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Guidelines

European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults

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ABSTRACT

Scope: In 2009, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published the first treatment guidance document for *Clostridioides difficile* infection (CDI). This document was updated in 2014. The growing literature on CDI antimicrobial treatment and novel treatment approaches, such as faecal microbiota transplantation (FMT) and toxin-binding monoclonal antibodies, prompted the ESCMID study group on *C. difficile* (ESGCD) to update the 2014 treatment guidance document for CDI in adults.

Methods and questions: Key questions on CDI treatment were formulated by the guideline committee and included: What is the best treatment for initial, severe, severe-complicated, refractory, recurrent and multiple recurrent CDI? What is the best treatment when no oral therapy is possible? Can prognostic factors identify patients at risk for severe and recurrent CDI and is there a place for CDI prophylaxis? Outcome measures for treatment strategy were: clinical cure, recurrence and sustained cure. For studies on surgical interventions and severe-complicated CDI the outcome was mortality. Appraisal of available

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literature and drafting of recommendations was performed by the guideline drafting group. The total body of evidence for the recommendations on CDI treatment consists of the literature described in the previous guidelines, supplemented with a systematic literature search on randomized clinical trials and observational studies from 2012 and onwards. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) system was used to grade the strength of our recommendations and the quality of the evidence. The guideline committee was invited to comment on the recommendations. The guideline draft was sent to external experts and a patients' representative for review. Full ESCMID endorsement was obtained after a public consultation procedure.
Recommendations: Important changes compared with previous guideline include but are not limited to: metronidazole is no longer recommended for treatment of CDI when fidaxomicin or vancomycin are available, fidaxomicin is the preferred agent for treatment of initial CDI and the first recurrence of CDI when available and feasible, FMT or bezlotoxumab in addition to standard of care antibiotics (SoC) are preferred for treatment of a second or further recurrence of CDI, bezlotoxumab in addition to SoC is recommended for the first recurrence of CDI when fidaxomicin was used to manage the initial CDI episode, and bezlotoxumab is considered as an ancillary treatment to vancomycin for a CDI episode with high risk of recurrence when fidaxomicin is not available. Contrary to the previous guideline, in the current guideline emphasis is placed on risk for recurrence as a factor that determines treatment strategy for the individual patient, rather than the disease severity. **Joffrey van Prehn, Clin Microbiol Infect 2021;27:S1**

Introduction

After publication of the first treatment guidance document on *Clostridioides difficile* infection (CDI) in 2009 by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), an update was published in 2014 [1]. The growing body of literature on CDI antimicrobial treatment and novel treatment approaches, such as faecal microbiota transplantation (FMT) and toxin-binding monoclonal antibodies, merits an update of the 2014 ESCMID guideline. This is supported by a literature review performed by the European Study group for *Clostridioides difficile* (ESGCD) for clinical trials published between 2013 and 2017 [2]. Indeed, the most recent guidance document of ESCMIDs American counterparts the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America (SHEA/IDSA), provided important changes in the treatment recommendations for (recurrent) CDI [3]. The objective of this new document is to provide clinicians with an updated overview of currently available CDI treatment options, and a systematic, transparent, evidence-based update on the optimal CDI treatment strategy based on patient and disease characteristics. The treatment options for CDI are subdivided into the initial episode of CDI, severe CDI, severe-complicated CDI, refractory CDI, recurrent CDI, multiple recurrent CDI and CDI prophylaxis. Management of paediatric patients with CDI is not included in this guideline. Diagnostic strategies and prevention and control measures are described in separate ESCMID guidance documents and are outside the scope of this document [4,5].

Update methodology

Panel composition and guideline process

In 2018, a proposal for an update of *C. difficile* treatment was submitted to the ESCMID guidelines committee by the drafting group chair on behalf of the ESGCD. After approval of the proposal a small drafting group was constituted from ESGCD members to formulate questions to be answered and to perform a review of the literature. The questions were discussed and approved at the ESCGD group meeting at ECCMID 2019. Literature review and appraisal was supported by a clinical epidemiologist/methodologist. After literature review and appraisal, the small drafting group formulated draft recommendations. The recommendations were subsequently discussed and adjusted as appropriate by the larger ESCGD draft committee during a series of online meetings in February–March 2021. All recommendations were agreed upon by consensus. Recommendations were based on the best available medical treatment and patient important outcomes below, and were not led by economic considerations. Possible economic restraints are acknowledged and alternatives are offered in case the treatment of first choice is not available or not feasible economically. The final draft of the guidance document was sent to the ESCMID guidelines manager for a public consultation procedure, and to experts from or affiliated with other infectious diseases organizations (see Appendix), and to a patients' representative for endorsement. Full ESCMID endorsement was obtained. All participating members were obliged to complete a Conflict of Interest form which was submitted to the ESCMID guidelines manager. We recommend that this guidance document is updated five years after publication, or sooner when new data becomes available that has a significant impact on the current recommendations. The ESGCD will evaluate the necessity to update the guideline at annual intervals.

Questions to be addressed

For the 2021 update on the guidance on *C. difficile* the ESGCD agreed to seek to answers for the following questions:

1. What is the best treatment for initial CDI?
2. What is the best treatment for severe and severe-complicated CDI?
3. What is the best treatment for CDI when no oral treatment is possible?
4. What is the best treatment for refractory CDI?
5. What is the best treatment for recurrent CDI?
6. What is the best treatment for multiple recurrences of CDI?
7. Can prognostic factors identify patients at risk for severe CDI?
8. Can prognostic factors identify patients at risk for recurrent CDI?
9. Is there a place for prophylaxis for prevention of CDI?

The committee found it relevant to also consider the following issues:

- How best to define severe CDI.
- The principles for economic considerations.
- The timing of start of empiric treatment.
- The role of probiotics.
- The role of ancillary treatment strategies.

- Anti-CDI therapy during pregnancy.
- The treatment of patients at risk for severe CDI.
- The treatment of patients at risk for recurrent CDI.

Outcome measures and literature search

The guideline committee prospectively defined patient important outcome measures for treatment strategy as follows: clinical cure, recurrence, and sustained cure. For studies on surgical interventions and severe-complicated CDI the outcome was mortality. The outcome for prophylaxis studies was occurrence of CDI. The outcome for prognostic factors for severe and recurrent CDI was occurrence of severe and recurrent CDI, respectively. To answer the key questions formulated by the committee, four PICOs (Patients Intervention Comparison Outcome) were constructed (please see supplementary material). The resulting four literature searches were directed at treatment strategies for CDI in adult patients, prophylactic strategies for CDI, identification of prognostic factors for severe CDI and identification of prognostic factors for recurrent CDI. The search strategies were constructed with the help of a trained librarian and can be found in the supplementary material. PubMed, Embase, Emcare, Web of Science and COCHRANE Library databases were searched (therapy and prophylaxis search 24 September 2019; prognosis severe CDI 2 October 2019; prognosis recurrent CDI 4 October 2019). An update of the search was performed on 11 March 2021. The search was restricted to articles published in the English language. Meeting abstracts were excluded. The search on treatment strategy was limited to articles published since 2012; the evidence before 2012 was derived from the previous guideline. The search on prognostic factors was not limited by year of publication.

Selection process

Study eligibility was assessed in a two-step selection process. Two independent reviewers per search screened Title and Abstracts for possible eligible articles (treatment search J.P. and E.J.K.; prognosis search T.R. and R.O.); any discrepancies were resolved by consensus. Full-text articles were retrieved for detailed assessment of suitability, risk of bias and data extraction (treatment J.P./E.V. and E.R./E.B.; prognosis T.R. and R.O.). Exclusion criteria were: no original data/meta-analysis, study population <18 years, no full-text available in the English language and $N_{\text{population of interest}}$ <30, except for randomized clinical trials (RCTs). Prognostic studies with $N_{\text{outcome of interest}}$ <30 were also excluded. All steps were performed *in duplicate*. Cross-references of interest meeting the inclusions could be manually added to the included studies.

Data extraction and quality assessment

Data were extracted using standardized data extraction forms. For the therapy search risk of bias assessment was based on an adapted version of the Cochrane Risk of Bias tool for RCTs, resulting in an individual classification for each study (see supplementary material) [6].

To assess the risk of bias for the prognostics studies, the Quality in Prognostic Research (QUIPS) tool was used [7]. The QUIPS tool is recommended by the Cochrane Prognosis Methods Group and appraises six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. The analysis of prognostic factors was limited to those factors that were analysed in three or more separate studies to minimize the risk of publication bias. Variables that were part of the definitions of severe/severe-complicated CDI, and laboratory factors that are not part of 'standard care' were excluded.

