

# European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for *Clostridium difficile* infection (CDI)

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## Abstract

*Clostridium difficile* infection (CDI) is a potentially fatal illness with an increasing incidence worldwide. Despite extensive ongoing research into CDI treatment, management of CDI still poses important problems, such as a high propensity to relapse and refractoriness to treatment, especially when there is an ileus and oral drugs cannot be administered. This guideline evaluates the available literature, discusses criteria for disease severity and provides recommendations for CDI treatment, indicating level of evidence and strength of recommendation.

**Keywords:** *Clostridium difficile*, guidelines, treatment

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## Summary of definitions and recommendations

### Definitions

Episode of CDI :

1. a clinical picture compatible with CDI and microbiological evidence of toxin-producing *Clostridium difficile* in stool without evidence of another cause of diarrhoea or
2. pseudomembranous colitis (as diagnosed during endoscopy, after colectomy or on autopsy)

Clinical pictures compatible with CDI:

1. diarrhoea :
  - a. loose stools, i.e. taking the shape of the receptacle or corresponding to Bristol stool chart types 5–7 and
  - b. a stool frequency perceived as too high by the patient
2. ileus :
  - a. signs of severely disturbed bowel passage such as vomiting and absence of stool and
  - b. radiological signs of bowel distension

3. toxic megacolon :

- a. radiological signs of distension of the colon and
- b. signs of a severe systemic inflammatory response

Signs of severe colitis:

- fever (core body temperature > 38.5°C)
- rigors (uncontrollable shaking and a feeling of cold followed by a rise in body temperature)
- hemodynamic instability including signs of septic shock
- signs of peritonitis, including decreased bowel sounds, abdominal tenderness, rebound tenderness and guarding
- signs of ileus, including vomiting and absent passage of stool
- marked leukocytosis (leukocyte count > 15 × 10<sup>9</sup>/L)
- marked left shift (band neutrophils > 20% of leukocytes)
- rise in serum creatinine (>50% above the baseline)
- elevated serum lactate
- pseudomembranous colitis (endoscopy)
- distension of large intestine (imaging)
- colonic wall thickening including low-attenuation mural thickening (imaging)
- pericolonic fat stranding (imaging)
- ascites not explained by other causes (imaging)

Severe CDI :

an episode of CDI with one or more signs of severe colitis.

CDI without signs of severe colitis in patients with advanced age ( $\geq 65$ ), serious comorbidity, ICU admission, or immunodeficiency may be regarded as severe.

CDI treatment response :

1. stool frequency as perceived by the patient decreases or stool consistency improves after 3 days and
2. no new signs of severe colitis develop

CDI treatment failure :

absence of CDI treatment response

CDI recurrence :

1. stool frequency as perceived by the patient increases for two consecutive days and stools become looser or new signs of severe colitis develop and
2. microbiological evidence of toxin-producing *C. difficile* in stools without evidence of another cause of diarrhoea after an initial CDI treatment response

## Recommendations

(implementation category between brackets)

1. Antiperistaltic agents and opiates should be avoided. (B-II)
2. In general, strive to use antibiotics covering a spectrum no broader than necessary and narrow the antibiotic spectrum of treatment after results of cultures and/or susceptibility tests become known. (B-III)
3. Mild CDI (stool frequency  $< 4$  times daily; no signs of severe colitis), clearly induced by the use of antibiotics, may be treated by stopping the inducing antibiotic. Observe patients closely for any signs of clinical deterioration and place on therapy immediately if this occurs. (B-III)
4. Treatment for an initial episode and a first recurrence of CDI:

If oral therapy is possible:

- non-severe: metronidazole 500 mg tid orally for 10 days (A-I)
- severe: vancomycin 125 mg qid orally for 10 days (A-I)

If oral therapy is impossible:

- non-severe: metronidazole 500 mg tid intravenously for 10 days (A-III)
- severe: metronidazole 500 mg tid intravenously for 10 days (A-III) + intracolonic vancomycin 500 mg in 100 mL of normal saline every 4–12 h (C-III) and/or vancomycin 500 mg qid by nasogastric tube (C-III)

5. Colectomy should be performed to treat CDI in any of the following situations:

- perforation of the colon
- systemic inflammation and deteriorating clinical condition not responding to antibiotic therapy; this includes the clinical diagnoses of toxic megacolon and severe ileus. Colectomy should preferably be performed before colitis is very severe. Serum lactate may, inter alia, serve as a marker for severity (operate before lactate exceeds 5.0 mmol/L).

6. Treatment for a second recurrence of CDI and later recurrences:

If oral therapy is possible:

- vancomycin 125 mg qid orally for at least 10 days (B-II)
- consider a taper (for example, decreasing daily dose with 125 mg every 3 days)/pulse (for example, a dose of 125 mg every 3 days for 3 weeks) strategy (B-II)

If oral therapy is impossible:

- metronidazole 500 mg tid intravenously for 10–14 days (A-III) plus retention enema of vancomycin 500 mg in 100 mL of normal saline every 4–12 h (C-III) and/or vancomycin 500 mg qid by nasogastric tube (C-III)

