with organ failure, changes in mental status, extreme leukocytosis (≥50,000 cells/μL), elevated lactic acid serum levels (≥5 mmol/L), or evidence of treatment failure after 5 days of conservative therapy (strong recommendation, moderate-quality evidence). Most guidelines, however, also call attention to the potentially disastrous consequences of a delayed intervention in cases where it is indicated, recommending performing surgery before patient serum lactate levels reach 5 mmol/L in order to keep perioperative mortality to a minimum.

Subtotal colectomy with the preservation of the rectum and end-ileostomy is the intervention of choice for the surgical treatment of CDI. Based on a case-controlled series published in 2011, however, diverting loop ileostomy and colonic lavage followed by intravenous metronidazole and vancomycin administered via the efferent limb of the ileostomy seems to be a good alternative to total colectomy in selected patients [111]. This novel colon-sparing method is mentioned by the ACG, ESCMID and ASID guidelines, and obtains a 2-C recommendation level in the WSES document.

Unresolved Issues

An emergency surgical intervention is indicated without any doubt in cases of colonic perforation and peritonitis. However, the exact patient population that could benefit from non-emergency surgery, and the optimal time-point of such an intervention are issues less clearly defined. According to two meta-analyses, prompt surgical intervention can reduce mortality in severe CDI [13, 112]. However, the authors of both of these studies admit that the optimal time-point for surgery is difficult to identify. The WSES guidelines also clearly state that there are no clinical or laboratory data currently that could reliably predict the eventual need of surgery in CDI patients. Future research should focus on a clearer definition of the precise indications and the optimal time of surgery in these patients.

A randomized controlled trial comparing diverting loop ileostomy with colectomy in severe CDI cases was prematurely terminated because of a low number of eligible patients (NCT01441271), but there is another clinical trial on the same issue that is currently recruiting participants (NCT02347280). This study may provide additional quality evidence to recommend the use of this promising new technique in everyday practice [113].

CONCLUSION

Clostridium difficile infection is one of the greatest burdens of modern medicine and probably will remain so in the foreseeable future. This is reflected in the increasing interest in CDI management of clinicians and researchers alike. Frequently updated

international guidelines are essential to provide the best available evidence-based therapy for most CDI patients. Current CDI guidelines are useful tools in achieving this goal, yet there are still a number of open questions about optimal CDI management that upcoming research has to address so that new guidelines updates can improve their recommendations for the benefit of these patients.

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