Grading of the evidence

The findings of the systematic literature review were discussed with the members of the drafting group, and recommendations were formulated. Recommendations were preferably based on RCTs or prospective observational studies. When prospective data was not available, retrospective data was considered. Due to heterogeneity of studies (e.g. definitions of severity of disease, duration of follow-up) no meta-analyses were performed. The guideline was developed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. The level of evidence for the recommendations was graded, taking into account any risk of bias, inconsistency, indirectness, imprecision, publication bias that may upgrade or downgrade the level of evidence and the strength of recommendation [8]. The strength of recommendation is expressed as weak or strong. The quality of evidence is expressed as very low, low, moderate or high. In instances were recommendations cannot be supported by evidence but guidance is deemed necessary by the committee, a good practice statement, i.e. expert opinion, is provided. For grading of prognostic factors, the starting point for the quality of evidence is based on the phase of investigation rather than the design of the studies: 1 = association (very low quality of evidence), 2 = independent association (low to moderate) and 3 = underlying mechanism (high) [9]. GRADE and summary of finding tables were generated using the GRADEpro GDT: GRADEpro Guideline Development Tool (McMaster University, 2020, developed by Evidence Prime, Inc.), available from gradepro.org. The Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument was used for self-assessment of reporting [10].

Summary of definitions

The definitions of the 2014 CDI treatment guideline remain largely unchanged, except for the definition of treatment response and severe CDI. The definitions are summarized below.

An ***episode of CDI*** is defined as clinical findings compatible with CDI and microbiological evidence of *C. difficile* free toxins by enzyme immunoassay without reasonable evidence of another cause of diarrhoea **OR** a clinical picture compatible with CDI and a positive nucleic acid amplification test (NAAT) preferably with a low cycle threshold (Ct) value [11,12], or positive toxigenic *C. difficile* culture **OR** pseudomembranous colitis as diagnosed during endoscopy, after colectomy or on autopsy, in combination with a positive test for the presence of toxigenic *C. difficile* [4,13–16]. Diarrhoea is defined as ≥3 loose stools, i.e. Bristol stool scale 6–7 [17], in 24 hours. Diagnostic methods vary between studies, and many studies used PCR-only detection of toxigenic *C. difficile*. Relying solely on NAAT may result in overdiagnosis of CDI, though in RCTs randomization should account for this.

Treatment response is present when the patient has resolution of diarrhoea, *and* has had a formed or normal stool for that patient, *with* maintenance of resolution for the duration of therapy and at least 48 hours after the end of treatment, *and* no further requirement for CDI therapy, **AND** parameters of disease severity (clinical, laboratory, radiological) have improved and no new signs of severe disease have developed. In all other cases, treatment is considered a failure. A significant decrease in bowel movement frequency may also be considered a sign of (at least partial) response. Treatment response should be observed daily and evaluated after at least 3 days, assuming that the patient is not worsening on treatment.

Treatment with metronidazole, in particular, may result in a clinical response only after 3–5 days [18–20]. After clinical response, it may take weeks for stool consistency and frequency to normalise [20,21].

Refractory CDI is CDI not responding to recommended CDI antibiotic treatment, i.e. no response after 3–5 days of therapy. Refractory CDI can be part of either non-complicated or complicated CDI, which are described below.

Recurrence is present when CDI recurs within 8 weeks after a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment [14,22]. However, follow-up duration for assessment of recurrence varies between studies, and many studies use 4 or 12 weeks. It is not feasible to distinguish recurrence due to relapse (renewed symptoms from already present CDI) from recurrence due to reinfection in daily practice because genotyping is not readily available [23–27].

Sustained cure is defined as treatment response without recurrence of CDI during follow-up.

The 2014 ESCMID guideline defined severe CDI as an episode of CDI with (one or more specific signs and symptoms of) severe colitis or a complicated course of disease, with significant systemic toxin effects and shock, resulting in need for ICU admission, colectomy or death [1,22,28,29]. However, randomized clinical trials refer to the presence of one or more signs to define severe CDI, or use self-constructed or IDSA definitions. Patients with toxic megacolon, ileus or imminent surgery were typically excluded from these trials. For the current guideline and future purposes, the committee found the distinction between non-complicated and complicated CDI most relevant. To this end, the definitions of severe CDI has been changed and a severe-complicated category is introduced.

Severe CDI is characterized by one of the following factors at presentation: fever, i.e. core body temperature >38.5°C, marked leucocytosis, i.e. leucocyte count >15 × 10^9/L, and rise in serum creatinine, i.e. >50% above the baseline. Additional supporting factors, when available are distension of the large intestine, pericolonic fat stranding or colonic wall thickening (including low-attenuation mural thickening) at imaging.

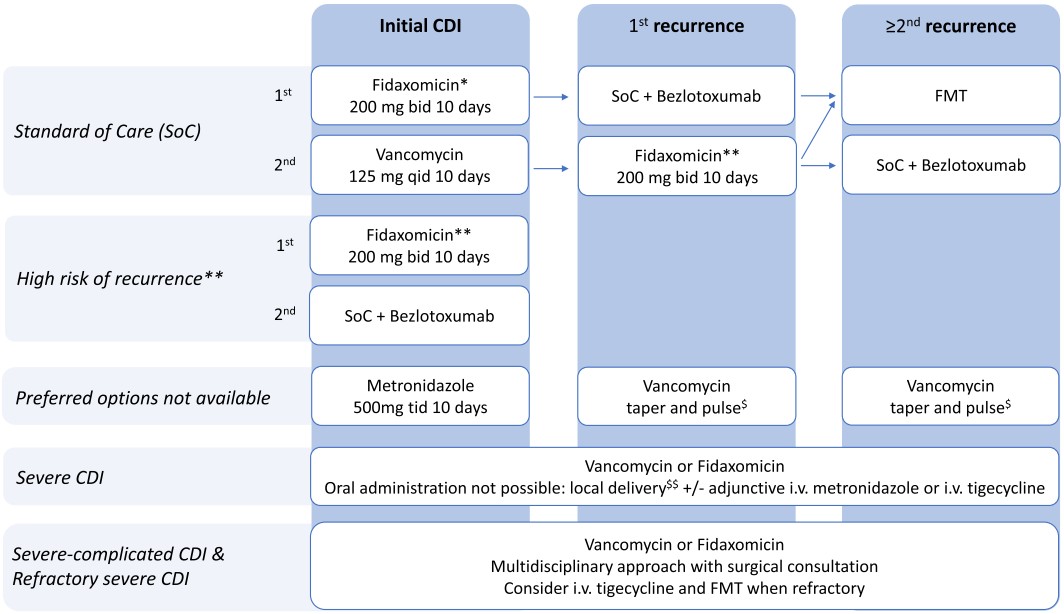
Severe-complicated CDI (or fulminant CD) is defined by the presence of one of the following factors that needs to be attributed to CDI: hypotension, septic shock, elevated serum lactate, ileus, toxic megacolon, bowel perforation or any fulminant course of disease (i.e. rapid deterioration of the patient).

Results

Flowcharts of the literature search results for therapy and prophylaxis can be found in the Supplementary material. Detailed results of the literature search and grading of prognostics factors for severe and recurrent CDI are found in a separate document that can be found at https://doi.org/10.1016/j.cmi.2021.09.026 [289]. The literature search was last updated on 11 March 2021. After removal of duplicates, the therapy search resulted in 3565 unique references available for title/abstract screening; 257 articles were assessed in more detail, of which 171 articles were used for this guideline. A dedicated search for prophylaxis resulted in 290 additional references, of which 11 were assessed in more detail; one extra study was included for prophylaxis [30], and one for CDI therapy [31]. The prognostic search on severe CDI yielded 1242 references; 126 studies were assessed in more detail and 76 were included for analysis [29,32–106; 12 more studies were manually added from cross-references [107–118], resulting in 88 studies for final analysis. The prognostic search on recurrent CDI yielded 1104 references; 105 studies were assessed in more detail and 36 were included for analysis [99,106,119–152]; seven cross-references were added [25,108,153–157], resulting in 43 studies for final analysis.

Summary of recommendations

A synthesis of treatment recommendations is shown in the treatment algorithm Fig. 1. In addition to these therapeutic



* Risk stratification for risk of recurrence may be applied for selective use of fidaxomicin in case of limited access or resources.
** Consider extended fidaxomicin: 200 mg bid on day 1-5, 200 mg q48h on day 7-25. Most important risk factor for recurrence is age >65-70 years. Additional risk factor(s) to consider are healthcare-associated CDI, prior hospitalization ≤ 3 months, prior CDI episode, continued non-CDI antibiotic use, and PPI therapy started during/after CDI diagnosis. The risk of recurrence is assumed higher with more risk factors present.
$ Vancomycin taper and pulse: 2 weeks 125 mg qid, followed by 1 week 125 mg bid, then 1 week 125 mg qd, then 1 week 125 mg q48h, and finally 125 mg q72h for 1 week.
$$ Rectal or nasoduodenal delivery

Fig. 1. Suggested treatment algorithm.