7. In all the above-mentioned cases, oral vancomycin may be replaced by teicoplanin 100 mg twice daily, if available.

## Introduction

*Clostridium difficile* infection (CDI) may arise when a patient's bowel is colonized by *C. difficile* after ingestion of spores; the spores subsequently germinate and the vegetative bacteria start producing toxins. Colonization is inhibited by the normal intestinal flora, which is hypothesized to compete with *C. difficile* for nutrients and space on the mucosal surface. Therefore, the use of antibiotics is the most important risk factor for CDI. The vegetative state of the bacterium is resistant to a varying but broad range of antibiotics and the spores are highly resistant to antibiotics and can withstand many forms of chemical attack, e.g. most high-level disinfectants. The most important problem in treating CDI is the high recurrence rate. Various factors, such as the need to continue treatment with the inciting antibiotic, have been associated with this (see 'Prognostic criteria and criteria for disease severity'). The antibiotics needed to kill the vegetative bacteria do not kill the spores and might even contribute to recurrence by disrupting the normal gut flora even further. Individuals who suffer a recurrence may enter a repetitive cycle of recurrences, leading to exhaustion and

protein-losing enteropathy. A second problem in treating CDI is the fact that, in severe forms of CDI, antibiotics may fail, resulting in progressive colitis with high morbidity and mortality. Several factors may play a role in this, such as a time lag for antibiotics to reach adequate intracolonic levels [1] and possibly the fact that a systemic inflammatory response due to severely damaged colonic mucosa may persist some time after removal of the etiological agent.

## Objective

Since treatment of CDI can be complicated by these many problems, the need for this evidence-based guideline seems obvious. The objective of this study was to evaluate the available evidence concerning treatment of CDI and formulate recommendations for treatment.

## Update Methodology

Studies on CDI treatment were found with a computerized literature search of PUBMED using the terms '*Clostridium difficile* AND (treatment OR trial)'. All randomized and non-randomized trials investigating the effect of an intervention on the clinical outcome (resolution or recurrence of diarrhoea; incidence of complications) of CDI published in any language were included. Studies investigating carriage or other purely microbiological parameters were not considered sufficient evidence for treatment strategies. The resulting literature from 1978 was reviewed and analyzed. Furthermore, systematic reviews from the Cochrane Library and the guidelines of the Infectious Diseases Society of America (IDSA) were evaluated. Recommendations were based on a systematic assessment of the quality of evidence. For indicating the quality of evidence and weight of recommendations the system of the Canadian Task Force on the Preventative Health Care was used (Table 1).

## Definitions

### Criteria for the diagnosis of CDI

Pseudomembranous colitis, which is an endoscopic diagnosis, is caused by *C. difficile* in the vast majority of cases and therefore may suffice for the diagnosis of CDI in the absence of an obvious other cause. In the rest of the cases, a combination of symptoms and signs, in conjunction with microbiological evidence of toxin-producing *C. difficile* in stools and the absence of another cause is necessary. Compatible clinical

**TABLE 1. Strength of recommendation and quality of evidence according to the Canadian Task Force on Preventative Health Care**

#### Strength of recommendation

- A: Good evidence to support a recommendation
- B: Moderate evidence to support a recommendation
- C: Poor evidence to support a recommendation

#### Quality of evidence

- I: Evidence from  $\geq$ one properly randomized, controlled trial
- II: Evidence from  $\geq$ one well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from  $\geq$ one centre); from multiple time-series; or from dramatic results from uncontrolled experiments
- III: Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

cal pictures are diarrhoea, ileus and toxic megacolon. Diarrhoea is defined as loose stools, i.e. taking the shape of the receptacle or corresponding to Bristol stool chart types 5–7 [2], plus a stool frequency perceived as too high by the patient. Faecal incontinence may be a part of the disease. Ileus in the context of CDI is defined as signs of severely disturbed bowel passage such as vomiting and absence of stool, combined with radiological signs of bowel distension. Toxic megacolon is defined as radiological signs of distension of the colon combined with signs of a severe systemic inflammatory response. The above-mentioned criteria are largely in line with the recommendations of the American Ad Hoc *C. difficile* surveillance working group [3] and the European Study Group for *C. difficile* [4].

### Prognostic criteria and criteria for disease severity

Outcome measures of CDI comprise complications, mortality and recurrences. It is difficult to set a rigid set of criteria for the assessment of prognosis and severity of CDI. First, surprisingly little research has been done on clinical predictors of outcome. Second, prognostic markers have not been validated in prognostic studies. Third, prognosis depends on disease severity and other prognostic factors, such as age, comorbidity, admission to an intensive care unit, and anti-peristaltic and immunosuppressive medication. It is unknown what the weight of these prognostic factors is in comparison with assessed disease severity.

Possible features of severe colitis that have been linked to a higher chance of recurrence are faecal incontinence [5], the endoscopic finding of pseudomembranous colitis [6], and longer cumulative duration of previous episodes of CDI [7]. Leukocytosis (leukocyte count  $> 20 \times 10^9/L$ ) has been associated with a high mortality rate in CDI [8], a complicated course [9], refractoriness to therapy [6] and risk of recurrence [9]. Hypoalbuminaemia ( $< 25 \text{ g/L}$ ) has also been associated with a high mortality rate in CDI [8] and refractoriness to therapy [6,10,11]. However, since it may be seen as a result of malnutrition or protein-losing enteropathy in

longstanding disease, as a negative acute phase protein in acute disease, and as a marker for comorbidity (e.g. liver cirrhosis, nephrotic syndrome, wasting) this feature may be too heterogeneous to be a reliable marker of severe disease.

Factors associated with unfavourable outcome that are not direct markers of severe colitis include advanced age, comorbidity, a decreased antibody response, gastric acid suppressants, and the need to prolong inciting antibiotic therapy. Advanced age has been associated with a complicated course [12] and recurrence [9,12]. Comorbidity has been associated with a high mortality rate [8] and a higher chance of recurrence [13]. A decreased humoral immune response against Clostridial toxins TcdA and TcdB has been associated with a higher chance of recurrence and longer duration of symptoms [14,15], although other studies did not find this association. Use of H<sub>2</sub>-antagonists has been associated with a higher chance of recurrence [5] and use of proton pump inhibitors has been associated with refractoriness to therapy [16]. Also, the need to continue the use of inciting antibiotic has been associated with refractoriness to therapy [16]. However, it is unclear whether the use of gastric acid suppressants and the need to continue antibiotics have a causal relationship with unfavourable outcome or whether they are markers of more severe comorbidity. Obviously, admission to an ICU is an unfavourable prognostic factor [6,11].

#### Markers of severe colitis

Markers that could reasonably be assumed to correlate positively with the severity of colitis are mentioned below, although we must stress that the prognostic value of these markers is uncertain. Obviously, markers should not be attributable to a concomitant disease, if they are to be regarded as a marker of severe CDI. Ideally, markers should be obtainable at the earliest stage in the disease course to be a predictor of outcome.

#### Physical examination.

- fever (core body temperature > 38.5°C)
- rigors (uncontrollable shaking and a feeling of cold followed by a rise in body temperature)
- haemodynamic instability including signs of distributive (vasodilatory, septic) shock
- signs of peritonitis, including decreased bowel sounds, abdominal tenderness, rebound tenderness and guarding
- signs of ileus including vomiting and absent passage of stool

Admixture of blood with stools is rare in CDI and the correlation with severity of disease is uncertain.

#### Laboratory investigations.

- marked leukocytosis (leukocyte count > 15 × 10<sup>9</sup>/L)
- marked left shift (band neutrophils > 20% of leukocytes)
- rise in serum creatinine (>50% above the baseline)
- elevated serum lactate

#### Colonoscopy or sigmoidoscopy.

- pseudomembranous colitis

There is insufficient knowledge concerning the correlation of endoscopic findings compatible with CDI, such as oedema, erythema, friability and ulceration, and the severity of disease.

#### Imaging.

- distension of large intestine
- colonic wall thickening including low-attenuation mural thickening
- pericolonic fat stranding
- ascites not explained by other causes

The correlation of haustral or mucosal thickening, including thumbprinting, pseudopolyps and plaques, with severity of disease is unclear.

#### Prognostic markers other than disease severity

- advanced age (≥65)
- serious comorbidity and ICU admission
- immunodeficiency

#### Criteria for response, failure and recurrence in the treatment of CDI

Treatment response is present when either stool frequency decreases or stool consistency improves, and parameters of disease severity (clinical, laboratory, radiological) improve, and no new signs of severe disease develop. In all other cases, treatment is considered a failure. It is only reasonable to evaluate treatment response 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 [1,16]. After clinical response, it may take weeks for stool consistency and frequency to become entirely normal [17]. Recurrence is present when, after an initial response, stool frequency increases for two consecutive days and stools become looser, or new signs of severe disease develop and microbiological evidence of toxin-producing *C. difficile* in stool is present without evidence of another cause. It is impossible to distinguish recurrence due

to relapse (renewed symptoms from already present CDI) from recurrence due to reinfection in daily practice.

## Overview of Medical Treatment Options Available for CDI

There is an increasing body of evidence concerning treatment of CDI, both initial (Table 2 [6,18–32], Table 3 [17,33–36] and Table 4 [9,11,13,15,37–48]) and recurrent episodes (Table 5 [33,49–52] and Table 6 [7,53–68]). Tables 2, 3 and 5 report the evidence from randomized trials, with comments on methodology. It is difficult to compare these studies because of differences in diagnostic criteria, exclusion of co-pathogens, severity of CDI, co-morbidity, inciting antibiotics and concomitant use of antibiotics. Moreover, these studies usually have endpoints of clinical cure or microbiological cure. However, the definition of clinical cure and recurrence is highly variable. Patients seldom have normal stools directly after treatment of CDI. With respect to microbiological cure, the significance of persistently or recurrently positive stool toxin tests or cultures is not clear. Furthermore, it is not possible to distinguish relapse from reinfection. Lastly, the number of participants in most trials is small. In conclusion, we need more randomized controlled trials on CDI treatment.

It is important to realize that several experimental treatment options are not widely available, such as toxin-binding resins and polymers and specific immunotherapy.

### Discontinuing the inciting antibiotic without antibiotic treatment

The rate of spontaneous resolution is unknown in patients with mild CDI. In one study [40], the spontaneous recovery rate in hospitalized patients with diarrhoea and a positive toxin assay who did not undergo endoscopy or had no pseudomembranous colitis on colonoscopy was 33%. More antibiotics after discontinuing the inciting antibiotic might increase the chance of subsequent recurrence, since gut flora will be exposed to a second antibiotic with a different spectrum (i.e. metronidazole). It may therefore be prudent to discontinue the inciting antibiotic only in the case of mild CDI, while closely monitoring the patient.

### Oral antibiotics

There is only one placebo-controlled trial investigating the effectiveness of antibiotics for CDI and it had very few participants. Several antibiotics have been compared to each other. Oral administration of the glycopeptides vancomycin and teicoplanin appears most effective in inducing both clinical cure and microbiological cure, especially in severe CDI. The

difficulty is how to define severe CDI. In one prospective, randomized, and blinded study [6], which evaluated the efficacy of vancomycin vs. metronidazole according to disease severity, the diagnosis of severe CDI was based on age, body temperature, albumin level and leukocyte count. Vancomycin proved to be superior to metronidazole in cases of severe CDI. Two trials investigating the efficacy of the toxin-binding polymer, tolevamer [34,35], also showed the superiority of oral vancomycin over metronidazole in severe cases. A recent Cochrane systematic review [70] has examined the available literature on antibiotic treatment options for CDI and concluded that teicoplanin is the most effective antibiotic treatment for moderate to severe CDI and vancomycin has no superiority over metronidazole. However, this review did not include the above-mentioned recent studies. It seems likely that the effectiveness of teicoplanin and vancomycin is in the same range.