Table 1
Question: Metronidazole compared with vancomycin for initial CDI

Certainty assessment							No. of patients		Effect		Certainty	References
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metronidazole	Vancomycin	Relative (95% CI)	Absolute (95% CI)		
Treatment response												
5	Randomized trials	Not serious	Serious[a]	Not serious	Not serious	None	336/430 (78.1%)	359/413 (86.9%)	RR 0.90 (0.84 to 0.96)	87 fewer per 1000 (from 139 fewer to 35 fewer)	⊕⊕⊕◯ MODERATE	Teasley 1983 [161] Wenisch 1996 [162] Zar 2007 [163] Johnson 2014 [164]
Recurrence (follow-up: range 21 days to 30 days)												
5	Randomized trials	Not serious	Serious[a]	Not serious	Not serious	None	59/343 (17.2%)	65/362 (18.0%)	RR 0.96 (0.70 to 1.32)	7 fewer per 1000 (from 54 fewer to 57 more)	⊕⊕⊕◯ MODERATE	Teasley 1983 [161] Wenisch 1996 [162] Zar 2007 [163] Johnson 2014 [164]

CI, confidence interval; RR, risk ratio.
[a] Equivalence in 2 RCTs before 2000 ($N \leq 45$ per treatment group) by Teasley and Wenisch, and in mild subgroup by Zar. Metronidazole inferior in pooled analysis of 2 RCTs by Johnson.

interventions, the following general measures are advised as described in the 2014 treatment guideline [1,13,22,28,158,159]:

- Discontinuation of unnecessary antimicrobial therapy
- Adequate replacement of fluid and electrolytes
- Avoidance of anti-motility medications
- Reviewing proton pump inhibitor (PPI) use.

Detailed results of recent (published 2012 and onwards) randomized clinical trials and prospective studies on initial, recurrent, severe, severe complicated and refractory CDI, and prophylaxis can be found in the Tables S1–S4. Grading and a summary of key findings for therapeutic options can be found in Tables 1–5. Detailed results and evidence tables on prognostics factors can be found at https://doi.org/10.1016/j.cmi.2021.09.026 [289].

Recommendations

The recommendations regarding treatment and prognostic factors are described below per key question.

I. **What is the best treatment for an initial episode of CDI?**

- In case of non-severe CDI, we recommend to discontinue antibiotic therapy if possible with the inciting antibiotic and closely monitor the patient for 48 hours. *Good practice statement*
- For the initial episode of CDI we recommend fidaxomicin 200 mg twice daily for 10 days. *Strong (recommendation), Moderate (level of evidence)*
- When access to fidaxomicin is limited, it is reasonable to make a risk stratification for selected use. In this case, fidaxomicin is recommended whenever the clinicians deems the risk of recurrence high. This can be supported by an older age of the patient (>65 years) plus the presence of one or more additional risk factor(s), i.e. healthcare-associated CDI, prior hospitalization in the last 3 months, use of concomitant antibiotics, PPIs started during/after CDI diagnosis and a prior CDI episode. The risk of recurrence is assumed to be higher with more risk factors present. *Good practice statement*
- When fidaxomicin is not available or feasible, oral vancomycin 125 mg four times daily for 10 days is a suitable alternative. *Strong, High*
- Oral metronidazole 500 mg three times daily for 10 days should be used only when vancomycin and fidaxomicin are not available or feasible. *Strong, Moderate*
- The use of vancomycin 500 mg four times daily is not recommended. *Strong, Very low*
- Consider prolonged administration of fidaxomicin (extended fidaxomicin), i.e. 200 mg twice daily on days 1–5, and 200 mg once daily on alternate days on days 7–25, for an episode of CDI with increased risk of recurrence, especially in elderly hospitalized patients. *Weak, Low*
- Consider to add bezlotoxumab to oral standard of care treatment for an episode of CDI with increased risk of recurrence, when fidaxomicin is not available or feasible. In patients with a history of congestive heart failure, bezlotoxumab should be reserved for use when the benefits outweigh the risk. *Weak, Moderate*

Discontinue therapy with the inciting antimicrobial agent

As per 2014 ESCMID guideline [1], in case of non-severe CDI with a non-epidemic hypervirulent strain, i.e. in a non-epidemic situation, and CDI clearly induced by the use of antibiotics, it may be acceptable to discontinue therapy with the inciting antibiotic

Table 2
Question: Fidaxomicin compared to vancomycin for initial CDI

Certainty assessment							No. of patients		Effect		Certainty	References
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fidaxomicin	Vancomycin	Relative (95% CI)	Absolute (95% CI)		
Treatment response												
3	Randomized trials	Not serious	Not serious	Not serious	Not serious	None	414/478 (86.6%)	431/513 (84.0%)	RR 1.03 (0.98 to 1.09)	25 more per 1000 (from 17 fewer to 76 more)	⊕⊕⊕⊕ HIGH	Louie 2011 [166] Cornely 20212 [167] Mikamo 2018 [170]
Recurrence (follow up: 28 days)												
3	Randomized trials	Not serious	Serious[a]	Not serious	Not serious	None	66/414 (15.9%)	112/431 (26.0%)	RR 0.61 (0.47 to 0.81)	101 fewer per 1000 (from 138 fewer to 49 fewer)	⊕⊕⊕◯ MODERATE	Louie 2011 [166] Cornely 20212 [167] Mikamo 2018 [170]

CI, confidence interval; RR, risk ratio.
[a] Significantly higher global/sustained cure rates with fidaxomicin in the studies by Louie and Cornely. No difference in primary endpoint of global (sustained) cure by Mikamo; considerable loss to follow-up in this study.

agent and observe the clinical response for 48 hours, providing that patients are followed very closely for any signs of clinical deterioration and placed on anti-CDI therapy immediately if this occurs. This advices is based on clinical experience and an observational cohort [160]. In this cohort the sole intervention in a subgroup was cessation of the inciting antibiotic; this resulted in treatment response in 135 of 154 patients. Of note, the study was performed before increased incidence of hypervirulent *C. difficile* strains.

Metronidazole

Two RCTs published before 2000 showed equivalent efficacy for metronidazole and vancomycin, but conclusions are limited by small sample sizes ($n \leq 45$ per treatment group) and no details on severity of disease [161,162]. Previous ESCMID and IDSA/SHEA guidelines recommended metronidazole as the initial choice for mild CDI [1,3,28]. This was driven by a RCT that demonstrated a non-significant difference in cure rate for metronidazole versus vancomycin in a subgroup of patients with mild CDI ($n = 81$, 90% vs. 98%), as opposed to cure rates for severe disease ($n = 69$, 76% vs. 97%) [163]. A more recent analysis of two RCTs demonstrated inferiority of metronidazole compared with vancomycin ($n = 555$, 73% vs. 81%), also in subanalyses of mild ($n = 150$), moderate ($n = 229$) and severe CDI ($n = 157$) [164]. Also, in a prospective longitudinal cohort of 75 patients with uncomplicated initial CDI, treatment with metronidazole and diagnosis via EIA were the most robust predictors of CDI recurrence [165]. Therefore, metronidazole is no longer recommended as a first line agent for CDI treatment.

Fidaxomicin and vancomycin as standard of care

A phase 3 RCT conducted in the United States and Canada compared fidaxomicin to vancomycin and found similar cure rates ($n = 596$, 88% vs. 86%), but an absolute risk reduction of 9.9% for recurrence at 4 weeks in favour of fidaxomicin ($n = 518$, recurrence 15% vs. 25%, reduction 95% CI −16.6 to −2.9) [166]. Likewise, non-inferiority for cure was shown in a RCT conducted in the United States, Canada and Europe, and a 14.2% reduction of recurrence at 4 weeks ($n = 244$, recurrence 13% vs. 27% reduction 95% CI −21.4 to −6.8) [167]. Of note, the recurrence rates for CDI caused by BI/NAP1/027 epidemic strains were either similar [166], or the benefit of fidaxomicin was non-significant [167]. A *post hoc* subgroup analysis of patients with cancer in both trials found higher initial cure for fidaxomicin compared with vancomycin ($n = 183$, 85% vs. 74%), driven by a decreased cure rate with vancomycin in this subgroup [168]. Two small(er) RCTs were conducted but were graded a lower quality of evidence [169,170]. Fidaxomicin has the narrowest spectrum of activity, and is less detrimental to the bacterial gut microbiome [171,172], which in the setting of CDI is preferred. It must be noted that fidaxomicin has higher acquisition costs than vancomycin, which may limit widespread prescription. The decreased recurrence rate and subsequent decreased re-hospitalization rate partially offsets the higher acquisition costs of fidaxomicin and may result in cost-effectiveness [173–175], although many cost-effectiveness studies are co-authored by employees of pharmaceutical companies [176–178] or funded by the manufacturer or holder of market authorization [179,180]. In general, the committee agreed that medical aspects should guide our recommendations and that the best available treatment should be recommended; however, limited resources must also be acknowledged. Therefore, we have chosen to recommended fidaxomicin as the preferred option because on reduced recurrence rates, advise vancomycin as a

Table 3
Question: Extended fidaxomicin compared to vancomycin for initial CDI

Certainty assessment							No. of patients		Effect		Certainty	References
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Extended fidaxomicin	Vancomycin	Relative (95% CI)	Absolute (95% CI)		
Treatment response												
1	Randomized trial	Serious[a]	Not serious	Not serious	Not serious	None	138/177 (78.0%)	147/179 (82.1%)	RR 0.95 (0.86 to 1.05)	41 fewer per 1000 (from 115 fewer to 41 more)	⊕⊕⊕◯ MODERATE	Guery 2018 [184]
Recurrence (follow-up: 30 days)												
1	Randomized trial	Serious[a]	Not serious	Not serious	Not serious	None	14/138 (10.1%)	41/147 (27.9%)	RR 0.36 (0.21 to 0.64)	179 fewer per 1000 (from 220 fewer to 100 fewer)	⊕⊕⊕◯ MODERATE	Guery 2018 [184]

CI, confidence interval; RR, risk ratio.
[a] Considerable loss to follow-up and discontinuation of treatment.

suitable alternative when the preferred option is not feasible or available, recommend metronidazole only when fidaxomicin and vancomycin are not available, and offer a stratification strategy for selected use of fidaxomicin.

High-dose vancomycin

There is insufficient evidence to support the use of high dose oral vancomycin 500 mg four times daily [181]. The standard dose of 125 mg four times daily already results in high intraluminal levels [182], and high-dose vancomycin increases risk of possible adverse effects, e.g. systemic levels of vancomycin [183]. Additionally, concerns regarding increased antibiotic selection pressure resulting in resistance selection (e.g. vancomycin-resistant enterococci, VRE) remain.

Extended fidaxomicin

A multinational European open-label RCT compared an extended fidaxomicin regimen (200 mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7–25) to vancomycin in hospitalized patients aged 60 years or older [184]. For randomization, patients were stratified by baseline CDI severity, cancer presence, age (≥75 years vs. <75 years) and number of previous CDI episodes. Sustained clinical cure at 30 days was 70% in 177 patients that received extended fidaxomicin, of which 21% had one or two CDI episodes within the prior 3 months; sustained cure with vancomycin was 59%. It should be also noted that, in contrast to the fidaxomicin RCTs with a standard regimen, the difference in sustained cure between fidaxomicin and vancomycin was more pronounced in patients with *C. difficile* PCR ribotype 027: 39.1% (95% CI 13.2–64.9). Further, it is of interest that although the mean age of patients in this study was 75 years, sustained cure rates were similar to previous reports [166,167], and the recurrence rate at 90 days was only 6%. A direct comparison with fidaxomicin administered for 10 days would have increased the level of evidence supporting the use of extended fidaxomicin. The committee agrees that an extended (off-label) approach may be considered for treatment of the population studied in the RCT, i.e. older patients who are at risk for CDI recurrence.

Bezlotoxumab

Bezlotoxumab is a monoclonal antibody directed against *C. difficile* toxin B. Addition of bezlotoxumab to standard of care (SoC) CDI antibiotics resulted in similar cure rates but a 10% reduced risk of recurrences in the placebo controlled MODIFY-I and II trials [185]. It should be noted that the proportion of patients receiving vancomycin as SoC was 48%, while fidaxomicin was given in 4%. The benefit of adding bezlotoxumab to fidaxomicin is therefore unclear. Post-hoc analysis of pre-specified risk factors revealed that these were appropriate to identify patients at risk for rCDI [186]. Reduction of recurrence was 25% (95% CI −39 to −9) in patients with ≥3 risk factors and 2% (−11 to 7) in patients with no risk factors. Prespecified risk factors included age ≥65 years, history of CDI in the previous 6 months, immunocompromised, severe course of CDI and CDI caused by *C. difficile* strains associated with poor outcomes (ribotype 027, 078 or 244). Caution should be exercised with prescription of bezlotoxumab to patients with a history of congestive heart failure. In these patients, heart failure was reported more commonly compared to the placebo group, 12.7% (15/118) versus 4.8% (5/104) and more deaths were reported, 19.5% (23/118) versus 12.5% (13/104) respectively [187]. Even though the acquisition costs of bezlotoxumab are even higher than for fidaxomicin, Markov

Table 4
Question: SoC plus bezlotoxumab compared to SoC alone for (increased risk of) recurrent CDI

Certainty assessment							No. of patients		Effect		Certainty	References
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SoC plus bezlotoxumab	SoC alone	Relative (95% CI)	Absolute (95% CI)		
Treatment response												
2	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	625/781 (80.0%)	621/773 (80.3%)	RR 1.00 (0.95 to 1.05)	0 fewer per 1000 (from 40 fewer to 40 more)	⊕⊕⊕◯ MODERATE	Wilcox 2017 [185]
Recurrence (follow-up: 12 weeks)												
2	Randomized trials	Not serious	Not serious	Serious[a]	Not serious	None	129/625 (20.6%)	206/621 (33.2%)	RR 0.62 (0.51 to 0.75)	126 fewer per 1000 (from 163 fewer to 83 fewer)	⊕⊕⊕◯ MODERATE	Wilcox 2017 [185]

CI, confidence interval; RR, risk ratio.
[a] The trials included 72% initial CDI and 28% recurrent CDI. *Post hoc* analysis of pre-specified risk factors for recurrence revealed that reduction of recurrence was 25% (95% CI −39 to −9) in patients with ≥3 risk factors, and 2% (−11 to 7) in patients with no risk factors.

modelling—with its inherent limitations—indicates that bezlotoxumab might be cost-effective [175,188,189]. Of note, two of these studies were financially supported by the manufacturer of bezlotoxumab. Considering the higher acquisition costs and no clear benefit when comparing with fidaxomicin for the treatment of CDI, we have recommended the addition of bezlotoxumab to SoC for an episode of CDI with increased risk of recurrence when fidaxomicin is not available or feasible. The quality of evidence was graded moderate because the population of interest was studied in a *post hoc* analysis [186]. In patients with a history of congestive heart failure, bezlotoxumab should be reserved for use when the benefits outweigh the risk.

Other agents

Ridinilazole (SMT19969) is a potential CDI antibiotic of interest and was superior to vancomycin for sustained cure at the 10% level in a phase 2 RCT [190]. A comparative trial with fidaxomicin (NCT2784002) is currently enrolling patients [191]. Development of cadazolid, tolevamer and surotomycin were halted after failure to demonstrate non-inferiority in RCTs [164,192,193]. LFF571 was non-inferior to vancomycin for cure in a phase 2 RCT, but its development was discontinued [194].

II. What is the best treatment for severe and severe-complicated CDI?

- Options for treatment of any severe and severe-complicated CDI episode include vancomycin 125 mg four times daily for 10 days or fidaxomicin 200 mg twice daily for 10 days. There is no data supporting the superiority of one over the other. *Good practice statement*
- For severe CDI, routine addition of iv metronidazole to oral SoC therapy is not recommended. *Weak, Very Low*
- When a patient is deteriorating or progressing to severe-complicated CDI while on anti-CDI antibiotic therapy, addition of iv tigecycline 50 mg twice daily (100 mg loading dose) may be considered on a case-by-case basis. *Weak, Very Low*
- Consult a surgeon for any severe-complicated case. *Good practice statement*
- Total abdominal colectomy might be prevented by partial colectomy or loop ileostomy.*Weak, Very Low*

Antibiotic treatment

The previous guideline included a different antibiotic regimen for non-severe and severe initial CDI. This was based on the non-inferiority of metronidazole in mild disease [163]. Since metronidazole is no longer a preferred agent for treatment of any CDI episode, the distinction between non-severe and severe course of the disease has become less relevant. In the current guideline, the most relevant distinction is between non-severe/severe CDI and severe complicated CDI.

Vancomycin is the traditional agent for oral antibiotic therapy in severe and severe complicated CDI. The use of vancomycin in these groups is based on historical grounds. In the subgroup of patients with severe CDI in two pivotal RCTs ($n = 235$ and $n = 124$), oral vancomycin and fidaxomicin had similar outcomes in terms of cure rate and recurrence rate [166,167]. Patients with severe complicated disease were excluded from these trials. The optimal antibiotic therapy for critically ill patients, i.e. severe complicated CDI is unknown, as these patients are typically excluded from prospective (randomized) clinical trials that investigate CDI agents. A retrospective multinational post-authorization study of fidaxomicin ($n = 271$) found diarrhoea response rates ranging from 68% to 82%

Table 5
Question: FMT (after ≥3 days vancomycin pre-treatment) compared to vancomycin alone for multiple recurrent CDI

Certainty assessment							No. of patients		Effect		Certainty	References
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FMT (after ≥3 days vancomycin pre-treatment)	Vancomycin alone	Relative (95% CI)	Absolute (95% CI)		
Sustained cure (follow-up: range 8 weeks to 12 weeks)												
3	Randomized trials	Serious[a]	Not serious	Not serious	Serious[b]	Strong association	48/60 (80.0%)	15/48 (31.3%)	RR 2.56 (1.65 to 3.97)	488 more per 1000 (from 203 more to 928 more)	⊕⊕⊕◯ MODERATE	Van Nood 2013 [229] Camarota 2015 [227] Hvas 2019 [223]

CI, confidence interval; RR, risk ratio.
[a] Unblinded trials.
[b] Small sample sizes.

and recurrence rates ranging from 14% to 19% in patients with concomitant inflammatory bowel disease (IBD), fulminant CDI, moderate-to-severe hepatic impairment and severe renal impairment [195]. A propensity score matched cohort study compared 213 fidaxomicin to 639 vancomycin courses and found similar outcomes in patients with severe disease [196]. This study did not include fulminant CDI or toxic megacolon. A single centre retrospective analysis found that fidaxomicin response among patients admitted to the critical care unit was similar to patients admitted to general wards [197]. Another retrospective study included a subset of 16 patients with severe-complicated CDI of which 11 were initially cured and three had a recurrence [198]. Mortality was 44% in this subset, and 75% of patients were prescribed fidaxomicin after failure of another agent. Overall, there are no data that demonstrate superiority of fidaxomicin or vancomycin over the other for severe and severe-complicated CDI.