Oral metronidazole is also very effective in inducing a response and has the advantage of low cost and the fact that it may contribute less to the emergence of vancomycin-resistant enterococci.

If metronidazole is indeed less effective than glycopeptides, this may be explained by the low levels metronidazole reaches in the colon, since it is absorbed in the small intestine and then excreted again in the bile and in the inflamed colon, whereas glycopeptides are not absorbed. Different doses of oral vancomycin have been used, but only one small randomized trial [22] has compared high- vs. low-dose vancomycin and found no statistically significant difference. Since low doses of oral vancomycin result in high concentrations in stool, there is no need to treat with high doses, except in an attempt to reach sufficient concentrations in the colon when administering vancomycin by nasogastric tube in a patient with ileus. Given the poor faecal concentrations of metronidazole achieved following a 500 mg 8-hourly dose, lower doses (e.g. 250 mg at a 6–8 hourly dose) should be less effective. Several studies, however, have used lower doses, usually with good results [6,7,19,27,28,34,35]. Even a modest increase in the MIC of metronidazole for *C. difficile* might result in insufficient faecal antibiotic concentrations to inhibit (vegetative) bacteria. Metronidazole resistance is to be regarded as exceedingly rare. However, the emergence of reduced susceptibility to metronidazole has recently been reported in UK *C. difficile* strains [1,71,72]. No reduced susceptibility to vancomycin was observed. The exact mechanism of reduced susceptibility to metronidazole remains to be determined. Notably, there is also evidence that inactivation of metronidazole occurs in the presence of gut contents, possibly due to metabolism by enterococci [73].

Oral bacitracin and fusidic acid seem to be less effective than vancomycin and metronidazole, respectively, although

**TABLE 2.** Randomized controlled trials of antibiotic treatment of initial CDI. Initial cure rate as a percentage of all patients and relapse rate as a percentage of initially cured patients