Intravenous metronidazole

There is no new evidence that supports the routine addition of iv metronidazole in severe CDI. A large retrospective analysis ($n = 2114$) found no association between dual therapy and 90-day mortality, colectomy and CDI recurrence in patients with non-severe ($n = 727$), severe ($n = 861$) and fulminant CDI ($n = 526$) [199]. A prospective observational trial suggests that iv metronidazole monotherapy may result in a higher mortality rate when compared with oral metronidazole or vancomycin treatment [200]. Cure rate (52%), recurrence rate (50%) and 30-day mortality (38%) in patients with mild CDI treated with iv metronidazole ($n = 42$) were disappointing. However, choice of treatment was at the discretion of the treating clinician and therefore results are prone to bias. A recent retrospective analysis of 138 patients found that addition of iv metronidazole to oral vancomycin was not associated with better clinical outcomes in severe non-fulminant CDI in ICU patients [201]. In contrast, a retrospective study in patients admitted to the ICU supports the suggestion that addition of iv metronidazole to oral CDI therapy in critically ill patients might be beneficial [202]. Forty-four patients treated with monotherapy were matched to 44 patients with combination therapy, based on APACHE II score. Mortality was 20% lower in the iv metronidazole combination therapy group. However, there were more oncological patients and patients with neutropenia in the monotherapy group. Overall, we do not recommend routine addition of iv metronidazole to oral antibiotic therapy in severe CDI. For use of iv metronidazole, we refer to section III: CDI treatment when no oral treatment is possible.

Intravenous tigecycline

Tigecycline shows in vitro activity against *C. difficile* and intravenous tigecycline has been studied in observational cohorts. No (randomized) clinical trial has investigated tigecycline for treatment of CDI. A retrospective single centre study compared iv tigecycline monotherapy ($n = 45$) to oral vancomycin + metronidazole iv ($n = 45$) in severe CDI and found a better cure rate for tigecycline monotherapy (50 mg twice daily) after a loading dose (100 mg), 76% versus 53%, and less CDI sepsis, 16% versus 40% [203]. The majority of patients received tigecycline as a last resort therapy after failure of standard antibiotics. In contrast, a recent propensity matched study found no benefit for the addition of tigecycline ($n = 62$) to vancomycin ($n = 204$) with OR 0.92 (95% CI 0.6–1.44) for favourable outcome with tigecycline [204], although in the propensity score analysis, a small sample size was included (43 pairs, 86 patients). A recent literature review concluded that tigecycline might be considered as potential therapeutic option for severe CDI

cases, although this is based on retrospective observational studies [205]. Nevertheless, the committee concludes that tigecycline merits consideration when a patient is deteriorating or progressing to severe-complicated disease.

Surgery for severe-complicated CDI

Analysis of a nationwide US database (2007–2015) confirms that 30-day mortality in patients that underwent total or partial colectomy for CDI is high, 37% and 35% respectively. It is difficult to provide an evidence-based recommendation on the optimal timing of surgery for severe complicated CDI. A review from 2010 suggests that colectomy is associated with a lower mortality than continued medical treatment when the patient is no longer improving [206]. Total abdominal colectomy (TAC) is the standard when surgery is needed, but might be prevented by partial colectomy or loop ileostomy. Loop ileostomy (LI) for CDI includes intraoperative colonic lavage with warmed polyethylene glycol 3350/electrolyte solution via the ileostomy, with postoperative antegrade instillation of vancomycin flushes via the ileostomy. Using the aforementioned protocol, the first study that described LI found a lower mortality than a historical cohort: 19% vs 50% [207]. Unfortunately, a RCT aimed at comparing LI with TAC (NCT01441271) was terminated due to hampered inclusion. A recent retrospective multicentre study also found a survival benefit for LI (mortality 17% vs. 40%, $n = 98$) [208]. In contrast, two national US database reviews (2011–2016 and 2011–2015) did not demonstrate a mortality benefit (mortality LI 36% vs. 31% TAC, $n = 47$ vs. $n = 410$; and LI 26% vs 31% TAC, $n = 613$ and $n = 2408$) [209,210]. Although the quality of evidence is low and reported mortality benefits are conflicting, partial colectomy or loop ileostomy should be considered to prevent TAC. The committee considers it good clinical practice to consult a surgeon for any severe complicated case.

III. **What is the best treatment for CDI when no oral treatment is possible?**

- When oral therapy is not possible, attempt intraluminal (gastroduodenal or coloscopic) delivery of vancomycin or fidaxomicin. *Good practice statement*
- and consider adjunctive treatment with iv metronidazole 500 mg three times daily or iv tigecycline 50 mg two times daily (100 mg loading dose). *Weak, Very Low*

The evidence regarding iv metronidazole and iv tigecycline is discussed in the previous section (severe and severe-complicated CDI). It should be noted that the standard of care treatment for CDI is based on high intraluminal concentrations of the active agents which are minimally absorbed in the gastro-intestinal tract. Therefore, when oral treatment with vancomycin or fidaxomicin is not possible, intraluminal delivery should be attempted. The evidence for intraluminal vancomycin is limited to case series and dosages range from 250 mg once daily to 1 g four times a day [211]. There are no data on intraluminal fidaxomicin delivery. It seems reasonable use standard oral dosages for intraluminal delivery. Addition of an intravenous antibiotic might be beneficial on a theoretical basis when low intraluminal concentrations of oral CDI agents are expected.

IV. **What is the best treatment for refractory CDI?**

Consideration of adjunctive intravenous treatment has been described in the previous sections. Here we will advise on refractory non-complicated CDI and the role of surgery and FMT in refractory complicated CDI.

- When non-complicated CDI is not responding to CDI treatment and the patient is not deteriorating or progressing to complicated CDI, carefully re-evaluate the diagnosis of CDI and consider an alternative diagnosis. *Good practice statement*
- Consult a surgeon as soon as a patient's condition is deteriorating and the patient is not responding to CDI treatment. *Good practice statement*
- FMT may be a rescue therapy for patients with severe complicated CDI that have deteriorated despite CDI antibiotic treatment and for whom surgery is not feasible. The risk-benefit analysis of FMT and/or surgical management should be taken on a case-by-case basis and discussed by the multidisciplinary team. *Weak, Very Low*

Non-complicated refractory CDI

For patients with non-complicated CDI who are not responding to standard of care oral treatment, who do not have a deteriorating condition and are not progressing to complicated CDI, the diagnosis of CDI should be reconsidered as vancomycin and fidaxomicin resistance is very rare in Europe. The susceptibility percentages for vancomycin and fidaxomicin were 96.8% and 100%, respectively, in a pan-European study that included 918 *C. difficile* isolates [212]. In addition, an alternative diagnosis or underlying pathology in combination with *C. difficile* colonization, may be present in a significant portion of patients suspected for CDI. For example, a paper on the experiences of a multidisciplinary expert panel that assesses applications for FMT reported that 27% of requests were rejected; the majority because of *C. difficile* colonization with diarrhoea due to another cause [213]. In an outpatient setting, non-adherence to the prescribed treatment should also be considered.

The role of surgery in severe-complicated refractory CDI

The committee finds a multidisciplinary approach to the management of patients refractory to antibiotic CDI treatment of utmost importance. Thus, a surgical opinion should be sought early in the process, i.e. as soon as a patient's condition is deteriorating and the patient is not responding to CDI treatment. See the previous section for our conclusion on TAC, partial colectomy or loop ileostomy.

The role of FMT in severe-complicated refractory CDI

FMT has become an accepted treatment for multiple recurrent CDI [1,3]. As experience with FMT increases, it has become apparent that there might be a role for FMT in severe complicated refractory CDI. An observational cohort study found an 87% cure rate at 1 month for severe complicated refractory CDI [214]. In this study, patients with severe CDI ($n = 19$) and severe complicated CDI ($n = 38$) were offered FMT instead of surgery after a multidisciplinary evaluation [214]. Vancomycin was continued after FMT, and 5 days post FMT the treatment response was evaluated. Sequential FMT was performed when necessary. Treatment success at 1 month was 100% for severe and 87% for severe-complicated disease. Survival rate was 95% at 1 month and 77% at 3 months. Thirty patients had a single FMT to reach clinical cure. A small RCT in patients with therapy refractory severe ($n = 23$) and severe complicated ($n = 33$) CDI compared bowel preparation plus a single FMT followed by 14 days oral vancomycin to multiple FMT infusions, and found cure rates of 75% and 100%, respectively [215]. Although patients were randomized, a control group with maximum conservative or surgical treatment was lacking. Both studies that are mentioned above indicate that multiple FMT infusions may be warranted, using continued presence of pseudomembranes as an indicator for the

need for an additional FMT infusion [214,215]. Although not included in our search strategy, it is important to note that a prospective series of 15 patients indicated less favourable results with 87% response at day 7, but 33% sustained cure at day 30, with one colectomy and two (of five) deaths attributable to CDI [216]. Although the level of evidence is very low, considering the high mortality associated with surgical therapy for CDI and the fact that some patients are too ill to be surgical candidates, the committee believes there is a place for FMT in patients with refractory severe complicated CDI for whom surgery is not feasible, providing that surgical consultation is always sought, standardized and screened FMT products are readily available, the treating or consulting physicians have experience with FMT and a careful risk assessment of the benefits and risk are made on a case-by-case basis. The expert team should specifically also discuss intravenous antibiotic pre- and post FMT treatment, dependent on the patient's underlying condition, follow-up parameters and necessary treatment with other non-CDI antibiotics.

V. **What is the best treatment for recurrent CDI?**

- If the initial CDI episode was treated with vancomycin or metronidazole, then fidaxomicin 200 mg twice daily for 10 days is the preferred agent to treat a first CDI recurrence. *Strong, Low*
- If the initial CDI episode was treated with fidaxomicin, consider addition of bezlotoxumab (when available and feasible) to an oral SoC antibiotic treatment, i.e. vancomycin or fidaxomicin. *Addition to vancomycin: Weak, Moderate / Addition to fidaxomicin: good practice statement*
- Consider a vancomycin tapering and pulse scheme for recurrent CDI when fidaxomicin or bezlotoxumab are not available or feasible. *Weak, Very low*

Fidaxomicin and bezlotoxumab

As described under section I 'the best treatment for an initial episode of CDI', fidaxomicin results in similar cure as vancomycin but a 10–14% lower absolute risk CDI recurrence rate [166,167]. In a combined subset analysis ($n = 178$) of the two RCTs, a 16% lower recurrence rate with fidaxomicin was reported in patients with a first CDI recurrence within 3 months of a prior episode [217]. However, a multicentre retrospective study ($n = 81$) found that patients with prior CDI episodes are less likely to respond to therapy and more likely to have a recurrence [218]. Hence, use of fidaxomicin earlier in the course of (recurrent episodes of) CDI, may lead to increased benefit.

In the subgroup of patients with at least one CDI episode in the previous 6 months in the MODIFY trials, addition of bezlotoxumab also resulted in an absolute reduction in recurrence rates, 13% in MODIFY-I ($n = 212$) and 19% in MODIFY-II ($n = 223$). Therefore, when available and feasible, bezlotoxumab might be added to SoC anti-CDI antibiotics (vancomycin or fidaxomicin) when treating a recurrent episode of CDI [185]. It should be noted that the proportion of patients receiving fidaxomicin as SoC in the MODIFY-I and II trials was 4%, whereas the proportion receiving vancomycin was 48%.

In conclusion, prospective data on treatment of first recurrences is limited to subanalysis of RCTs and quality of evidence can therefore be graded moderate at best. It should be noted that the initial episodes were within 3 and 6 months of the recurrent episode, rather than the 2 months suggested by the ESCMID guidelines [185,217]. The reduction of recurrences rates with fidaxomicin and bezlotoxumab seems sustained in patients with prior CDI. Regarding bezlotoxumab, the *post hoc* analysis of prespecified risk factors in the MODIFY trials indicates that the benefit of bezlotoxumab is most pronounced in patients with rCDI and who had other risk factors for CDI recurrence [186]. The committee considers fidaxomicin the agent of choice for a first CDI recurrence when the initial episode was treated with vancomycin or metronidazole, and considers SoC + bezlotoxumab when the initial episode was treated with fidaxomicin.

Vancomycin taper and pulse

When other options for treatment of a first or second recurrent CDI episode are not available, i.e. fidaxomicin, bezlotoxumab and FMT, a vancomycin taper and pulse regimen may be considered. A secondary analysis of patients with recurrent CDI placebo arms of two RCTs found fewer recurrences with vancomycin taper ($n = 29$, recurrence rate 31%) or pulse ($n = 7$, 14%) than with vancomycin 1–2 weeks ($n = 83$, 43–71%) [219]. The mean number of prior episodes of these patients was 3.2 [219]. A small RCT that studied patients with four or five prior CDI episodes found no significant difference in recurrence rates of vancomycin taper treatment arm (44%) compared with a full course of vancomycin followed by FMT (56%). The analysis included only 28 patients, because the trial was terminated for futility to demonstrate superiority of FMT [220]. The tapering scheme used in the trial was: 2 weeks of vancomycin 125 mg orally four times daily, followed by 1 week 125 mg twice daily, then 1 week 125 mg daily, then 1 week 125 mg every second day, and finally 125 mg orally every third day for 1 week.

Other strategies

Follow on rifaximin after SoC treatment might also be effective for prevention of recurrent CDI [31,221]; however, concerns for resistance development remain and some European countries showed high percentages of resistance to rifampicin (the same class of antibiotics as rifaximin) in currently circulating *C. difficile* strains [222]. In the future, non-toxigenic *C. difficile* (NTCD), bacterial spores, bacterial consortia, or other live biotherapeutic products may provide a viable strategy to prevent CDI recurrences. An interesting phase 2 trial that are actively recruiting patients is investigating ACX-362E, which is a novel DNA polymerase IIIC inhibitor (NCT04247542).

VI. **What is the best treatment for multiple recurrent CDI?**

- Treatment options for a second or further CDI recurrence include FMT after SoC antibiotic pre-treatment or bezlotoxumab in addition to SoC antibiotic treatment. The choice between either depends on patients' characteristics, previous treatment, local regulations, availability and feasibility. For FMT an adequate multidisciplinary risk assessment is mandatory and FMT products should be available with standardized preparation and screening. *Weak, Moderate (FMT) / Low (bezlotoxumab)*

Prospective data on the treatment of second or further CDI recurrences is limited. A small RCT included 24 patients in the fidaxomicin treatment arm, with a median of four prior CDI episodes [223]. Of these patients, 13 (54%) had resolution of *C. difficile* associated diarrhoea at 8 weeks. Effectiveness of fidaxomicin (200 mg BID for 10 days) seems to decrease with multiple recurrences [218]. A report on the use of bezlotoxumab in Finland revealed that bezlotoxumab was mostly used in severely immunocompromised patients with (multiple) prior CDI episodes [224]. The

majority (73%) of 44 patients had not experienced a relapse at 3 months. Importantly, this study illustrates that FMT could be avoided in patients that were awaiting FMT. A report on Spanish real-world experience showed similar results: sustained cure at 12 weeks with bezlotoxumab was 75% in patients with a second or further recurrence ($n = 24$), while sustained cure was 93% in patients with a first recurrence [225]. Likewise, in a real-world experience report from the United States, sustained cure after bezlotoxumab treatment was 79% in patients with two or more recurrences ($n = 120$) and 90% in patients with one recurrence ($n = 49$) ever [226].

Multiple small RCTs and prospective cohorts studied FMT in patients with (multiple) recurrent CDI with success rates ranging from 44% to 100% with one infusion, and from 69% to 100% with multiple infusions [220,223,227–234]. It should be noted that the mode of FMT administration differs among these studies: duodenal or colonic infusion, instillation via enema or administration via capsules. However, only three RCTs used a control group that included recommended SoC antibiotics, vancomycin or fidaxomicin [223,227,229]. These trials found resolution of *C. difficile* associated diarrhoea in 65%, 81% and 92% after one infusion, and ≥90% after multiple infusions [223,227,229]. Results of registries both in The Netherlands and North America indicate cure rates with one FMT administration of 89% at 1–2 months [213,235]. We cannot underestimate the importance of standardized donor screening programs and best practices [236–239] to prevent transmission of enteropathogens and multidrug-resistant pathogens, as illustrated by two Food and Drug Administration (FDA) warnings [240,241]. FMT should preferably be performed with products from non-commercial and approved stool banks which undergo regularly independent quality assessments and also maintain a registry with appropriate follow up of donors and patients to recognize early and late complications of FMT. For standardization and screening of donor suspensions we refer to applying guidance documents [236,239]. Nevertheless, FMT may result in transfer of (innocuous) parasites or procarcinogenic bacteria with unknown long-term effects, or transfer of unknown infectious, pathogenic or carcinogenic agents [242,243]. In patients with inflammatory bowel disease (IBD), FMT may result in a disease flare, but this effect may be overestimated due to incomplete assessment of pre-FMT IBD activity [244]. This illustrates that the risks and benefits of FMT have to be carefully evaluated on a case-by-case basis. Ideally, candidates for FMT are carefully assessed by a multidisciplinary expert panel [245]. For the purpose of this guideline we will not discuss the various formulations, dosages and delivery routes for FMT. Efforts are undertaken to produce standardized faecal microbiota suspensions that are manufactured conforming to Good Manufacturing Practice to address regulatory issues.