Trial	Treatment	Number of patients	Cure (%)	Relapse (%)
Keighley <i>et al.</i> [18]	Vancomycin 125 mg qid, 5 days	9	78	0
	Placebo	7	14	–
No clear case definition. No description of allocation of treatment. Only data of patients with toxin-positive stool shown. Unclear length of follow-up and incidence or relapse in placebo group. $p < 0.02$ for comparison of cure rates				
Teasley <i>et al.</i> [19]	Vancomycin 500 mg qid, 10 days	32	100	19
	Metronidazole 250 mg qid, 10 days	32	97	6
Only data of patients with toxin-positive stools or pseudomembranous colitis shown. Per-protocol analysis. Follow-up 21 days. Differences not statistically significant				
Young <i>et al.</i> [20]	Vancomycin 125 mg qid, 7 days	21	86	33
	Bacitracin 20 000 U qid, 7 days	21	76	42
Double-blind. 25% drop-out during follow-up of bacitracin group. Follow-up 5 weeks. Differences not statistically significant				
Dudley <i>et al.</i> [21]	Vancomycin 500 mg qid, 10 days	15	100	20
	Bacitracin 25 000 U qid, 10 days	15	80	42
Double-blind. Patients had leukocytosis, fever or abdominal pain. 29% drop-out in vancomycin group, 12% in bacitracin group. Per-protocol analysis. Unclear definition of failure ('worsening during treatment'). Failing patients crossed over to alternate drug. Interruption of study drug in vancomycin group for a mean of 2.8 days and in bacitracin group for a mean of 1.8 days. Unclear length of follow-up. Differences not statistically significant				
Fekety <i>et al.</i> [22]	Vancomycin 125 mg qid, mean 10.6 days	24	100	21
	Vancomycin 500 mg qid, mean 10.1 days	22	100	18
Variable duration of therapy. 18% dropout rate. Per-protocol analysis. Unclear length of follow-up. Differences not statistically significant				
Boero <i>et al.</i> [23]	Vancomycin 500 mg bid, 10 days	10	100	–
	Rifaximin 200 mg tid, 10 days	10	90	–
Article in Italian. Patients had diarrhoea, abdominal pain and fever. No description of allocation of treatment. Unclear definition of cure. Differences not statistically significant				
de Lalla <i>et al.</i> [24]	Vancomycin 500 mg qid, 10 days	20	100	20
	Teicoplanin 100 mg bid, 10 days	26	96	8
No description of allocation of treatment. Per-protocol analysis. Unclear length of follow-up. Differences not statistically significant				
Wiström [25]	Teicoplanin 100 mg qid, 3 days, followed by 100 mg bid, 4 days	24	96	35
	Teicoplanin 100 mg bid, 7 days	23	70	50
Double-blind. Outcome of 'improvement, but not cure' (2 loose stools per day or 1 loose stool per day with fever or cramps) was counted as failure. Three patients with improvement in bid group; 1 in qid group. Follow-up 5 weeks. $p 0.02$ for comparison of cure rates. Relapse rates not statistically different				
Wenisch <i>et al.</i> [26]	Vancomycin 500 mg tid, 10 days	31	94	17
	Metronidazole 500 mg tid, 10 days	31	94	17
Wullt [27]	Teicoplanin 400 mg bid, 10 days	28	96	7
	Fusidic acid 500 mg tid, 10 days	29	93	30
Follow-up 30 days. Only statistically significant difference was relapse rate of fusidic acid vs. teicoplanin ( $p 0.042$ )				
Musher <i>et al.</i> [28]	Metronidazole 400 mg tid, 7 days	55	93	30
	Fusidic acid 250 mg tid, 7 days	59	83	30
Double-blind. 13% drop-out during treatment; 15% further drop-out during follow-up. Per-protocol analysis. Follow-up 35 days. Differences not statistically significant				
Musher <i>et al.</i> [28]	Metronidazole 250 mg qid, 10 days	34	82	30
	Nitazoxanide 500 mg bid, 7 days	40	90	26
	Nitazoxanide 500 mg bid, 10 days	36	89	16
No definition of relapse. Double-blind. 23% drop-out during treatment. Per-protocol analysis. Follow-up 31 days. Differences not statistically significant				
Lagrotteria <i>et al.</i> [29]	Metronidazole 500 mg tid, 10 days	20	65	38
	Metronidazole 500 mg tid + rifampicin 300 mg bid, 10 days	19	63	42
Intention-to-treat analysis. Follow-up 40 days. Differences not statistically significant				
Zar <i>et al.</i> [6]	Vancomycin 125 mg qid, 10 days	71	97	7
	Metronidazole 250 mg qid, 10 days	79	84	14
Double-blind. 13% drop-out during treatment. Per-protocol analysis. Follow-up 21 days. $p 0.006$ for comparison of cure rates. $p 0.27$ for comparison of relapse rates. The original protocol was stratified in a group with mild and a group with severe disease (based on age, fever, albumin level and leukocyte count), which resulted in a larger difference between cure rates in the group with severe disease and a statistically non-significant difference between cure rates in the group with mild disease				
Louie <i>et al.</i> [30]	Fidaxomicin 50 mg bid, 10 days	14	71	8
	Fidaxomicin 100 mg bid, 10 days	15	80	0
	Fidaxomicin 200 mg bid, 10 days	16	94	6
Open-label. Patients with signs of highly severe CDI (>12 bowel movements per day, vomiting, severe abdominal tenderness, ileus, WBC > 30, toxic megacolon) were excluded. Cure = complete resolution of diarrhoea. Follow-up 6 weeks after end of treatment				
Musher <i>et al.</i> [31]	Vancomycin 125 mg qid, 10 days	27	74	7
	Nitazoxanide 500 mg bid, 10 days	22	77	5
CDI = stool EIA for toxin A or B positive AND (temperature > 38.3°C OR abdominal pain OR leukocytosis). Patients with >1 episode in preceding 6 months. 12% dropout rate during treatment. Double-blind, placebo-controlled. Modified intention-to-treat analysis. Industry-sponsored. Cure = complete resolution of symptoms during 3 days after completion of therapy. Per-protocol analysis: 87% vs. 94% cure. Follow-up 31 days after start of treatment. No differences in severity subgroups. Differences not statistically significant				
Louie <i>et al.</i> [32]	Vancomycin 125 mg qid, 10 days	284	90	24
	Fidaxomicin 200 mg bid, 10 days	265	92	13
Unpublished trial				

this has not convincingly been demonstrated. Currently, there is insufficient evidence to advocate the use of the rifamycin derivative rifaximin, to which resistance has been

noted, and the antiprotozoal/anthelmintic nitazoxanide, which has been shown to be statistically similar to metronidazole in a small prospective randomized trial [28], but

**TABLE 3.** Randomized controlled trials of non-antibiotic treatment of initial CDI. Initial cure rate as a percentage of all patients and relapse rate as a percentage of initially cured patients

Trial	Treatment	Number of patients	Cure (%)	Relapse (%)
<b>Probiotics</b>				
McFarland <i>et al.</i> [33]	Vancomycin or metronidazole + <i>Saccharomyces boulardii</i> $2 \times 10^{10}$ CFU/day, 4 weeks	31	–	19
	Vancomycin or metronidazole + placebo	33	–	24
Double-blind. No control for type, duration or dose of antibiotic. Unclear definition of relapse. Follow-up 8 weeks after start of treatment. <i>p</i> 0.86 for comparison of relapse rates				
<b>Toxin-binding resins and polymers</b>				
Louie <i>et al.</i> [17]	Tolevamer 1 g tid, 14 days + placebo	94	60	16
	Tolevamer 2 g tid, 14 days + placebo	91	79	7
	Vancomycin 125 mg qid, 10 days + placebo	94	91	19
Non-inferiority trial. Patients with stool frequency >12 per day or abdominal pain were excluded. Tolevamer could be prolonged when inciting antibiotic could not be stopped. Double-blind. 23% drop-out. Per-protocol analysis. Cure rate of tolevamer 2 g non-inferior in comparison with vancomycin (Chow-test <i>p</i> 0.03). Non-inferiority of tolevamer 1 g compared with vancomycin could not be demonstrated. <i>p</i> 0.05 for comparison of relapse rates of tolevamer 2 g with vancomycin. Relapse rates of tolevamer 1 g and vancomycin not statistically different. Follow-up 6–8 weeks				
Louie <i>et al.</i> [34]	Tolevamer 3 g tid, 14 days	266	47	3
	Vancomycin 125 mg qid, 10 days	134	81	23
	Metronidazole 375 mg qid, 10 days	143	72	27
Unpublished trial				
Bouza <i>et al.</i> [35]	Tolevamer 3 g tid, 14 days	268	42	6
	Vancomycin 125 mg qid, 10 days	125	81	18
	Metronidazole 375 mg qid, 10 days	135	73	19
Unpublished trial				
<b>Immunotherapy</b>				
Lowy [36]	MDX-066 and MDX-1388 (intravenously administered monoclonal antibodies against TcdA and TcdB) after standard antimicrobial therapy	101	–	7
	Placebo after standard antimicrobial therapy	99	–	25
Unpublished trial. Follow-up 12 weeks				