The evidence supporting FMT is graded moderate: the RCTs were unblinded and small, however the outcome was consistent with a large effect size. The evidence supporting bezlotoxumab for multiple recurrent CDI is accumulating, though at this point based on retrospective analysis only. However, all reports indicate consistent sustained cure rates of 73% or higher for a second or further recurrences. Therefore evidence is upgraded from very low to low.

VII. **Can prognostic factors identify patients at risk for severe CDI?**

- The most important risk factors for severe CDI are older age (>65 years old) and presence of multiple comorbidities. *Strong, Moderate*

An important characteristic of our literature review is the selection of articles complying to predefined criteria and a strict prognostic GRADE approach, as described in the 'update methodology' section. To our knowledge, this approach has not been previously used for prognostic factors for CDI. Therefore results may differ from conclusions from previous systematic reviews. In general, the evidence was limited by the mainly retrospective nature of the data and small sample sizes. Hence, the overall quality of evidence regarding prognostic factors for severe CDI in the selected articles was graded very low to moderate.

We identified *older age* [29,32–36,41,43,44,47,50,54,56–59,61,66,71,72,74,75,77,78,81–83,88–90,92,94,97,101,103,106–108,110,111,113–115] and *presence of multiple comorbidities* [34–36,41–44,47,57,60,61,65,67,81,83,84,89,90,93,111,113,114] as the most important risk factors. This is supported by the fact that for these variables a dose effect was observed: the risk of severe disease was higher with increasing age or increasing number of comorbidities. We did not identify an association between a specific medical condition and severe CDI. Defining cut-off values for age and number of comorbidities is challenging since many studies used continuous values or varying cut-off values. Here, we define older age as >65 years old, as the majority of studies reported a higher risk for severe infection in patients aged over 65–70 years when compared with younger patients [29,32–34,50,54,56,59,61,66,72,74,75,81,88,89,92,94,101,107,108,110,115]. Due to the heterogeneity of studies reporting on comorbidities as a risk factor, we cannot define an exact number of comorbidities required to predict a severe course of CDI. The use of PPIs, H2 receptor antagonists and antibiotics did not appear to influence the risk of severe CDI, nor did the presence of *C. difficile* strains capable to produce binary toxin [32,34,36,38,39,42,44,52,54,57–60,67,68,71,72,74,77–79,81,83,84,87–90,94,97,103,108,111,113–116,118]. We observed a high level of inconsistency in the results of studies assessing infection with the *C difiicle* NAP1/027 strain as a risk factor. The results of the literature review and GRADING are discussed in more detail at https://doi.org/10.1016/j.cmi.2021.09.026 [289]. In the current guideline the distinction between mild and severe CDI currently has no consequences for choice of treatment (now that metronidazole is no longer recommended as first-line treatment). Therefore, the prediction of severe CDI is less relevant at this moment. However, new therapies and studies may lead to different insights in the future. We aimed to provide a complete and clear overview of available data on risk factors for severe CDI based on a systematic search and grading, which can be used and built upon in future guidelines.

VIII. **Can prognostic factors identify patients at risk for recurrent CDI?**

- Older age (>65 years old) is the most important risk factor for recurrent CDI. *Strong, Moderate*
- Patients with prior CDI episode(s) are at an increased risk for recurrent CDI. *Strong, Moderate*
- Patients with healthcare-associated CDI and prior hospitalization in the last three months are considered at increased risk for recurrent CDI. *Weak, Low*
- Patients with concomitant non-CDI antibiotic use after the diagnosis of CDI are considered at increased risk for recurrence of CDI. *Weak, Very low*
- Patients using PPIs started during/after CDI diagnosis are considered at increased risk for recurrent CDI. *Weak, Very low*

As mentioned in the previous paragraph, an important characteristic (albeit limitation or strength) of our analysis is the selection of articles complying to predefined criteria and a strict GRADE approach. We found that the overall quality of evidence for the prognosis of recurrent CDI was low to moderate. Most of the studies were retrospective, with a high to moderate risk of bias. A

complete overview and discussion of all risk factors studied is provided at https://doi.org/10.1016/j.cmi.2021.09.026 [289].

Older age was the only risk factor for which we found a moderate to large effect size and a dose dependent effect [25,106,108,119,120,122–125,127,129–135,137–142,144–155]. In line with the prognostic factors for severe CDI we define older age as >65 years old.

Patients with *healthcare-associated CDI* have a higher risk of recurrence than patients with community-acquired CDI [108,122,123,127,142,145,146,151–153]. This is supported by the association of prior hospitalization (within 3 months) and CDI recurrence [122,127,131,133,139,144,147,152].

In the 23 included studies that investigated *Proton pump inhibitor (PPI)* use, univariate analysis did not show a clear association with rCDI, while on multivariate analyses there appeared to be an association [106,119,120,123,129,130,132,133,135,136,138,140,142,146,147,149–155,157]. However, the quality of evidence was low. Bias may have arisen here as most studies did not include PPIs in multivariate analyses when there was no significant association in univariate analysis. Several meta-analyses suggest that PPI use is a risk factor for rCDI [246–249]. PPI prescribed during or shortly after initial CDI appears to be associated with an increased risk of rCDI, but with a low quality of evidence. See reference at https://doi.org/10.1016/j.cmi.2021.09.026 [289].

The data on *prior CDI episodes* as a risk factor was inconsistent [108,122–124,131,133,141,146], though the two prospective studies of higher quality found a clear association between previous recurrence and a subsequent CDI episode on multivariate analysis [108,141]. Furthermore, data of the pivotal trials on fidaxomicin and bezlotoxumab show higher recurrences rates in patients with a previous CDI episode [166,167,185,186,250]. Consequently, we have upgraded the level of evidence from low to moderate.

Data on *concomitant non-CDI antibiotic use* was also conflicting [120,128,134,137,142,146,148,150]. A high-quality prospective study points towards no significant association in both uni- and multivariate analysis [137]. However, several case–control studies have identified antibiotic use as an important risk factor for CDI, most notably fluoroquinolones, cephalosporins, carbapenems and clindamycin use [251–256]. Overall, we consider patients with concomitant non-CDI antibiotic use at increased risk for recurrent CDI.

We found insufficient evidence to consider severe CDI [120,123,125,130,135,141–143,149,153], and presence of comorbidities as risk factors for recurrent CDI [25,60,108,119,120,122,123,125,127,129–135,137,139–156]. Severe CDI and immunocompromised status were prespecified risk factors for CDI recurrence in the MODIFY trails, although in the placebo arms the CDI recurrence rate was lower in the severe CDI subgroup (28/125, 22%) and similar in the immunocompromised subgroup (42/153, 27%) when compared with the overall placebo arm (206/773, 27%) [185]. The *C. difficile* ribotype 027 strain was not evidently associated with CDI recurrence [108,120,128,146,150]. Of note, in the placebo arms of the MODIFY trials the recurrence rate for patients with ribotypes 027/078/244 was 41%. We did not find changes in white blood cell count, albumin, creatinine and C-reactive protein levels at the time of admission to be clear prognostic markers for recurrent CDI [108,124,131,134,135,142,145–149,151,152].

IX. Is there a place for prophylaxis for prevention of CDI?

- Routine administration of probiotics to prevent CDI when on antibiotic treatment is not recommended. *Strong, low*
- Routine prophylaxis with anti-CDI antibiotics when on systemic antibiotic treatment is not recommended. *Good practice statement*
- In very selected patients with a history of multiple recurrent CDI precipitated by systemic antibiotic use, prophylaxis with microbiota sparing anti-CDI antibiotics may be warranted, after carefully balancing the risk and benefits, and after consultation with an Infectious Diseases or Clinical Microbiology specialist. *Good practice statement*

Prophylaxis with probiotics

The previous ESCMID guideline concluded that there was insufficient evidence to support administration of probiotics, toxin-binding resins and polymers or monoclonal antibodies for the treatment of non-severe disease [1]. An updated Cochrane review on the use of probiotics for prevention of CDI found that probiotics are effective in trials with a *C. difficile* associated diarrhoea baseline risk of >5% (NNTB = 12; moderate certainty evidence) [257]. We consider such a high incidence not representative of clinical practice; the PLACIDE trial for example found occurrence of CDI to be around 1% in patients ≥65 years with iv antibiotics. Further, the trials that were included in the Cochrane meta-analysis used different probiotic formulations which complicates interpretation of the results. For example, a recent retrospective cohort study (n = 8763) found that coadministration of *S. boulardii* led to a reduced risk of hospital onset CDI: OR 0.57 with a CDI incidence of 0.66% [258]. In contrast, the results of a large RCT, the PLACIDE trial (n = 2941) found no effect of lactobacilli and bifidobacteria formulation on incidence of CDI [259]. Probiotics mat actually delay microbiome reconstitution after antibiotic treatment [260], and concerns about adverse effects remain as illustrated by increased mortality in a pancreatitis trial [261].

Prophylaxis with CDI antibiotics

The use of CDI antibiotics for primary prevention of CDI has not been discussed in previous ESCMID and IDSA guidelines [1,3]. However, several recent retrospective observational studies have been published that reported a 5–30% reduction in CDI occurrence with oral vancomycin prophylaxis in patients receiving broad-spectrum antibiotics [257,262–268]. These studies in general focused on patients considered at risk for CDI, such as haematological patients, patients with a prior CDI episode, stem cell transplant patients or solid organ transplant patients. An open label RCT (n = 100) with a follow-up of 3 months found a benefit of oral vancomycin prophylaxis vs. no prophylaxis (CDI occurrence 0% vs. 16%) in patients aged 60 years or older who received systemic antibiotics and who had prior hospitalization with systemic antibiotic therapy in the previous month [269]. It should be noted that the CDI incidence of 16% in the placebo group was rather high. A placebo-controlled RCT in patients undergoing stem cell transplantation with planned fluoroquinolone prophylaxis found no difference between fidaxomicin prophylaxis and placebo in the composite end-point of prophylaxis failure (confirmed CDI, receiving CDI active medication, missing CDI assessment) [270]. However, follow-up was limited to 30 days and a sensitivity analysis found a 6.4% reduction (95% CI 2.2–10.6) in CDI occurrence with fidaxomicin prophylaxis. We acknowledge the potential benefit of prophylaxis in selected patients, but are cautious with widespread application because of potential side-effects, microbiome distortion, the potential for development or acquisition of antimicrobial resistance and an associated increased risk for recurrent CDI [271,272]. Some studies on vancomycin prophylaxis have attempted to assess the risk for VRE colonization [266,268,269,273,274]. However, these assessments are hampered by short follow-up, unclear microbiological methods or a focus on

VRE infection rather than colonization. Therefore, concerns regarding resistance selection and development remain. Overall, the committee does not support routine prophylaxis with CDI antibiotics when on systemic antibiotic treatment. However, we feel that in very selected patients with a history or multiple recurrent CDI incited by systemic antibiotic use, prophylaxis with microbiota sparing CDI antibiotics may be warranted, after carefully balancing the risk and benefits, and after consultation with an Infectious Diseases or Clinical Microbiology specialist.

Alternative preventive strategies

A novel approach for primary prevention of CDI is co-administration of a poorly absorbed beta-lactamase (ribaxamase, SYN004) when administering broad-spectrum antibiotics [275]. A phase 2b trial ($n = 412$) found a 2.4% risk reduction for CDI occurrence when co-administering ribaxamase with ceftriaxone, although the lower boundary of the 95% CI crossed the border of no effect (-0.6). Clinical development of ribaxamase is ongoing. Another approach for primary prevention might be active immunization. Although preclinical studies have been promising, a phase 3 *C. difficile* toxoid vaccine trial was terminated because of futility and clinical development of this vaccine candidate was stopped [276].

Other considerations

The role of probiotics and ancillary treatment strategies such as FMT and bezlotoxumab have been discussed above. We did not identify new trials on the use of intravenous immunoglobulins (IVIGs) that allow for recommendations on the use of IVIG.

Regarding optimal CDI therapy during pregnancy there remains a paucity of data. Pregnant or breast-feeding woman are typically excluded from pivotal trials. A post-market study on fidaxomicin in patients with a medical condition of specific interest did not include pregnant women [195]. Fidaxomicin, oral vancomycin and metronidazole were originally classified as pregnancy category B by the FDA (no evidence in risk studies), whereas iv vancomycin hydrochloride was designated category C (risk cannot be ruled out) [277–280]. It should be noted the pregnancy labelling scheme has recently been revised by the FDA from alphabetical to descriptive. Importantly, some pre-constituted iv formulation of vancomycin contain the excipients PEG 400 and NADA and therefore cannot be used for oral administration in pregnant woman, as these have caused foetal malformations in animal reproductive studies [281]. Vancomycin use (iv) in the second and third trimester ($n = 10$) did not result in foetal nephrotoxicity or sensoneural hearing loss at 3 months [282]. Perinatal iv vancomycin prophylaxis did not result in sensoneural hearing loss of the new-born, or any major adverse events in mothers ($n = 55$) and newborns [282]. Vancomycin crosses the placenta, but oral vancomycin is minimally absorbed from the gastrointestinal tract, although measurable serum levels may occur [288]. Therefore, it is reasonable to use vancomycin oral tablets during pregnancy. Therapeutic drug monitoring may be considered. During pregnancy, prolonged administration and high dosing of vancomycin should be discouraged as this is a proposed risk factors for measurable serum concentrations [288]. Fidaxomicin is also poorly absorbed from the gastrointestinal tract and resulted in serum levels around the limit of detection (5 ng/mL) in a phase 1 study with healthy volunteers [283]. No foetal harm was found in reproduction studies in rats and rabbits [277]. Bezlotoxumab has not been investigated in pregnant woman or animal reproductive and developmental studies. In the absence of clinical data and experience with fidaxomicin, we prefer vancomycin during pregnancy. Fidaxomicin may be used after carefully balancing the risks and benefits.

The timing of the start of empirical treatment was not included in our PICO search. The 2017 IDSA guideline advised to start empiric treatment only when a significant delay in laboratory confirmation is expected or when dealing with fulminant CDI (weak recommendation) [3]. We concur with the suggested approach and strongly discourage the start of empirical therapy without diagnostic testing in other cases. In the absence of evidence and based on clinical experience, we also discourage treatment beyond the recommended standard duration of 10–14 days with SoC antibiotics because of lack of response or co-administered antibiotic treatment.

We have retrieved several cost-effectiveness studies. These studies found that different treatments were (most) cost-effective: vancomycin [284], fidaxomicin [173–180], bezlotoxumab [175,188,189] and FMT [285–287] have all been described as cost-effective. Decreased recurrence rate and subsequent costs of re-hospitalization and complications may result in cost-effectiveness depending on the willingness-to-pay threshold per gained quality-adjusted life-year. Importantly, many cost-effectiveness studies are co-authored or funded by employees of pharmaceutical companies [176–180,188,189]. However, selection of CDI treatments based on cost-benefit analysis of health-economic studies is beyond the scope of this guideline and will remain an interesting next project, though it is probably better to perform these studies on a national level.

Formulating guideline recommendations, especially for a multinational ESCMID guideline is challenging, considering differences in regulations, availability and reimbursements of treatments. On the one hand one should advise the best treatment available, but on the other hand a guideline that recommends agents that the majority of physicians will not prescribe due to economic restraints is useless. We acknowledge that each country or local institution should adapt the guideline to its local economic situation. With this guideline, we have aimed to make evidence-based recommendations for the best treatments available and offer alternatives when the treatment of first choice might not be available or feasible due to economic restraints, or when access to the preferred agent is limited.

Research gaps

While drafting this guideline and appraising the evidence for the optimal treatment of CDI we identified several key topics that deserve further attention and will be of great interest for future treatment algorithms. The most important topics for future research are:

1. Assessing the optimal treatment in severe-complicated and refractory CDI.
2. Comparing the effectiveness of bezlotoxumab and FMT for the treatment of multiple recurrent CDI.
3. Assessing the benefit of adding bezlotoxumab to fidaxomicin treatment.
4. Discontinue therapy with the inciting antimicrobial agent in non-severe CDI as a single intervention.
5. Investigation into optimal CDI treatment and treatment algorithms in large scale trials independent from pharmaceutical industry (i.e. not as sponsor or subsidising party).
6. Optimal identification of patients at risk for recurrent CDI. These patients might be offered adjuvant bezlotoxumab or FMT earlier in the course of disease.
7. Insight into the exact mechanism of FMT for CDI treatment. This might enable a more regulated and standardized preparation process of FMT products.

8. Insight into the benefit of FMT and bezlotoxumab in specific populations such as patients with IBD and the immunocompromised hosts.
9. Assessment of other adjunctive treatments such as NTCD and follow-on rifaximin.
10. Effectiveness of microbial consortia and spore formulations that are under development.
11. Selection of CDI treatments based on independent cost-benefit analysis of health-economic studies in different settings and populations, e.g. the general CDI population, patients with IBD, the hospitalized versus non-hospitalized patient, and the immunocompromised host.

Transparency declaration

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Appendix A. Supplementary data

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