**TABLE 4.** Observational studies of treatment of initial CDI.

Trial	Treatment	Number of patients	Cure (%)	Relapse (%)
<b>Antibiotics</b>				
Bartlett <i>et al.</i> [37]	Vancomycin	79	96	14
Silva <i>et al.</i> [38]	Vancomycin	16	100	13
Cherry <i>et al.</i> [39]	Metronidazole	13	100	15
Bartlett [40]	Vancomycin	189	97	24
de Lalla <i>et al.</i> [41]	Vancomycin 500 mg qid, 10 days	23	100	13
	Teicoplanin 200 mg bid, 10 days	22	100	0
Olson <i>et al.</i> [42]	Metronidazole	632	98	6
	Vancomycin	122	99	10
Kyne <i>et al.</i> [15]	Metronidazole	44	?	50
Fernandez <i>et al.</i> [11]	Metronidazole	99	62	?
Musher <i>et al.</i> [43]	Metronidazole	207	78	28
Pépin <i>et al.</i> [9]	Metronidazole	1123	84	29
	Vancomycin	112	?	28
Louie [44]	Difimicin varying dose	45	91	5
Musher <i>et al.</i> [45]	Nitazoxanide 500 mg bid, 10 days	35	74	27
	Patients first failed metronidazole			
Al Nassir <i>et al.</i> [16]	Metronidazole	34	>90	12
	Ten patients switched to vancomycin			
Herpers <i>et al.</i> [46]	Vancomycin	18	>90	11
	Tigecycline varying duration	4	100	0
Severe CDI. Follow-up at least 3 months				
<b>Toxin-binding resins and polymers</b>				
Mogg <i>et al.</i> [47]	Coolestipol 10 g qid, 5 days	12	25	–
Originally set up as a randomized placebo-controlled trial. Placebo group was merged with historical control, however. Only six patients had toxin-positive stool				
<b>Passive immunotherapy with immune whey</b>				
van Dissel <i>et al.</i> [48]	Metronidazole or vancomycin followed by immune whey protein concentrate, 14 days	16	100	0
	56% of patients had recurrent CDI; mean follow-up 333 days			
Numan <i>et al.</i> [13]	Metronidazole or vancomycin followed by immune whey protein concentrate, 14 days	109	100	10
109 episodes; 101 patients; 40% of patients had recurrent CDI				

whose non-inferiority to vancomycin could not be shown in another trial due to lack of power [31]. As yet, there is also insufficient evidence to justify routine use of fidaxomicin

(OPT-80), an inhibitor of RNA polymerase of gram-positive bacteria, although preliminary results of a recently presented study are very promising [32].

**TABLE 5. Randomized controlled studies of treatment of recurrent CDI**

Trial	Treatment	Number of patients	Failure <sup>a</sup> (%)	
Probiotics	McFarland <i>et al.</i> [33]	Vancomycin or metronidazole + <i>Saccharomyces boulardii</i> $2 \times 10^{10}$ CFU/day, 4 weeks	26	35
		Vancomycin or metronidazole + placebo	34	65
	Double-blind. No control for type, duration or dose of antibiotic. Unclear definition of relapse. Follow-up 8 weeks after start of treatment. $p = 0.04$ for comparison of failure rates			
	Surawicz <i>et al.</i> [49]	Vancomycin 500 mg qid, 10 days, followed by <i>Saccharomyces boulardii</i> $2 \times 10^{10}$ CFU/day, 4 weeks	18	17
		Vancomycin 500 mg qid, 10 days, followed by placebo	14	50
		Vancomycin 125 mg qid, 10 days, followed by <i>Saccharomyces boulardii</i> $2 \times 10^{10}$ CFU/day, 4 weeks	45	51
		Vancomycin 125 mg qid, 10 days, followed by placebo	38	45
		Metronidazole 1 g/day, 10 days, followed by <i>Saccharomyces boulardii</i> $2 \times 10^{10}$ CFU/day, 4 weeks	27	48
		Metronidazole 1 g/day, 10 days, followed by placebo	26	50
	Follow-up 5 months after completion of study drug. $p = 0.05$ for the comparison of failure rates in patients who received 500 mg of vancomycin qid. Drop-out was 22%. No further statistically significant differences			
Wullt <i>et al.</i> [50]	Metronidazole 400 mg tid, 10 days + <i>Lactobacillus plantarum</i> 299v $5 \times 10^{10}$ CFU/day, 38 days	12	42	
	Metronidazole 400 mg tid, 10 days + placebo	9	67	
Double-blind. 28% cent drop-out. Follow-up 70 days. Difference not statistically significant				
Lawrence <i>et al.</i> [51]	Vancomycin or metronidazole followed by <i>Lactobacillus GG</i> $6 \times 10^{11}$ CFU/day, 21 days	8	38	
	Vancomycin or metronidazole followed by placebo	7	14	
Patients blinded. No control for type, duration or dose of antibiotic. Follow-up 60 days after completion of antibiotic. Difference not statistically significant				
Passive immunotherapy with immune whey				
Mattila <i>et al.</i> [52]	Colostrum immune whey 200 mL tid + placebo, 14 days	18	44	
	Metronidazole 400 mg tid + placebo, 14 days	20	45	
Double-blind. Multi-centre trial. Follow-up 70 days. Difference not statistically significant.				

<sup>a</sup>Non-response or relapse.

### Duration of antibiotic therapy

The duration of antibiotics has been 10 days in most studies. Occasionally, a shorter duration (e.g. 7 days) has been reported. We feel that there is insufficient evidence of success with a shorter duration of therapy with any antibiotic to consider shorter regimens a treatment option.

There is no definitive evidence that taper or pulse regimens with vancomycin are effective in reducing the incidence of relapses. This strategy is mainly based on favourable experience and the theoretical rationale that spores can still germinate long after the clinical symptoms have resolved. McFarland *et al.* [7] retrospectively compared a standard course of antibiotics, vancomycin taper strategies (gradually decreasing the daily dose of vancomycin by 125–750 mg per day from varying starting doses) and vancomycin pulse strategies (125–500 mg of vancomycin every 2–3 days during a period of usually 3 weeks). They found the recurrence rate to be lowest in pulse regimens (14%), followed by taper regimens (31%) and the standard regimen of vancomycin (54%; average for all dose groups). No other studies investigating taper or pulse regimens have been published. Further studies are needed.

### Probiotics

Probiotics may be of value when added to antibiotics, but the studies that have investigated this have major drawbacks such as small numbers, non-randomized allocation of antibiotics to which the probiotics were added, and lack of homogeneity among study groups. This is also the con-

clusion reached by a recent Cochrane systematic review [74]. Therefore, there is insufficient evidence to recommend the addition of probiotics to antibiotics. In addition, several studies of invasive disease have been reported, resulting from the use of probiotics such as *Saccharomyces boulardii* in debilitated or immunocompromised patients [75,76]. Moreover, probiotics were associated with increased mortality, partly due to nonocclusive mesenteric ischemia, in a randomized controlled trial in acute pancreatitis [77].

### Treatment when oral administration is not possible

The only parenteral antibiotic therapy for CDI, supported by case series, is metronidazole [78]. Several case reports regarding the use of intravenous immunoglobulin have been published, but the data do not provide sufficient evidence to support its use. Thus, it is unknown how to best treat patients with ileus due to CDI. There are some anecdotal reports on delivery of vancomycin to the gut by means other than orally, mainly through intracolonic delivery. Questions regarding the efficacy, optimal dosing and duration of treatment with intracolonic vancomycin are unanswered. The introduction of faecal collector drainage systems has facilitated the use of glycopeptide retention enemas in ICUs, but they are very expensive. Tigecycline appeared useful as salvage therapy, as reported in a recent case series of patients with severe CDI complicated by ileus, but these promising findings require confirmation in prospective clinical trials [46]. Faecal transplantation has been performed through

**TABLE 6. Observational studies of treatment of recurrent CDI**

Trial	Treatment	Number of patients	Failure <sup>a</sup> (%)	Mean follow-up
<b>Antibiotics</b>				
Buggy <i>et al.</i> [53]	Vancomycin 125 mg qid + rifampicin 600 mg bid, 7 days	7	0	12 months
McFarland <i>et al.</i> [7]	Vancomycin 1–2 g/day	14	71	59 days
	Vancomycin <1 g/day	48	54	59 days
	Vancomycin ≥2 g/day	21	43	59 days
	Vancomycin taper	29	31	80 days
	Vancomycin pulse	7	14	80 days
	Metronidazole <1 g/day	29	45	59 days
	Metronidazole 1.5 g/day	5	40	59 days
	Metronidazole 2 g/day	2	0	59 days
Johnson <i>et al.</i> [54]	Vancomycin, 14 days, followed by rifaximin varying dose, 14 days	8	13	233 days
Garey <i>et al.</i> [55]	Rifaximin 400 mg tid, 14 days, followed by rifaximin 200 mg tid, 14 days	5	0	310 days
	Rifaximin 400 mg tid, 36 days	1	100	–
<b>Probiotics</b>				
Gorbach <i>et al.</i> [56]	Metronidazole or bacitracin, 10 days, followed by <i>Lactobacillus</i> GG 10 <sup>10</sup> CFU/day, 7–10 days	5	20	–
Billler <i>et al.</i> [57]	<i>Lactobacillus</i> GG 6 × 10 <sup>8</sup> CFU/day, 14 days	4	0	11 months
<b>Faecal or bacterial instillation</b>				
Bowden <i>et al.</i> [58]	Faecal enema	16	19	–
Tvede and Rask-Madsen [59]	Faecal or bacterial enema	6	0	–
Lund-Tønnesen <i>et al.</i> [60]	Faecal instillation through colonoscope or gastrostoma	18	17	–
Aas <i>et al.</i> [61]	Faecal instillation through nasogastric tube, median 3 courses	16	6	90 days
Jorup-Rönström <i>et al.</i> [62]	Faecal enema	5	0	–
Nieuwdoorp <i>et al.</i> [63]	Vancomycin 500 mg qid, followed by faecal instillation by nasoduodenal tube or colonoscopy	7	29	150 days
Borody <sup>b</sup>	Faecal enema	61	10	–
Lund-Tønnesen <sup>b</sup>	Faecal instillation through nasojejunal tube	20	17	–
Moore <sup>b</sup>	Faecal enema	65	3	–
Aas <sup>b</sup>	Faecal instillation through nasogastric tube	9	0	–
Maccconnachie <i>et al.</i> [64]	Faecal instillation through nasogastric tube	15	27	–
<b>Immunotherapy</b>				
Leung <i>et al.</i> [65]	iv gammaglobulin 400 mg/kg every 3 weeks, 4–6 months	5	0	5 months
Beales [66]	iv gammaglobulin 400 mg/kg day 1 and 21	4	0	7.5 months
	iv gammaglobulin, varying dose	5	40	2.8 months
Wilcox [67]	iv gammaglobulin 300–500 mg/kg, 1–6 doses	5	40	86 days
McPherson <i>et al.</i> [68]	iv gammaglobulin 150–400 mg/kg	14	71	6.6 months

<sup>a</sup>Non-response or relapse.

<sup>b</sup>As reported by Bakken [69].

instillation with a colonoscope or enemas, but there is insufficient evidence to recommend this.

There are no prospective studies assessing which CDI patients benefit from surgical intervention. One study found that colectomy was most successful at a relatively early stage of the disease, i.e. before lactate exceeds 5.0 mmol/L [79].

## Recommendations for the Treatment of CDI

### Recommendations for medical treatment of initial CDI

In the case of mild CDI (stool frequency < 4 times daily; no signs of severe colitis), clearly induced by the use of antibiotics, it is acceptable to discontinue the inducing antibiotic and observe the clinical response, but patients must be followed very closely for any signs of clinical deterioration and placed on therapy immediately if this occurs. Theoretic rationale, anecdotic evidence, and one case-control study suggest that antiperistaltic and opiate agents should be avoided, especially in the acute setting [80]. There is no evidence that switching to 'low-risk' antibiotics when the antibiotic treatment that cited the episode of CDI cannot be discontinued, nor its

spectrum narrowed, is effective. It seems rational, however, to always strive to use antibiotics covering a spectrum no broader than necessary. When the inciting antibiotic cannot be discontinued, antibiotic treatment for CDI should be initiated. Furthermore, there is no proof that discontinuing gastric acid suppressants is effective, either.

In all cases other than mild CDI medical treatment for CDI should be started. Antibiotics may be started while awaiting diagnostics when there is sufficient clinical suspicion. We recommend treatment of an initial episode of CDI with the following antibiotics, according to disease severity (implementation category between brackets), when oral therapy is possible:

- non-severe: metronidazole 500 mg tid orally for 10 days (A-I)
- severe: vancomycin 125 mg qid\* orally for 10 days (A-I)

\*Oral vancomycin may be replaced by teicoplanin 100 mg bid, if available.

CDI is judged to be severe when one or more of the markers of severe colitis mentioned under 'definitions' is present. It is unclear whether moderate disease in a patient with other unfavourable prognostic factors, such as advanced

age and comorbidity, should be regarded as severe. This is left to the judgment of the treating physician. There is no evidence that various genotypes of *C. difficile* should be treated differently if disease severity does not differ.

When oral therapy is impossible, we recommend the following antibiotics, according to disease severity (implementation category between brackets):

- non-severe: metronidazole 500 mg tid intravenously for 10 days (A-III)
- severe: metronidazole 500 mg tid intravenously for 10 days (A-III) + intracolonic vancomycin 500 mg in 100 mL of normal saline every 4–12 h (C-III) and/or vancomycin 500 mg qid by nasogastric tube (C-III)

#### Recommendations for surgical treatment of CDI

Colectomy should be performed to treat CDI in any of the following situations:

- perforation of the colon
- systemic inflammation and deteriorating clinical condition not responding to antibiotic therapy; this includes the clinical diagnoses of toxic megacolon and severe ileus.

Since mortality following colectomy in patients with advanced disease is high, it is recommended to operate at a less severe stage. No definite recommendations on the timing of colectomy can be given. Serum lactate may, inter alia, serve as a marker for severity, and one should attempt to operate before the threshold of 5.0 mmol/L [79].

#### Recommendations for medical treatment of recurrent CDI

Observational data [12] suggest that the incidence of a second recurrence after treatment of a first recurrence with oral metronidazole or vancomycin is similar. Therefore, we recommend treating a first recurrence of CDI as a first episode, unless disease has progressed from non-severe to severe.

We recommend treatment of recurrent CDI with the following antibiotics (implementation category between brackets):

First recurrence:

See *Recommendations for medical treatment of initial CDI*.

Second recurrence and subsequent recurrences:

If oral therapy is possible:

- vancomycin 125 mg qid\* orally for at least 10 days (B-II) and consider a taper/pulse strategy (B-II)

\*Oral vancomycin may be replaced by teicoplanin 100 mg bid, if available.

If oral therapy is impossible:

- metronidazole 500 mg tid intravenously for 10–14 days (A-III) + retention enema of vancomycin 500 mg in 100 mL of normal saline every 4–12 h (C-III) and/or vancomycin 500 mg qid by nasogastric tube (C-III)

#### Recommendation for prophylaxis of CDI

Currently, there is no evidence that medical prophylaxis for CDI is efficacious and therefore we do not recommend prophylactic antibiotics. Of course, other preventive measures should be taken, such as hand hygiene of hospital personnel, prompt isolation of patients suspected of having CDI, and prudent use of antibiotics [81].

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Three draft versions of this guideline document were written by three authors (MB, EK, JvD) and critiqued by the Committee and Advisors. A consensus was reached, resulting in the final version.

## Transparency Declaration

The authors declare that they have no conflicts of interest.

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